Clinical Study Protocol

Biotest AG

Title: 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

Clinical Phase: I/III
Version incl. date: Version 6.0, 08-May-2018
EudraCT Number: 2011-004154-25
Study No.: 984

Coordinating Investigator

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Sponsor

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Overview of Amendments integrated in the protocol text of version 6.0 of 08-May-2018

Amendment No	Date	Sections concerned	Rationale
1	**16 Jan 2013**	Cover page	Title page amended to change the telephone number of the Director Clinical Operations Corporate Clinical Research.
1	**16 Jan 2013**		Introduction of overview table on protocol amendments added according to SOP.
1	**16 Jan 2013**	2	Modification of the involved countries and sites. Date of First Patient In.
1	**16 Jan 2013**	3	Minor corrections in the Study Flow Chart for adults. Introduction of two additional Flow-charts for the newly defined subgroups of children with different bodyweight: Children Group I (6 to 18 years, bodyweight > 43 kg) and Children Group II (6 to 18 years, bodyweight between 22 and 43 kg).
1	**16 Jan 2013**	13, 14	Reduction of time points of blood draw in children Group I (>43kg body weight) for the assessment of Coagulation, Hematology and Biochemistry. Reduction of time points of blood draw in children Group II (22-43 kg body weight) for the assessment of Coagulation, Hematology and Biochemistry as well as of pharmacokinetics and pharmacodynamics.
1	**16 Jan 2013**	14	Addition of a new chapter concerning Pregnancy Reporting.
2	**15-Jun-2014**	Cover page, 1, 2, 3, 5, 6, 9, 10, 12, 13, 14, 15	Update with clarification of wording, additions, corrections and formatting.
2	**15-Jun-2014**	2, 7, 11.1.5, 12.1.2, 13.3, 14.3	Implementation of a Data Monitoring Committee (DMC) to approve the inclusion of children and adolescents after the 10th adult patient treated and to survey the study as a whole. The DMC is to ensure the safety of the study participants in particular with regard to the inclusion of children and adolescents. Implementation of an appropriate procedure and a related stopping rule.
2	**15-Jun-2014**	2, 12.2, 12.3,	Inclusion criterion 1 (now 1 and 2) and exclusion criterion 12 were modified to clarify the target population.
2	**15-Jun-2014**	2, 13.2	The study duration has been extended due to slow patient recruitment. Furthermore, study subjects already on trial will be offered to extend their study participation (in part II) until the last subject enrolled has finished study part II.
2	**15-Jun-2014**	3	Tables 3.1, 3.2, 3.3 ‘Flowcharts of Study’ were changed according to the above mentioned changes.

Amendment No	Date	Sections concerned	Rationale
2	**15-Jun-2014**	3 13.1.1.2, 13.1.2.2 14.1.1	Modified method for determination of Fibrinogen Antigen (Assay); ELISA changed to nephelometry.
2	**15-Jun-2014**	3, 13.1.1.2, 13.1.2.2 13.1.2.4 13.5.6, 14.5.1.12	Assessments of risk and burden in children and adolescents and a justification regarding the risks and burden these age groups are exposed by the clinical trial.
2	**15-Jun-2014**	13.5.3, 13.5.4, 13.5.5	Implementation of risk minimization measures for all study participants as well as for the enrolment and treatment of children and adolescents.
2	**15-Jun-2014**	14.5.1.4	The determination of Fibrinogen inhibitory antibodies was stated more precisely. The development of Fibrinogen inhibitory antibodies has to be reported as serious adverse events (SAEs).
3	**15-Jul-2015**	Cover page, 1, 2, 3, 6, 9, 11, 12, 13, 14, 15	Update with clarification of wording, additions, corrections and formatting.
3	**15-Jul-2015**	1, 2, 3, 7, 9, 11, 12, 13, 14, 15	Extension of the ongoing phase I/II study into a phase I/III study. Treatment of at least 10 additional patients into part II (without part I PK/PD).
3	**15-Jul-2015**	3	Tables 3.4.1, 3.4.2, 3.4.3 'Flowcharts of Study' were introduced according to the above mentioned changes.
3	**15-Jul-2015**	11.1.1	The calculation of the BT524 dose to be administered to the patients was revised in regard to the specifications in the certificate of analysis.
4	**15-Mar-2017**	Cover Page, 1, 5, 6, 9	Update with clarification of wording, additions, corrections and formatting. Introduction of the new statistician.
4	**15-Mar-2017**	2, 8, 9, 11, 12, 13, 14, 15	Update and revision of study protocol covering the Paediatric Investigational Plan (Inclusion of children below 6 years).

Amendment No	Date	Sections concerned	Rationale
4	**15-Mar-2017**	3	Update and formatting of flowcharts. Deletion of redundant abbreviations in order to streamline the flowcharts. Deletion of redundant flowcharts in section 3.6.2 and 3.6.3 and cross reference to the corresponding sections 3.1 to 3.5. Correction of Fibrinogen antigen and activity assessments in flowchart 3.6.1 (Screening visit for the additional patients) in order to reflect the actual assessments. Introduction of 6 additional flowcharts for the newly defined subgroups of children below 6 years (Pre-school Children Group III and Newborns/ Infants and Toddlers Group IV)
4	**15-Mar-2017**	19	Update of scientific literature.
4	**15-Mar-2017**	20	Deletion of Appendix 20.1 'Overview of Protocol Changes' and transfer of this section to a separate document (SOP-K-00044_A02) in order to adhere to the updated SOP template K-00044_A01 (previous SOP-CCR-007-T001). Introduction of a new Appendix 20.1 'Dosage for Newborns, infants and children.
5	**08-May-2018**	Cover Page 2, 3, 5, 8, 11, 12, 13, 14, 15, 20	Introduction of a new project manager CCR&D. Update with clarification of wording, additions, corrections and formatting.
5	**08-May-2018**	2, 0 20.2	Adaption of exclusion criterion 12 in order to clarify that this criterion is only applicable for patients in PK part I. Adaption of exclusion criterion 13 in order to harmonize the 'lower body weight limit' (the 5th percentile of the normal range) between all children age groups. Information regarding the WHO Child Growth Standards was included in appendix 20.2.
5	**08-May-2018**	14.6	Introduction of new sections 'Adverse Event of Special Interest (AESI)' and 'Follow-up of Adverse Events'
5	**08-May-2018**	15.1	Correction of Sample Size Calculation as this section was adapted within amendment 3 (CSP V4.0) to the new patient numbers in error.
5	**08-May-2018**	14.4, 20.3	The investigator is asked to classify any bleeding event post-dose as minor or major. A recommendation for the assessment of bleeding events was introduced in the appendix.

1 SIGNATURE PAGE

This clinical study is carried out in accordance with the international guidelines on Good Clinical Practice (ICH-GCP) and in compliance with applicable regulatory authority requirements. It is confirmed that the clinical study will be carried out and documented in accordance with this study protocol.

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1.1 Signature Page for Investigators

Declaration of the Principal Investigator

I have read and understood this clinical study protocol and agree to the following:

- To adhere to the ethical and scientific principles of good clinical practice, and the principles of the Declaration of Helsinki, the local laws and regulations, and the applicable regulatory requirements.
- To conduct the clinical study as set out in the protocol.
  This includes:
  - To wait until I have received approval from the appropriate Independent Ethics Committee / Institutional Review Board (IEC/IRB) before enrolling any patient in this study.
  - To obtain informed consent of each patient prior to any study-related measure performed.
  - To permit study-related monitoring, audits, IEC/IRB review, and regulatory authority inspections.
  - To provide direct access to all study-related records, source documents, and patient files for the monitor, auditor, IEC/IRB, or regulatory authority upon request.
  - To use the IMP and all study materials only within the framework of this clinical study protocol.
  - To understand that changes to the clinical study protocol must be made in the form of an amendment that has the prior written approval of Biotest and, as applicable, of the appropriate IEC/IRB and regulatory authority.
  - To comply with the reporting obligations for Adverse Events / Serious Adverse Events (AE/SAEs).

I understand that all documentation that has not been previously published will be kept in the strictest confidence. This documentation includes the Clinical Study Protocol, Investigator's brochure (IB), Case Report Forms (CRF), and other scientific data.

Principal Investigator
<Name>

_____
Date, signature

Investigator stamp:

2 STUDY SYNOPSIS

Title	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 of patients with congenital fibrinogen deficiency
Clinical Phase	I/III
Coordinating Investigator	PPD
Study Objectives	**Primary objective:** To investigate the 14 day single-dose pharmacokinetics (PK) of BT524 following intravenous infusion in patients with congenital fibrinogen deficiency (afibrinogenemia or severe hypofibrinogenemia). **Secondary objectives:** To investigate the 14 day single-dose pharmacodynamics (PD), the surrogate efficacy and safety of the single intravenous infusion of BT524. To investigate efficacy, surrogate efficacy and safety, of single and/or repetitive intravenous infusions of BT524 for *on-demand* prophylaxis (ODP) and/or *on-demand* treatment (ODT) of bleeding events.
Study Design	Prospective, open-label, multicentre
Study Population	Patients with congenital afibrinogenemia or severe congenital hypofibrinogenemia. **Enrolment Procedures:** **Part I** The first 5 patients are to be enrolled consecutively with a dosing-free safety interval of 7 days between each patient. Subsequently, patients 6 to 20 are allowed to be treated simultaneously, if applicable. A Data Monitoring Committee (DMC) will review and assess the safety and PK data from the first 10 adult patients prior to enrolment of any children or adolescents into the study. Children ≥ 6 years and adolescents are only allowed to be enrolled after completion of the 7-day dosing-free safety interval of the 10th adult patient and assessment of these data by the DMC. Subsequently, after the first 20 patients of ≥ 6 to ≤ 75 years finished part I, at least 3 additional paediatric patients < 6 years of age are planned to be enrolled in the study part I.

Study Population (continued)	**Part II** All patients included in part I will be eligible for participation in part II. At least 10 additional patients ≥ 6 to ≤ 75 years and at least 3 additional patients < 6 years will be enrolled in part II (ODT/ODP) without PK/PD assessments (part I). Prior to enrolment of any children < 6 years of age a DMC will review and assess all available safety and PK/PD data from adults and children ≥ 6 years enrolled in the study so far (including data of least 3 children ≥ 6 to < 12 years and of at least 3 adolescents ≥ 12 to < 18 years). All patients will be offered to extend their study participation (in part II) until the last enrolled subject (of these additional patients) has finished study part II (12 months).
Inclusion Criteria	Only patients meeting all of the following **inclusion criteria** will be considered for study inclusion: 1. Known congenital afibrinogenemia or severe congenital hypofibrinogenemia 2. Plasma fibrinogen activity ≤ 0.5 g/l and antigen ≤ 0.5 g/l 3. Male or female 4. Age 0 to 75 years, with the first ten patients will be 18 years or older 5. Presumed to be compliant with the study procedures and to terminate the study as scheduled 6. Willing and able to be hospitalized for 3 days for the pharmaco-kinetic assessment (if applicable) 7. Willing and able to be hospitalized - if required - in case of interventions (e.g., surgical procedures, major bleeds) 8. Written informed consent by the patient, his/her parents or by the patient's legal / authorized representative as applicable
Exclusion Criteria	Patients having any of the following **general exclusion criteria**, either at screening (pre-visit) or at enrolment (visit 1) are to be excluded from the study: 1. Known congenital dysfibrinogenemia 2. Known bleeding disorder other than congenital fibrinogen deficiency 3. History of esophageal variceal bleeding 4. Known presence or history of venous/arterial thrombosis or thromboembolic event (TEE) in the preceding 6 months 5. Known presence or history of fibrinogen inhibitory antibodies 6. Known presence or history of hypersensitivity to human fibrinogen or human plasma proteins e.g., immunoglobulins, vaccines or hypersensitivity to any of the excipients 7. Known positive serology for HIV-1 and HIV-2 8. Clinically relevant biochemical or hematological findings (except due to underlying disease or emergency bleeding) outside the normal range (at the investigator's discretion) 9. Clinically relevant pathological findings in physical examination including electrocardiogram (ECG)

	10. Treatment with any fibrinogen concentrate and/or fibrinogen-containing product within 2 weeks prior to infusion of BT524 11. Concomitant medication interacting relevantly with the coagulation system (e.g., low molecular weight heparin, unfractioned heparin, factor Xa inhibitors, factor IIa inhibitors or PY12 inhibitors) within 2 weeks prior to infusion of BT524 12. Recent vaccination within 3 weeks prior to infusion* 13. Body weight (BW) below 22 kg for patients ≥ 6 years*; BW below the 5th percentile of the normal range for children ** 14. End stage disease 15. Abuse of drugs 16. Unable to understand and follow the study requirements (refers to the patient, his/her parents or to the patient's legal / authorized representative as applicable) 17. Participation in another interventional clinical study within 30 days before entering the study or during the study 18. Pregnant/ nursing woman, or woman of childbearing potential not using reliable/ effective contraceptive method(s) during the study and at least one month after the last administration of study drug (e.g., oral/ injectable/ implantable/ insertable/ topical hormonal contraceptives, intrauterine devices, female sterilization, partner's vasectomy or condoms) 19. Any other condition that, to the investigator's judgment, could have an impact on patient's safety or the study results * only applicable for patients in PK part I ** refers to local standards (Appendix 20.12)
Exclusion Criteria (continued)	**Pharmacokinetics (PK)** In addition to the general exclusion criteria mentioned above, patients meeting any of the following **PK-specific exclusion criteria** at enrolment are to be excluded from the pharmacokinetic assessment. Patient enrolment is to be postponed until no PK exclusion criterion applies. 20. Elective surgery during the 14 day PK blood sampling period 21. Acute infection 22. Clinically relevant increase or decrease in body temperature 23. Actively bleeding or anticipated bleeding (including female menorrhea) at the time point of or within 7 days prior to infusion of BT524 24. Surgery within 7 days prior to infusion of BT524 25. Immobilization within 7 days prior to infusion of BT524 26. Intake of alcohol or significantly increased intake of caffeine containing products within 24 hours prior to infusion of BT524 27. Blood donation or comparable blood loss within 60 days prior to infusion of BT524 28. Excessive physical exercise (extreme sports activities, sauna) within 72 hours prior to infusion of BT524

Number of Study Patients	**Part I** Approximately 20 patients ≥ 6 to ≤ 75 years will be included to have about 15 evaluable patients for the analyses of the PK/PD of BT524 and the surrogate efficacy parameter. At least 3 additional patients 0 to < 6 years of age are to be included to have 3 evaluable datasets for PK/PD assessment. **Part II** At best, all patients who have completed part I will continue with the extended *on-demand prophylaxis* (ODP)/ *on-demand treatment* (ODT). Subsequent to completion of part I by the first 20 subjects ≥ 6 to ≤ 75 years, at least 10 additional patients and at least 3 additional patients < 6 years will be treated in part II without PK/PD assessments in part I. In total, approximately 36 patients 0 to ≤ 75 years should be treated in part II. Thereof, at least 6 patients should be < 6 years, 6 patients should be ≥ 6 to < 12 years and 6 patients should be ≥ 12 to < 18 years of age. With respect to the evaluation of efficacy, surrogate efficacy and safety of the single or repetitive intravenous infusions of BT524, each bleeding event (part II) will be considered as an *individual case* in the primary analysis.
Countries/ Number of Study Sites	5-7 sites in the European Union and in non-EU countries
Investigational Medicinal Product (IMP)	BT524 is a heat-treated, lyophilized fibrinogen concentrate manufactured from human plasma. BT524 is presented as a single-use vial containing 1 g of lyophilized fibrinogen. The lyophilisate is to be reconstituted with 50 ml of water for injections, resulting in a final concentration of 20 mg/ml for infusion.
Dosage and Mode of Administration	The dosage and duration of the substitution therapy depend on the severity of the disorder, location and extent of bleeding and the patient's clinical condition. In addition, dosage is always based on individual BW and fibrinogen baseline level. Similar dosage strategy will be applied to planned subjects < 6 years, as for subjects ≥ 6 to ≤ 75 years. Unless valid information on the recovery rate of BT524 is available, the dosage regimen for surgical interventions and spontaneous bleedings will target (functional) fibrinogen levels recommended by the Core SmPC for Human Fibrinogen Products.

Dosage and Mode of Administration (continued)

Dosage for the PK dose (part I) and Guidance for On-demand Prophylaxis and/ or On-demand Treatment

	Dose	Target Level	No. of Doses	MOA	Infusion Rate
Pharmacokinetics					
	70 mg/kg BW	—	single	IV	5 ml/min* < 5 ml/min** (< 100 mg/min)
* for Adults and Children/Adolescents Group I and Group II (≥ 6 years) ** for Pre-school Children Group III and Newborns/Infants + Toddlers Group IV (< 6 years)					
Surgical intervention					
On-demand prophylaxis (ODP)	variable*	1 g/l**	as required	IV	max 100 mg/min
On-demand treatment (ODT)	variable*	1 g/l** maintained until hemostasis is secure	as required	IV	max 100 mg/min
		> 0.5 g/l** until wound healing is complete			
Spontaneous bleeding					
On-demand treatment	variable*	—	as required	IV	max 100 mg/min

Target levels recommended by the Core SmPC for Human Fibrinogen Products

BW: body weight; IV: intravenous; max: maximum; min: minute; MOA: mode of administration;

Values given are guidance only, and higher or lower levels and increased frequency of administration may be necessary

* adapted on severity, location and extent of bleeding, and patient's clinical condition

** depending on the severity of the event fibrinogen levels may be raised in individual cases to a maximum of 1.5 g/l at the discretion of the investigator.

In children < 6 years the reconstituted solution of BT524 will be administered intravenously (IV) via an infusion pump with an adapted infusion rate below 5 ml/min (100 mg/minute) according to age, BW, and medical condition at the discretion of the treating physician of the patient.

Once valid information on the recovery rate of BT524 is available, the dose to be administered is to be calculated according to the formula given by the Core SmPC:

Dose (g) = [desired levels (g/l) – baseline level (g/l)] x 1/recovery (g/l / g/kg) x BW (kg).

Duration of Treatment

Part I: A single intravenous infusion for the assessment of PK/PD.

Part II: *On-demand prophylaxis (ODP):*
Single or repetitive intravenous infusion(s)

On-demand treatment (ODT):
Single or repetitive intravenous infusion(s)

For each patient the individual treatment period in part II will last at least 12 month upon enrollment.

Duration of Follow-up	**Part I** Individual follow-up (virus safety) is 49±4 days after the administration of BT524 for PK/PD assessment. **Part II** For each bleeding event, individual follow-up (virus safety) is 49±4 days after the last administration of BT524 for the respective event.
Criteria for Evaluation	
Primary Criterion	**Pharmacokinetics (PK)** PK parameters will be derived from time concentration profiles using adapted methodology (non-compartmental analysis, compartment analysis, or population modeling, as appropriate/ required). Single-dose PK of fibrinogen antigen will be assessed by the following variables: • Terminal Elimination Half-life ($t_{1/2}$) for fibrinogen antigen • Time to reach Maximum Concentration (t_{max}) • Maximum Concentration (C_{max}) • Area Under the Concentration-Time Curve (AUC) calculated to the last measured concentration (AUC(0-t)) and extrapolated to infinity (AUC(0-inf) • Clearance (CL) • Mean Residence Time (MRT) • Volume of Distribution (V_{ss}) • Incremental Recovery (IR) • Classical in vivo Recovery (IVR)
Secondary Criteria	**Pharmacodynamics (PD)** Single-dose PD of fibrinogen activity will be assessed by the following variables: • Terminal Elimination Half-life ($t_{1/2}$) for fibrinogen activity • Time to reach Maximum Concentration (t_{max}) • Maximum Concentration (C_{max}) • Area Under the Concentration-Time Curve (AUC) calculated to the last measured concentration (AUC(0-t)) and extrapolated to infinity (AUC(0-inf) • Clearance (CL) • Mean Residence Time (MRT) • Volume of Distribution (V_{ss}) • Incremental Recovery (IR) • Classical in vivo Recovery (IVR)

Secondary Criteria (continued)	**Surrogate Efficacy** **Maximum clot firmness (MCF, mm)** measured by rotational thromboelastometry Part I • Comparison of MCF pre-dose and at 1 and 8 hours post-end of IV infusion • Correlation between MCF and fibrinogen activity pre-dose and at 1 and 8 hours post-end of IV infusion Part II • Comparison of MCF pre-dose and at 1 hour post-end of each IV infusion • Correlation between MCF and fibrinogen activity pre-dose and at 1 hour post-end of each IV infusion **Clinical Efficacy** The following efficacy parameters will be assessed after each bleeding event: • Overall hemostatic 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" • Total loss of blood (e.g., intra- and postoperatively, re-bleedings), if applicable • Units of other fibrinogen-containing products infused besides BT524 e.g., fresh frozen plasma or cryoprecipitate • Units of transfusion products infused e.g., allogenic or autologous blood (packed red blood cells, fresh whole blood), platelets • Consumption of BT524 (dose per kilogram BW required pre-, intra- or post-operatively for effective treatment) The following efficacy parameter will be assessed after wound healing is expected to be resolved • Quality of wound healing, if applicable **<u>Safety</u>** • Electrocardiogram • Adverse events • Development of fibrinogen antibodies • Changes in vital signs e.g., blood pressure, heart rate, body temperature • Change in physical examination • Change in clinical laboratory assessments of hematology, biochemistry, and urine analysis • Change in markers of coagulation activation: PT(INR), aPTT, TAT, F_{1+2}, D-dimer

Biostatistical Concept	All data collected will be listed and tabulated. Categorical variables will be presented with absolute and relative frequencies. For continuous variables descriptive statistics will be given including mean, standard deviation, median, quartiles, minimum, and maximum. Additionally, for PK data, efficacy and safety parameters, 95 % confidence intervals will be calculated where appropriate. PK parameters will be summarized by descriptive statistics for each age group, and compared descriptively between age groups. No formal statistical test will be used. All analyses of this open-label study will be performed on intention-to-treat (ITT) as well as per protocol population (PP). ITT population will include all patients who received at least any portion of BT524. The PP population will include all patients who received at least 90% of the planned total dose of BT524, met all inclusion and no exclusion criteria, complied with the protocol procedures and had no major deviations impacting on study analysis. Response to therapy with BT524 will be evaluated per bleeding event using a 4-point scale ('none', 'moderate', 'good', 'excellent') by the investigator. The clinical response, summarizing the excellent and good rating, will be analysed descriptively (providing estimate and 95% confidence interval). These estimations will be compared with a historical control from a retrospective physician survey, where the outcome excellent/good was reported with 90%. All analyses will be described in detail within a statistical analysis plan (SAP). The PK of BT524 will be analyzed and reported in a separate report after completion of study part I.
First Patient In *(planned)*	Adults: 20-Mar-2013 Children/Adolescents (≥ 6 to < 18 years): 09-Nov-2014 Children < 6 years: Q2/2018 (planned)
Last Patient Last Visit *(planned)*	Q1/2020

3 FLOWCHARTS OF STUDY

3.1 Flowchart of Study - Adults (18 to 75 years)

PART I: PK/PD — **Visit Day**	**Screening Day 17 to -1**	**PK Dosing Day 0**	**PK FU Day 1**	**PK FU Day 2**	**PK FU Day 4**	**PK FU Day 7**	**PK FU Day 10**	**PK FU Day 14**	**PK Safety Day 49±4**
Assessments — **Periods**	**Screening**	**Hospitalization**			**Visit at the site**				
Informed consent (patient and/or legal representative)	•								
Check/re-check **of inclusion / exclusion criteria**	•	•							
Medical history	•								
Plasma concentration of: **Fibrinogen antigen**, to be done locally (ELISA) and centrally **Fibrinogen activity** (Clauss assay), to be done locally and centrally	•								
Single IV infusion of BT524 (at 70 mg/kg BW)		•							
PK sampling period - Plasma concentration of: **Fibrinogen antigen**, to be done centrally (Nephelometry) **Fibrinogen activity** (Clauss assay), to be done centrally		pre-dose, end of infusion, 0.5, 1, 2, 4, 8 h post-end of infusion	24 h	48 h	96 h	168 h	240 h	336 h	
Maximum clot firmness (MCF) by Fib-tem S of ROTEM, *to be done centrally (locally, if possible)*		pre-dose, 1 and 8 h post-end of infusion							
Fibrinogen inhibitory antibodies, *to be done locally*	•	pre-dose (centrally)							•
Coagulation activation: PT(INR), aPTT, TAT, F_{1+2}, D-dimer, *to be done locally or centrally*	•	pre-dose, 1, 4, 8 h post-end of infusion	•	•	•	•	•	•	•
Safety laboratory, *to be done locally*									
Hematology : RBC, WBC, platelet count, hemoglobin, hematocrit	•	pre-dose	•	•	•	•	•	•	
Biochemistry: ASAT, ALAT, creatinine, urea	•	pre-dose	•	•	•	•	•	•	
γ-GT, AP, total bilirubin, potassium, sodium, calcium, chloride		pre-dose		•				•	
Urine analysis: pH, blood, WBC, protein, glucose, ketone bodies, nitrite, bilirubin, urobilinogen	•	pre-dose		•				•	
IgE, to be done centrally		pre-dose	in case of any		suspected hypersensitivity/allergy				anaphylaxis
Viral safety (collection of retention sample)		pre-dose (collection and analysis)							•
Vital signs (pulse, blood pressure, temperature)	•	pre-dose, 0.5 h after start of infusion, 0.5, 1, 2, 4, 8 h post-end of infusion	•	•	•	•	•	•	•
Physical examination	•	pre-dose, 2 h post-end of infusion	•	•	•	•	•	•	•
ECG	•	6 h post-end of infusion	•						
Ultrasonography of the lower limbs	•	whenever a thromboembolic event			(TEE) is suspected			•	
Pregnancy test (urine), only in females of childbearing potential	•	pre-dose						•	
Adverse events		•	•	•	•	•	•	•	•
Concomitant disease / concomitant medication	•	•	•	•	•	•	•	•	•

PART II: ODP/ODT WITHOUT HOSPITALISATION **SURGERY OR BLEEDING FOR WHICH 24H HOPITALISATION IS NOT NEEDED (to the investigator/surgeon judgement)**	**Discharge to be done at least 5 hours post-end of infusion(s) and only if test results required before allow so**						**OPTIONAL**	
	Prophylaxis/Treatment Dosing Day 0		**DAY 1**	**DAY 2**	**DAY 5**	**DAY 10**	**Within 3 weeks after discharge at investigator request**	**DAY 49±4**
Assessments **Periods**	**Pre-dose**	**Post-end of infusion**	**Phone call**	**Phone call**	**Phone call**	**Phone call**	**Optional Visit**	**Safety Visit**
Type of event (i.e., spontaneous bleeding, surgery)	•							
Re-check of Inclusion / Exclusion criteria	•							
Fibrinogen inhibitory antibodies, *to be done locally*	• (only if patient received fibrinogen since last test)							•
Single or repetitive doses of BT524 for ODP and/or ODT, as required (individually tailored)	•							
Plasma concentration of **fibrinogen activity** (Clauss assay), *to be done locally and centrally*	•	1 h post-end of infusion and as required						
Maximum clot firmness (MCF) by Fib-tem S of ROTEM, *to be done centrally (locally, if possible)*	•	1 h post-end of infusion and as required						
Coagulation activation: PT(INR), aPTT, TAT, F_{1+2}, D-dimer, *to be done locally or centrally*	•	before discharge					•	•
Safety laboratory, *to be done locally* - Haematology (RBC, WBC, platelet count, haemoglobin, haematocrit) - Biochemistry (ASAT, ALAT, γ-GT, AP, total bilirubin, creatinine, urea, potassium, sodium, calcium, and chloride) - Urine analysis (pH, blood, WBC, protein, glucose, ketone bodies, nitrite, bilirubin, urobilinogen)	•	before discharge					•	
Viral safety (collection of retention sample)	•							•
Ultrasonography of lower limbs (Not mandatory in emergency care; at the investigator's discretion)	•	whenever a thrombosis or TEE is suspected					If susp of TEE	If susp of TEE
Vital signs (pulse, blood pressure, temperature)	•	0.5 h after start of infusion, 0.5 h post-end of infusion, before discharge					•	•
Physical examination	•	before discharge					•	•
Pregnancy test (urine), only in females of childbearing potential	•						•	•
Adverse events	•	•	•	•	•	•	•	•
Concomitant disease / concomitant medication	•	•	•	•	•	•	•	•

PART II: ODP/ODT WITH HOSPITALISATION **SURGERY OR BLEEDING FOR WHICH HOPITALISATION IS NEEDED (to the investigator/surgeon judgement)**	**Prophylaxis/ Treatment Dosing Day 0**		**24 hours after the end of last infusion**	**From DAY 2 until day before discharge** (if applicable)	**DISCHARGE DAY** (if different than H24)	**Anytime before Day 49 at investigator request**	**DAY 49±4**
Assessments **Periods**	**Pre-dose**	**Post-end of infusion**				**Optional Visit**	**Safety Visit**
Type of event (i.e., spontaneous bleeding, surgery)	•		BT524 as required				
Re-check of Inclusion / Exclusion criteria	•						
Fibrinogen inhibitory antibodies, *to be done locally*	• (only if patient received fibrinogen since last test)						•
Single or repetitive doses of BT524 for ODP and/or ODT, as required (individually tailored)	•						
Plasma concentration of **fibrinogen activity** (Clauss assay), *to be done locally and centrally*	•	1 h post-end of infusion and as required					
Maximum clot firmness (MCF) by Fib-tem S of ROTEM, *to be done centrally (locally, if possible)*	•	1 h post-end of infusion and as required					
Coagulation activation: PT(INR), aPTT, TAT, F_{1+2}, D-dimer, *to be done locally or centrally*	•	1 h post-end of infusion and as required	•	as required	•	•	•
Safety laboratory, *to be done locally* - Haematology (RBC, WBC, platelet count, haemoglobin, haematocrit) - Biochemistry (ASAT, ALAT, γ-GT, AP, total bilirubin, creatinine, urea, potassium, sodium, calcium, and chloride) - Urine analysis (pH, blood, WBC, protein, glucose, ketone bodies, nitrite, bilirubin, urobilinogen)	•	as required	as required **(But at least to be done once after last infusion of BT524 and before discharge)**			as required	
Viral safety (collection of retention sample)	•						•
Ultrasonography of lower limbs (Not mandatory in emergency care, at the investigator's discretion)	•	whenever a thrombosis or TEE is suspected				if susp of TEE	If susp of TEE
Vital signs (pulse, blood pressure, temperature)	•	0.5 h after start of infusion, 0.5 h post-end of infusion, 4 h post-end of infusion, or as appropriate	•	as required	•	•	•
Physical examination	•		•		•	•	•
Pregnancy test (urine), only in females of childbearing potential	•					•	•
Adverse events	•	•	•	•	•	•	•
Concomitant disease / concomitant medication	•	•	•	•	•	•	•

3.2 Flowchart of Study - Children/Adolescents Group I (≥ 6 years, BW > 43 kg)

PART I: PK/PD — **Visit Day**	**Screening Day -17 to -1**	**PK Dosing Day 0**	**PK FU Day 1**	**PK FU Day 2**	**PK FU Day 4**	**PK FU Day 7**	**PK FU Day 10**	**PK FU Day 14**	**PK Safety Day 49±4**
Assessments — **Periods**	**Screening**	**Hospitalization**			**Visit at the site**				
Informed consent (patient and/or legal representative)	•								
Check/re-check **of inclusion / exclusion criteria**	•	•							
Medical history	•								
Plasma concentration of: **Fibrinogen antigen**, to be done locally (ELISA) and centrally **Fibrinogen activity** (Clauss assay), to be done locally and centrally	•								
Single IV infusion of BT524 (at 70 mg/kg BW)		•							
PK sampling period - Plasma concentration of: **Fibrinogen antigen**, *to be done centrally* (Nephelometry) **Fibrinogen activity**, (Clauss assay) *to be done centrally*		pre-dose, end of infusion, 0.5, 1, 2, 4, 8 h post-end of infusion	24 h	48 h	96 h	168 h	240 h	336 h	
Maximum clot firmness (MCF) by Fib-tem S of ROTEM, *to be done centrally (locally, if possible)*		pre-dose, 1 and 8 h post-end of infusion							
Fibrinogen inhibitory antibodies, *to be done locally*	•	pre-dose (centrally)							•
Coagulation activation: PT(INR), aPTT, TAT, F_{1+2}, D-dimer, *to be done locally or centrally*	•	pre-dose, 4 h and 8 h post-end of infusion	•			•		•	
Safety laboratory, *to be done locally*									
Hematology : RBC, WBC, platelet count, hemoglobin, hematocrit	•	pre-dose	•	•		•		•	
Biochemistry: ASAT, ALAT, creatinine, urea	•	pre-dose	•	•		•		•	
γ-GT, AP, total bilirubin, potassium, sodium, calcium, chloride		pre-dose		•				•	
Urine analysis: pH, blood, WBC, protein, glucose, ketone bodies, nitrite, bilirubin, urobilinogen	•	pre-dose		•				•	
IgE, to be done centrally		pre-dose	in case of any		suspected hypersensitivity/allergy/				anaphylaxis
Viral safety (collection of retention sample)		pre-dose (collection and analysis)							•
Vital signs (pulse, blood pressure, temperature)	•	pre-dose, 0.5 h after start of infusion, 0.5, 1, 2, 4, 8 h post-end of infusion	•	•	•	•	•	•	•
Physical examination	•	pre-dose, 2 h post-end of infusion	•	•	•	•	•	•	•
ECG	•	6 h post-end of infusion	•						
Ultrasonography of the lower limbs	•	whenever a thromboembolic event			(TEE) is suspected			•	
Pregnancy test (urine), only in females of childbearing potential	•	pre-dose						•	
Adverse events		•	•	•	•	•	•	•	•
Concomitant disease / concomitant medication	•	•	•	•	•	•	•	•	•
Assessment of risk and burden	•	•	•	•	•	•	•	•	•

PART II: ODP/ODT **WITHOUT HOSPITALISATION** **SURGERY OR BLEEDING FOR WHICH 24H HOPITALISATION IS NOT NEEDED (to the investigator/surgeon judgement)**	**Discharge to be done at least 5 hours post-end of infusion(s) and only if test results required before allow so**						**OPTIONAL**	
	Prophylaxis/ Treatment Dosing Day 0		**DAY 1**	**DAY 2**	**DAY 5**	**DAY 10**	**Within 3 weeks after discharge at investigator request**	**DAY 49±4**
Assessments **Periods**	**Pre-dose**	**Post-end of infusion**	**Phone call**	**Phone call**	**Phone call**	**Phone call**	**Optional Visit**	**Safety Visit**
Type of event (i.e., spontaneous bleeding, surgery)	•							
Re-check of Inclusion / Exclusion criteria	•							
Fibrinogen inhibitory antibodies, *to be done locally*	• (only if patient received fibrinogen since last test)							•
Single or repetitive doses of BT524 for ODP and/or ODT, as required (individually tailored)	•							
Plasma concentration of **fibrinogen activity** (Clauss assay), *to be done locally and centrally*	•	1 h post-end of infusion and as required						
Maximum clot firmness (MCF) by Fib-tem S of ROTEM, *to be done centrally (locally, if possible)*	•	1 h post-end of infusion and as required						
Coagulation activation: PT(INR), aPTT, TAT, F_{1+2}, D-dimer, *to be done locally or centrally*	•	before discharge					•	•
Safety laboratory, *to be done locally* - Haematology (RBC, WBC, platelet count, haemoglobin, haematocrit) - Biochemistry (ASAT, ALAT, γ-GT, AP, total bilirubin, creatinine, urea, potassium, sodium, calcium, and chloride) - Urine analysis (pH, blood, WBC, protein, glucose, ketone bodies, nitrite, bilirubin, urobilinogen)	•	before discharge					•	
Viral safety (collection of retention sample)	•							•
Ultrasonography of lower limbs (Not mandatory in emergency care; at the investigator's discretion)	•	whenever a thrombosis or TEE is suspected					If susp of TEE	If susp of TEE
Vital signs (pulse, blood pressure, temperature)	•	0.5 h after start of infusion, 0.5 h post-end of infusion, before discharge					•	•
Physical examination	•	before discharge					•	•
Pregnancy test (urine), only in females of childbearing potential	•						•	
Adverse events	•	•	•	•	•	•	•	•
Concomitant disease / concomitant medication	•	•	•	•	•	•	•	•
Assessment of risk and burden	•	•	•	•	•	•	•	•

PART II: ODP/ODT WITH HOSPITALISATION **SURGERY OR BLEEDING FOR WHICH HOPITALISATION IS NEEDED (to the investigator/surgeon judgement)**	**Prophylaxis/ Treatment Dosing Day 0**		**24 hours after the end of last infusion**	**From DAY 2 until day before discharge** (if applicable)	**DISCHARGE DAY** (if different than H24)	**Anytime before Day 49 at investigator request**	**DAY 49±4**
Assessments **Periods**	**Pre-dose**	**Post-end of infusion**				**Optional Visit**	**Safety Visit**
Type of event (i.e., spontaneous bleeding, surgery)	•		BT524 as required				
Re-check of Inclusion / Exclusion criteria	•						
Fibrinogen inhibitory antibodies, *to be done locally*	• (only if patient received fibrinogen since last test)						•
Single or repetitive doses of BT524 for ODP and/or ODT, as required (individually tailored)	•						
Plasma concentration of **fibrinogen activity** (Clauss assay), *to be done locally and centrally*	•	1 h post-end of infusion and as required					
Maximum clot firmness (MCF) by Fib-tem S of ROTEM, *to be done centrally (locally, if possible)*	•	1 h post-end of infusion and as required					
Coagulation activation: PT(INR), aPTT, TAT, F_{1+2}, D-dimer, *to be done locally or centrally*	•	1 h post-end of infusion and as required	•	as required	•	•	•
Safety laboratory, *to be done locally* - Haematology (RBC, WBC, platelet count, haemoglobin, haematocrit) - Biochemistry (ASAT, ALAT, γ-GT, AP, total bilirubin, creatinine, urea, potassium, sodium, calcium, and chloride) - Urine analysis (pH, blood, WBC, protein, glucose, ketone bodies, nitrite, bilirubin, urobilinogen)	•	as required	as required **(But at least to be done once after last infusion of BT524 and before discharge)**			as required	
Viral safety (collection of retention sample)	•						•
Ultrasonography of lower limbs (Not mandatory in emergency care, at the investigator's discretion)	•	whenever a thrombosis	or TEE is suspected			If susp of TEE	If susp of TEE
Vital signs (pulse, blood pressure, temperature)	•	0.5 h after start of infusion, 0.5 h post-end of infusion, 4 h post-end of infusion, or as appropriate	•	as required	•	•	•
Physical examination	•		•		•	•	•
Pregnancy test (urine), only in females of childbearing potential	•					•	
Adverse events	•	•	•	•	•	•	•
Concomitant disease / concomitant medication	•	•	•	•	•	•	•
Assessment of risk and burden	•	•	•	•	•	•	•

3.3 Flowchart of Study - Children/Adolescents Group II (≥ 6 years, BW ≤ 43 kg)

PART I: PK/PD — Visit Day	**Screening** Day -17 to -1	**PK Dosing** Day 0	**PK FU** Day 1	**PK FU** Day 2	**PK FU** Day 4	**PK FU** Day 7	**PK FU** Day 10	**PK FU** Day 14	**PK Safety** Day 49±4
Assessments — Periods	**Screening**	**Hospitalization**			**Visit at the site**				
Informed consent (patient and/or legal representative)	•								
Check/re-check **of inclusion / exclusion criteria**	•	•							
Medical history	•								
Plasma concentration of: **Fibrinogen antigen**, to be done locally (ELISA) and centrally **Fibrinogen activity,** (Clauss assay) *to be done locally and centrally*	•								
Single IV infusion of BT524 (at 70 mg/kg BW)		•							
PK sampling period - Plasma concentration of: **Fibrinogen antigen** to be done centrally (Nephelometry) **Fibrinogen activity** (Clauss assay) to be done centrally		pre-dose, end of infusion, 1 and 4 h post-end of infusion	24 h		96 h	168 h	240 h		
Maximum clot firmness (MCF) by Fib-tem S of ROTEM, *to be done centrally (locally, if possible)*		pre-dose, 1 and 8 h post-end of infusion							
Fibrinogen inhibitory antibodies, *to be done locally*	•	pre-dose (centrally)							•
Coagulation activation: PT(INR), aPTT, TAT, F_{1+2}, D-dimer, *to be done locally or centrally*	•	pre-dose, 4 h and 8 h post-end of infusion	•			•		•	
Safety laboratory, *to be done locally*									
Hematology : RBC, WBC, platelet count, hemoglobin, hematocrit	•	pre-dose	•	•		•		•	
Biochemistry: ASAT, ALAT, creatinine, urea	•	pre-dose	•	•		•		•	
γ-GT, AP, total bilirubin, potassium, sodium, calcium, chloride		pre-dose		•				•	
Urine analysis: pH, blood, WBC, protein, glucose, ketone bodies, nitrite, bilirubin, urobilinogen	•	pre-dose		•				•	
IgE, to be done centrally		pre-dose	in case of any		suspected hypersensitivity/allergy/				anaphylaxis
Viral safety (collection of retention sample)		pre-dose (collection and analysis)							•
Vital signs (pulse, blood pressure, temperature)	•	pre-dose, 0.5 h after start of infusion, 0.5, 1, 2, 4, 8 h post-end of infusion	•	•	•	•	•	•	•
Physical examination	•	pre-dose, 2 h post-end of infusion	•	•	•	•	•	•	•
ECG	•	6 h post-end of infusion	•						
Ultrasonography of the lower limbs	•	whenever a thromboembolic event			TEE is suspected			•	
Pregnancy test (urine), only in females of childbearing potential	•	pre-dose						•	
Adverse events		•	•	•	•	•	•	•	•
Concomitant disease / concomitant medication	•	•	•	•	•	•	•	•	•
Assessment of risk and burden	•	•	•	•	•	•	•	•	•

PART II: ODP/ODT **WITHOUT HOSPITALISATION** **SURGERY OR BLEEDING FOR WHICH 24H HOPITALISATION IS NOT NEEDED (to the investigator/surgeon judgement)**	**Discharge to be done at least 5 hours post-end of infusion(s) and only if test results required before allow so**						**OPTIONAL**	
	Prophylaxis/ Treatment Dosing Day 0		**DAY 1**	**DAY 2**	**DAY 5**	**DAY 10**	**Within 3 weeks after discharge at investigator request**	**DAY 49±4**
Assessments **Periods**	**Pre-dose**	**Post-end of infusion**	**Phone call**	**Phone call**	**Phone call**	**Phone call**	**Optional Visit**	**Safety Visit**
Type of event (i.e., spontaneous bleeding, surgery)	•							
Re-check of Inclusion / Exclusion criteria	•							
Fibrinogen inhibitory antibodies, *to be done locally*	• (only if patient received fibrinogen since last test)							•
Single or repetitive doses of BT524 for ODP and/or ODT, as required (individually tailored)	•							
Plasma concentration of **fibrinogen activity** (Clauss assay), *to be done locally and centrally*	•	1 h post-end of infusion and as required						
Maximum clot firmness (MCF) by Fib-tem S of ROTEM, *to be done centrally (locally, if possible)*	•	1 h post-end of infusion and as required						
Coagulation activation: PT(INR), aPTT, TAT, F_{1+2}, D-dimer, *to be done locally or centrally*	•	before discharge					•	•
Safety laboratory, *to be done locally* - Haematology (RBC, WBC, platelet count, haemoglobin, haematocrit) - Biochemistry (ASAT, ALAT, γ-GT, AP, total bilirubin, creatinine, urea, potassium, sodium, calcium, and chloride) - Urine analysis (pH, blood, WBC, protein, glucose, ketone bodies, nitrite, bilirubin, urobilinogen)	•	before discharge					•	
Viral safety (collection of retention sample)	•							•
Ultrasonography of lower limbs (Not mandatory in emergency care; at the investigator's discretion)	•	whenever a thrombosis or TEE is suspected					If susp of TEE	If susp of TEE
Vital signs (pulse, blood pressure, temperature)	•	0.5 h after start of infusion, 0.5 h post-end of infusion, before discharge					•	•
Physical examination	•	before discharge					•	•
Pregnancy test (urine), only in females of childbearing potential	•						•	
Adverse events	•	•	•	•	•	•	•	•
Concomitant disease / concomitant medication	•	•	•	•	•	•	•	•
Assessment of risk and burden	•	•	•	•	•	•	•	•

PART II: ODP/ODT WITH HOSPITALISATION **SURGERY OR BLEEDING FOR WHICH HOPITALISATION IS NEEDED (to the investigator/surgeon judgement)**	**Prophylaxis/ Treatment Dosing Day 0**		**24 hours after the end of last infusion**	**From DAY 2 until day before discharge** (if applicable)	**DISCHARGE DAY** (if different than H24)	**Anytime before Day 49 at investigator request**	**DAY 49±4**
Assessments **Periods**	**Pre-dose**	**Post-end of infusion**				**Optional Visit**	**Safety Visit**
Type of event (i.e., spontaneous bleeding, surgery)	•		BT524 as required				
Re-check of Inclusion / Exclusion criteria	•						
Fibrinogen inhibitory antibodies, *to be done locally*	• (only if patient received fibrinogen since last test)						•
Single or repetitive doses of BT524 for ODP and/or ODT, as required (individually tailored)	•						
Plasma concentration of **fibrinogen activity** (Clauss assay), *to be done locally and centrally*	•	1 h post-end of infusion and as required					
Maximum clot firmness (MCF) by Fib-tem S of ROTEM, *to be done centrally (locally, if possible)*	•	1 h post-end of infusion and as required					
Coagulation activation: PT(INR), aPTT, TAT, F_{1+2}, D-dimer, *to be done locally or centrally*	•	1 h post-end of infusion and as required	•	as required	•	•	•
Safety laboratory, *to be done locally* - Haematology (RBC, WBC, platelet count, haemoglobin, haematocrit) - Biochemistry (ASAT, ALAT, γ-GT, AP, total bilirubin, creatinine, urea, potassium, sodium, calcium, and chloride) - Urine analysis (pH, blood, WBC, protein, glucose, ketone bodies, nitrite, bilirubin, urobilinogen)	•	as required	as required **(But at least to be done once after last infusion of BT524 and before discharge)**			as required	
Viral safety: Collection of retention sample	•						•
Ultrasonography of lower limbs (Not mandatory in emergency care, at the investigator's discretion)	•	whenever a thrombosis or TEE is suspected				If susp of TEE	If susp of TEE
Vital signs (pulse, blood pressure, temperature)	•	0.5 h after start of infusion, 0.5 h post-end of infusion, 4 h post-end of infusion, or as appropriate	•	as required	•	•	•
Physical examination	•		•		•	•	•
Pregnancy test (urine), only in females of childbearing potential	•					•	
Adverse events	•	•	•	•	•	•	•
Concomitant disease / concomitant medication	•	•	•	•	•	•	•
Assessment of risk and burden	•	•	•	•	•	•	•

3.4 Flowchart of Study - Pre-school Children Group III (2 to < 6 years)

PART I: PK/PD — Visit Day	**Screening** Day -17 to -1	**PK Dosing** Day 0	**PK FU** Day 1	**PK FU** Day 2	**PK FU** Day 4	**PK FU** Day 7	**PK FU** Day 10	**PK FU** Day 14	**PK Safety** Day 49±4
Assessments — Periods	**Screening**	**Hospitalization**			**Visit at the site**				
Informed consent (patient and/or legal representative)	•								
Check/re-check **of inclusion / exclusion criteria**	•	•							
Medical history	•								
Plasma concentration of: **Fibrinogen antigen,** *to be done centrally (Nephelometry)* **Fibrinogen activity,** *to be done centrally (Clauss assay)*	•								
Single IV infusion of BT524 (at 70 mg/kg BW)		•							
PK sampling period - Plasma concentration of: **Fibrinogen antigen,** *to be done centrally (Nephelometry)* **Fibrinogen activity,** *to be done centrally (Clauss assay)*		pre-dose, end of infusion, 1 and 12 h post-end of infusion		48 h					
Maximum clot firmness (MCF) by Fib-tem S of ROTEM, *to be done centrally*		pre-dose, 1 h post-end of infusion							
Fibrinogen inhibitory antibodies, *to be done locally*	•								•
Coagulation activation: PT(INR), aPTT, TAT, F_{1+2}, D-dimer, *to be done locally or centrally*		pre-dose, 1 h post-end of infusion		•					
Safety laboratory: *to be done locally*									
Hematology : RBC, WBC, platelet count, hemoglobin, hematocrit		pre-dose		•					
Biochemistry: ASAT, ALAT, creatinine, urea	•			•					
γ-GT, AP, total bilirubin, potassium, sodium, calcium, chloride	•			•					
Urine analysis: pH, blood, WBC, protein, glucose, ketone bodies, nitrite, bilirubin, urobilinogen	•			•					
IgE, to be done centrally		only	in case of any		suspected hypersensitivity/allergy/				anaphylaxis
Viral safety (collection of retention sample)		pre-dose (collection and analysis)							•
Vital signs (pulse, blood pressure, temperature)	•	pre-dose, 0.5 h after start of infusion, 0.5, 1, 2, 4, 8 h post-end of infusion	•	•	•	•	•	•	•
Physical examination	•	pre-dose, 2 h post-end of infusion	•	•	•	•	•	•	•
ECG	•	6 h post-end of infusion	•						
Ultrasonography of the lower limbs	•	whenever a thrombosis or			TEE is suspected			•	
Adverse events		•	•	•	•	•	•	•	•
Concomitant disease / concomitant medication	•	•	•	•	•	•	•	•	•
Assessment of risk and burden	•	•	•	•	•	•	•	•	•

PART II: ODP/ODT WITHOUT HOSPITALISATION **SURGERY OR BLEEDING FOR WHICH 24H HOPITALISATION IS NOT NEEDED (to the investigator/surgeon judgement)**	**Discharge to be done at least 5 hours post-end of infusion(s) and only if test results required before allow so**							
	Prophylaxis/ Treatment Dosing Day 0		**DAY 1**	**DAY 2**	**DAY 5**	**DAY 10**	**Within 3 weeks after discharge at investigator request**	**DAY 49±4**
Assessments **Periods**	**Pre-dose**	**Post-end of infusion**	**Phone call**	**Phone call**	**Phone call**	**Phone call**	**Optional Visit**	**Safety Visit**
Type of event (i.e., spontaneous bleeding, surgery)	•							
Re-check of Inclusion / Exclusion criteria	•							
Fibrinogen inhibitory antibodies, *to be done locally*	• (only if patient received fibrinogen since last test)							•
Single or repetitive doses of BT524 for ODP and/or ODT, as required (individually tailored)	•							
Plasma concentration of **fibrinogen activity** *to be done locally and centrally (Clauss assay)*	•	1 h post-end of infusion and as required						
Maximum clot firmness (MCF) by Fib-tem S of ROTEM, *to be done centrally*	•	1 h post-end of infusion and as required						
Coagulation activation: PT(INR), aPTT, TAT, F_{1+2}, D-dimer, *to be done locally or centrally*	•	before discharge					•	
Safety laboratory: *to be done locally* - Haematology (RBC, WBC, platelet count, haemoglobin, haematocrit)	•	before discharge					as required	
- Biochemistry (ASAT, ALAT, γ-GT, AP, total bilirubin, creatinine, urea, potassium, sodium, calcium, and chloride)		before discharge					as required	
- Urine analysis (pH, blood, WBC, protein, glucose, ketone bodies, nitrite, bilirubin, urobilinogen)		before discharge					as required	
Viral safety (collection of retention sample)	•							•
Ultrasonography of lower limbs (Not mandatory in emergency care, at the investigator's discretion)	•	whenever a thrombosis or TEE is suspected					If susp of thrombosis or TEE	If susp of TEE
Vital signs (pulse, blood pressure, temperature)	•	0.5 h after start of infusion, 0.5 h post-end of infusion, before discharge					•	•
Physical examination	•	before discharge					•	•
Adverse events	•	•	•	•	•	•	•	•
Concomitant disease / concomitant medication	•	•	•	•	•	•	•	•
Assessment of risk and burden	•	•	•	•	•	•	•	•

PART II: ODP/ODT WITH HOSPITALISATION **SURGERY OR BLEEDING FOR WHICH HOPITALISATION IS NEEDED (to the investigator/surgeon judgement)**	**Prophylaxis/ Treatment Dosing Day 0**		**24 hours after the end of last infusion**	**From DAY 2 until day before discharge** (if applicable)	**DISCHARGE DAY** (if different than H24)	**Anytime before Day 49 at investigator request**	**DAY 49±4**
Assessments **Periods**	**Pre-dose**	**Post-end of infusion**				**Optional Visit**	**Safety Visit**
Type of event (i.e., spontaneous bleeding, surgery)	•						
Re-check of Inclusion / Exclusion criteria	•						
Fibrinogen inhibitory antibodies, *to be done locally*	• (only if patient received fibrinogen since last test)						•
Single or repetitive doses of BT524 for ODP and/or ODT, as required (individually tailored)	•		BT524 as required				
Plasma concentration of **fibrinogen activity** *to be done locally and centrally (Clauss assay)*	•	1 h post-end of infusion and as required					
Maximum clot firmness (MCF) by Fib-tem S of ROTEM, *to be done centrally*	•	1 h post-end of infusion and as required					
Coagulation activation: PT(INR), aPTT, TAT, F_{1+2}, D-dimer, *to be done locally or centrally*	•	as required	•	as required	as required	•	
Safety laboratory: *to be done locally* - Haematology (RBC, WBC, platelet count, haemoglobin, haematocrit)	•	as required	•	as required	as required	as required	
- Biochemistry (ASAT, ALAT, γ-GT, AP, total bilirubin, creatinine, urea, potassium, sodium, calcium, and chloride)			•				
- Urine analysis (pH, blood, WBC, protein, glucose, ketone bodies, nitrite, bilirubin, urobilinogen)			•				
Viral safety (collection of retention sample)	•						•
Ultrasonography of lower limbs (Not mandatory in emergency care, at the investigator's discretion)	•	whenever a thrombosis or	TEE is suspected			If susp of thrombosis or TEE	If susp of TEE
Vital signs (pulse, blood pressure, temperature)	•	0.5 h post start of infusion, 0.5 h post-end of infusion, 4 h post-end of infusion or as appropriate	•	as required	•	•	•
Physical examination	•		•		•	•	•
Adverse events	•	•	•	•	•	•	•
Concomitant disease / concomitant medication	•	•	•	•	•	•	•
Assessment of risk and burden	•	•	•	•	•	•	•

3.5 Flowchart of Study - Newborns/Infants and Toddlers Group IV (0 days to < 2 years)

PART I: PK/PD — **Visit Day**	**Screening Day -17 to -1**	**PK Dosing Day 0**	**PK FU Day 1**	**PK FU Day 2**	**PK FU Day 4**	**PK FU Day 7**	**PK FU Day 10**	**PK FU Day 14**	**PK Safety Day 49±4**
Assessments — **Periods**	**Screening**	**Hospitalization**			**Visit at the site**				
Informed consent (patient and/or legal representative)	•								
Check/re-check **of inclusion / exclusion criteria**	•	•							
Medical history	•								
Plasma concentration of: **Fibrinogen antigen,** *to be done centrally (Nephelometry)* **Fibrinogen activity,** *to be done centrally (Clauss assay)*	•								
Single IV infusion of BT524 (at 70 mg/kg BW)		•							
PK sampling period - Plasma concentration of: **Fibrinogen antigen,** *to be done centrally (Nephelometry)* **Fibrinogen activity,** *to be done centrally (Clauss assay)*		pre-dose, end of infusion, *(4 h post-end of infusion, only for infants and toddlers at the discretion of the investigator)*	24 h (only for infants and toddlers)						
Maximum clot firmness (MCF) by Fib-tem S of ROTEM *to be done centrally*		pre-dose, end of infusion							
Fibrinogen inhibitory antibodies, *to be done locally*	•								•
Coagulation activation: PT(INR), aPTT, TAT, F_{1+2}, D-dimer *to be done locally or centrally*		pre-dose, end of infusion	24 h (only for infants and toddlers)						
Safety laboratory: *to be done locally*									
Hematology : RBC, WBC, platelet count, hemoglobin, hematocrit		pre-dose	24 h (only for infants and toddlers)						
Biochemistry: ASAT, ALAT, creatinine, urea	•								
γ-GT, AP, total bilirubin, potassium, sodium, calcium, chloride	•								
Urine analysis: pH, blood, WBC, protein, glucose, ketone bodies, nitrite, bilirubin, urobilinogen	•								
IgE, to be done centrally		only	in case of any		suspected hypersensitivity/allergy/				anaphylaxis
Viral safety (collection of retention sample)		pre-dose (collection and analysis)							•
Vital signs (pulse, blood pressure, temperature)	•	pre-dose, 0.5 h after start of infusion and 0.5, 1, 2, 4, 8 h post-end of infusion	•	•	•	•	•	•	•
Physical examination	•	pre-dose, 2 h post-end of infusion	•	•	•	•	•	•	•
ECG	•	6 h post-end of infusion	•						
Ultrasonography of the lower limbs	•	whenever a thrombosis or			TEE is suspected			•	
Adverse events		•	•	•	•	•	•	•	•
Concomitant disease / concomitant medication	•	•	•	•	•	•	•	•	•
Assessment of risk and burden	•	•	•	•	•	•	•	•	•

PART II: ODP/ODT WITHOUT HOSPITALISATION **SURGERY OR BLEEDING FOR WHICH 24H HOPITALISATION IS NOT NEEDED (to the investigator/surgeon judgement)**	**Discharge to be done at least 5 hours post-end of infusion(s) and only if test results required before allow so**							
	Prophylaxis/ Treatment Dosing Day 0		**DAY 1**	**DAY 2**	**DAY 5**	**DAY 10**	**Within 3 weeks after discharge at investigator request**	**DAY 49±4**
Assessments **Periods**	**Pre-dose**	**Post-end of infusion**	**Phone call**	**Phone call**	**Phone call**	**Phone call**	**Optional Visit**	**Safety Visit**
Type of event (i.e., spontaneous bleeding, surgery)	•							
Re-check of Inclusion / Exclusion criteria	•							
Fibrinogen inhibitory antibodies, *to be done locally*	• (only if patient received fibrinogen since last test)							•
Single or repetitive doses of BT524 for ODP and/or ODT, as required (individually tailored)	•							
Plasma concentration of **fibrinogen activity** *to be done locally and centrally (Clauss assay)*	•	1 h post-end of infusion and as required						
Maximum clot firmness (MCF) by Fib-tem S of ROTEM, *to be done centrally*	•	1 h post-end of infusion and as required						
Coagulation activation: PT(INR), aPTT, TAT, F_{1+2}, D-dimer, *to be done locally or centrally*	•	before discharge					•	
Safety laboratory: *to be done locally* - Haematology (RBC, WBC, platelet count, haemoglobin, haematocrit)	•	before discharge					as required	
- Biochemistry (ASAT, ALAT, γ-GT, AP, total bilirubin, creatinine, urea, potassium, sodium, calcium, and chloride)		before discharge					as required	
- Urine analysis (pH, blood, WBC, protein, glucose, ketone bodies, nitrite, bilirubin, urobilinogen)		before discharge					as required	
Viral safety (collection of retention sample)	•							•
Ultrasonography of lower limbs (Not mandatory in emergency care, at the investigator's discretion)	•	whenever a thrombosis or TEE is suspected					If susp of thrombosis or TEE	If susp of TEE
Vital signs (pulse, blood pressure, temperature)	•	0.5 h after start of infusion, 0.5 h post-end of infusion, before discharge					•	•
Physical examination	•	before discharge					•	•
Adverse events	•	•	•	•	•	•	•	•
Concomitant disease / concomitant medication	•	•	•	•	•	•	•	•
Assessment of risk and burden	•	•	•	•	•	•	•	•

PART II: ODP/ODT WITH HOSPITALISATION **SURGERY OR BLEEDING FOR WHICH HOPITALISATION IS NEEDED (to the investigator/surgeon judgement)**	**Prophylaxis/ Treatment Dosing Day 0**		**24 hours after the end of last infusion**	**From DAY 2 until day before discharge** (if applicable)	**DISCHARGE DAY** (if different than H24)	**Anytime before Day 49 at investigator request**	**DAY 49±4**
Assessments **Periods**	**Pre-dose**	**Post-end of infusion**				**Optional Visit**	**Safety Visit**
Type of event (i.e., spontaneous bleeding, surgery)	•						
Re-check of Inclusion / Exclusion criteria	•						
Fibrinogen inhibitory antibodies, *to be done locally*	• (only if patient received fibrinogen since last test)						•
Single or repetitive doses of BT524 for ODP and/or ODT, as required (individually tailored)	•		BT524 as required				
Plasma concentration of **fibrinogen activity** *to be done locally and centrally (Clauss assay)*	•	1 h post-end of infusion and as required					
Maximum clot firmness (MCF) by Fib-tem S of ROTEM, *to be done centrally*	•	1 h post-end of infusion and as required					
Coagulation activation: PT(INR), aPTT, TAT, F_{1+2}, D-dimer, *to be done locally or centrally*	•	as required	•	as required	as required	•	
Safety laboratory: *to be done locally* - Haematology (RBC, WBC, platelet count, haemoglobin, haematocrit)	•	as required	•	as required	as required	as required	
- Biochemistry (ASAT, ALAT, γ-GT, AP, total bilirubin, creatinine, urea, potassium, sodium, calcium, and chloride)			•				
- Urine analysis (pH, blood, WBC, protein, glucose, ketone bodies, nitrite, bilirubin, urobilinogen)			•				
Viral safety (collection of retention sample)	•						•
Ultrasonography of lower limbs (Not mandatory in emergency care, at the investigator's discretion)	•	whenever a thrombosis or	TEE is suspected			If susp of thrombosis or TEE	If susp of TEE
Vital signs (pulse, blood pressure, temperature)	•	0.5 h post start of infusion, 0.5 h post-end of infusion, 4 h post-end of infusion or as appropriate	•	as required	•	•	•
Physical examination	•		•		•	•	•
Adverse events	•	•	•	•	•	•	•
Concomitant disease / concomitant medication	•	•	•	•	•	•	•
Assessment of risk and burden	•	•	•	•	•	•	•

3.6 Flowchart of Study - For additional patients without participation in PK/PD part I

Adults, Children/Adolescents Group I and Group II, Pre-school Children Group III, Newborns/Infants and Toddlers Group IV

3.6.1 Screening Visit

PART II: SCREENING	**Adults, Children/Adolescents Group I and Group II**	**Pre-school Children Group III**	**Newborns/Infants and Toddlers Group IV**
Assessments			
Informed consent (patient and/or legal representative)	•	•	•
Check/re-check **of inclusion / exclusion criteria**	•	•	•
Medical history	•	•	•
Plasma **concentration** of: **Fibrinogen antigen,** *to be done centrally (Nephelometry)* **Fibrinogen activity,** *to be done centrally (Clauss assay)*	•	•	•
Fibrinogen inhibitory antibodies, *to be done locally*	•	•	•
Coagulation activation: PT(INR), aPTT, TAT, F_{1+2}, D-dimer, *to be done locally or centrally*	•	only at pre-dose	only at pre-dose
Safety laboratory: *to be done locally*			
Hematology : RBC, WBC, platelet count, hemoglobin, hematocrit	•	only at pre-dose	only at pre-dose
Biochemistry: ASAT, ALAT, creatinine, urea, γ-GT, AP, total bilirubin, potassium, sodium, calcium, chloride	•	•	•
Urine analysis: pH, blood, WBC, protein, glucose, ketone bodies, nitrite, bilirubin, urobilinogen	•	•	•
Vital signs (pulse, blood pressure, temperature)	•	•	•
Physical examination	•	•	•
ECG	•	•	•
Ultrasonography of the lower limbs	•	•	•
Pregnancy test (urine), only in females of childbearing potential	•		
Concomitant disease / concomitant medication	•	•	•
Assessment of risk and burden (paediatric patients)	•	•	•

3.6.2 On-Demand Prophylaxis/Treatment without Hospitalisation

Please refer to the corresponding Flowcharts:

Flowchart 3.1	Part II	for Adults (18 to 75 years)
Flowchart 3.2	Part II	for Children/Adolescents Group I (≥ 6 years, BW > 43 kg)
Flowchart 3.3	Part II	for Children/Adolescents Group II (≥ 6 years, BW ≤ 43 kg)
Flowchart 3.4	Part II	for Pre-school Children Group III (2 to < 6 years)
Flowchart 3.5	Part II	for Newborns/ Infants and Toddlers Group IV (0 days to < 2 years)

3.6.3 On-Demand Prophylaxis/Treatment with Hospitalisation

Please refer to the corresponding Flowcharts:

Flowchart 3.1	Part II	for Adults (18 to 75 years)
Flowchart 3.2	Part II	for Children/Adolescents Group I (≥ 6 years, BW > 43 kg)
Flowchart 3.3	Part II	for Children/Adolescents Group II (≥ 6 years, BW ≤ 43 kg)
Flowchart 3.4	Part II	for Pre-school Children Group III (2 to < 6 years)
Flowchart 3.5	Part II	for Newborns/ Infants and Toddlers Group IV (0 days to < 2 years)

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5 LIST OF ABBREVIATIONS

ADR	Adverse Drug Reaction
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALAT	alanine aminotransferase (syn. ALT or GPT)
AP	alkaline phosphatase
aPTT	activated partial thromboplastin time
AR	Adverse Reaction
ASAT	aspartate aminotransferase (syn. AST or GOT)
AUC	area under the concentration-time curve
BW	body weight
°C	degrees centigrade
CHMP	Committee for Medicinal Products for Human Use
CL	clearance
C_{max}	maximum concentration
COA	certificate of analysis
CRO	Contract Research Organization
CTA	Clinical Trial Application
DIC	Disseminated Intravascular Coagulation
DMC	Data Monitoring Committee
dL	Deciliter
DVT	Deep Vein Thrombosis
ECG	electrocardiogram
eCRF	electronic Case Report Form
EDC	electronic data capture
e.g.	for example
ELISA	enzyme-linked immunosorbant assay
EMA	European Medicines Agency
EMEA	European Medicines Evaluation Agency (previous name for EMA)
FAS	Full Analysis Set
FDP	Fibrin/Fibrinogen degradation product
FFP	fresh frozen plasma
F_{1+2}	prothrombin fragment 1 and 2
FU	Follow-up
g	Gram
GCP	Good Clinical Practice
γ-GT	gamma glutamyl transferase
h	hour
HAV	hepatitis A virus
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
IB	Investigator's Brochure
ICH	International Conference on Harmonization
i.e.	that is
IEC	Independent Ethics Committee
Ig	Immunoglobulin
IMP	Investigational Medicinal Product
INR	International normalized ratio
IR	Incremental Recovery

IRAE(s)	Immediately Reportable Adverse Event(s)
IRB	Institutional Review Board
ISI	international sensitivity index
ITT	intent-to-treat population
IV	Intravenous(IV)
IVR	In Vivo Recovery
kg	Kilogram
l or L	Liter
LOCF	last-observation-carried-forward
LPLV	Last Patient Last Visit
max	maximum
MCF	maximum clot firmness
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
min	minute
Ml	Milliliter
MOA	mode of administration
MRT	mean residence time
ODP	on-demand prophylaxis (with BT524)
ODT	on-demand treatment (with BT524)
PCR	polymerase chain reaction
PD	pharmacodynamic(s)
PDCO	Paediatric Committee
PICC	peripherally inserted central catheter
PK	pharmacokinetic(s)
PP	per protocol population
PT	prothrombin time
RBC	red blood cell
RICD	Rare inherited coagulation disorder
ROTEM	rotational thromboelastometry
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SAP	Statistical Analysis Plan
SAS	statistical analysis software
SD	standard deviation
SDV	Source data verification
SmPC	Summary of Product Characteristics
SUSAR	Serious Unexpected Suspected Adverse Reactions
SOC	System Organ Class
TAT	thrombin antithrombin III complex
TEAE	treatment emergent adverse event
TEE	thromboembolic event
TMF	Trial Master File
TNBP	tri-n-butyl phosphate
$t_{1/2}$	terminal elimination half-life
t_{max}	time to reach maximum concentration
V_{ss}	volume of distribution
WBC	white blood cell

6 INTRODUCTION

BT524 is a fibrinogen concentrate manufactured from human plasma.

Fibrinogen (coagulation factor I) is a soluble plasma glycoprotein synthesized by hepatic parenchymal cells. Fibrinogen plays a central role by clot forming in wound healing and, furthermore, is important in primary hemostasis as it contributes to blood platelet aggregation. In the case of low fibrinogen levels or impaired function, blood coagulation is disordered, which leads to often severe hemorrhagic events. Normal blood fibrinogen concentration is between 1.5 - 4.5 g/l although this range can vary. The critical plasma fibrinogen level below which hemorrhages may occur is considered to be approximately 0.5 - 1.0 g/l.

Congenital fibrinogen deficiency is a rare inherited coagulation disorder (RICD) characterized by an impaired hemostatic function. *Congenital fibrinogen deficiencies* are categorized on the basis of plasma concentration as follows: quantitative deficiencies (including afibrinogenemia and hypofibrinogenemia) with reduced levels of antigen and functional activity and qualitative deficiencies (including dysfibrinogenemias and hypodysfibrinogenemias) with normal or reduced antigen levels associated with abnormal functional activity. Functional activity assay measures clottable protein e.g. on the basis of coagulation time (Clauss 1957). The antigen level is measured by most labs using a radioimmunodiffusion assay. Qualitative disorders are due to genetic mutations in any of the 3 genes that encode the α, ß, and γ chains of fibrinogen, which are located on chromosome 4 and thus have autosomal inheritance.

Afibrinogenemia is associated with a bleeding tendency, which is highly variable including life-threatening and spontaneous/trauma-related bleeds. *Afibrinogenemia* is often diagnosed in the newborn period because of umbilical cord bleeding. *Afibrinogenemia* is characterized by the complete absence or reduced amounts of immunoreactive fibrinogen as measured by antigenic and functional assays (< 0.1 g/l) (Acharya and Dimichele 2008).

Patients with *Hypofibrinogenemia* have similar bleeding patterns but have a milder course. *Hypofibrinogenemia* is associated with fewer bleeding episodes and may not be diagnosed until a traumatic or surgical challenge occurs. *Hypofibrinogenemia* is defined by a decreased level of normal fibrinogen (activity and antigen below lower limit of normal range for local laboratory) (Acharya and Dimichele 2008).

Dysfibrinogenemias are commonly diagnosed in adulthood. Patients with *Dysfibrinogenemia* have an unpredictable clinical phenotype which varies from asymptomatic (around 55%) to bleeding (25%) and/or thrombosis (20%) (Cheah et al. 2012). *Dysfibrinogenemia* is characterized by a structural abnormality of the fibrinogen molecule resulting in altered functional properties. Classically, the functional assay of fibrinogen yields low levels compared with immunological assays but levels may be concordant and functional levels may be normal. Therefore, a discrepancy between clottable protein and immunologically measured fibrinogen is characteristic of dysfibrinogenemia (Acharya and Dimichele 2008).

Hypodysfibrinogenemia is a subcategory of this disorder. Even in specialized laboratories, the precise diagnosis of some fibrinogen disorders may be difficult. *Hypodysfibrinogenemia* which is defined by both quantitative and qualitative defects in fibrinogen result in levels ranging from 0.5 to 1.2 g/l (Acharya and Dimichele 2008).

Compared with dysfibrinogenemia, patients are more often symptomatic. The prevalence of bleeding and cardiovascular events is high. Bleeding is frequently spontaneous and involves all tissues, including the central nervous system. Thrombosis develops in both arterial and venous territories and can be recurrent despite an adequate anticoagulant therapy (Casini et al. 2016).

Table 1 provides an overview of the prevalence, fibrinogen levels, and symptoms of congenital fibrinogen deficiency.

The present study is exclusively concerned with *congenital afibrinogenemia and congenital severe hypofibrinogenemia*.

Table 1: Types of Congenital Fibrinogen Deficiency

	Afibrinogenemia	**Hypofibrinogenemia**	**Dysfibrinogenemia**
Transmission	Autosomal recessive	Autosomal dominant and recessive	Autosomal dominant and recessive
Prevalence	~ 1 in 1 million	< 1 in 1 million	~ 1 in 1 million
Fibrinogen level	< 0.1 g/l plasma	Between 0.1 g/l and lower limit of normal	< 1.5 and 3.5 g/l plasma, but dysfunctional
Symptoms	Umbilical cord bleeding, cutaneous bleeding, gastrointestinal hemorrhage, intracranial bleeding, articular bleeding	Umbilical cord bleeding, cutaneous bleeding, gastrointestinal hemorrhage, intracranial bleeding, articular bleeding	No symptoms, or hemorrhage, thrombosis

Source: Adapted from Acharya 2008

There are wide discrepancies in reported incidences of congenital deficiencies and the true incidence is largely unknown as some patients are asymptomatic. In countries/ populations where consanguineous marriages are frequent, the prevalence of recessive coagulation disorders is higher (Fried and Kaufman 1980, Lak et al. 1999, Khalid et al. 2008).

Effective management of congenital fibrinogen deficiency is necessary to prevent potentially life-threatening bleeding, to reduce increased loss of blood, transfusion requirements and the risk of surgery, and to improve pregnancy outcomes. Currently, conventional replacement therapy in fibrinogen deficiency given to counteract hemodynamic instability consists of transfusion of allogenic blood products such as *fresh frozen plasma* (FFP) and *cryoprecipitate*. The therapeutic target of these options is to achieve a fibrinogen activity concentration of at least 1 - 1.5 g/l (Peyvandi et al. 2006).

However, treatments with these preparations have certain limitations and moreover, expose the patients to multiple risks. As compared with fibrinogen concentrates, infusion of FFP or cryoprecipitate is limited by the lack of a virus inactivation/ removal process, leaving a potential risk of pathogen transmission (e.g., HBV, HCV, HIV). Moreover, both contain large amounts of proteins (fibronectin, von Willebrand factor, factor VIII, factor XIII, alpha macroglobulins, and anaphylatoxins), increasing the risk of allergic reactions (Silberstein et al. 1989, Sonntag et al. 1997). In addition, FFP and cryoprecipitate are insufficiently standardized in composition and must be thawed

before use, which is a limitation in time-critical and potentially life-threatening situations of severe bleeding. Moreover, cryoprecipitate and FFP, for which precise concentrations of fibrinogen are not standardized, can be associated with transfusion reactions or volume overload (Bevan 2009, Casini et al. 2015). Risks of transfusion of plasma products and limitations in handling led to the development of *fibrinogen concentrate* as a further important therapeutic option. Fibrinogen concentrates have shown to be safe, well-tolerated (Henselmans et al. 1999, Fenger-Eriksen et al. 2009) and to rapidly restore and maintain hemostasis in patients with congenital as well as acquired fibrinogen deficiencies in different indications (e.g., obstetrics, cardiovascular surgery). Different fibrinogen concentrates are commercially available in certain countries. As the concentration of fibrinogen in fibrinogen concentrates is notably higher (20 mg/ml) than in plasma, the required dose to reach the desired fibrinogen target level can be administered in a small volume. As with FFP and cryoprecipitate, potential risks associated with the administration of fibrinogen concentrate are hypersensitivity and thrombosis.

In the present study, the 14 day single-dose pharmacokinetics/ pharmacodynamics following intravenous (IV) infusion of BT524 in patients with congenital afibrinogenemia or severe congenital hypo-fibrinogenemia will be evaluated (part I). Moreover, hemostatic efficacy of BT524 on single and/or repetitive administrations of BT524 in surgical procedures and/or spontaneous or post-traumatic severe bleeds will be assessed by means of clinical endpoints (part II) and a surrogate efficacy parameter. Furthermore, safety of BT524 will be evaluated. No final clinical data with BT524 are available so far. Based on all safety information from the ongoing Study 984 currently available, it can be considered that BT524 continues to have an adequate safety and tolerability.

7 STUDY OBJECTIVES

The primary objective of this study is to investigate the 14 day single-dose pharmacokinetics of BT524 following IV infusion in patients with congenital afibrinogenemia or severe congenital hypofibrinogenemia (part I).

Secondary objectives are to investigate the 14 day single-dose PD of BT524, and the surrogate efficacy and safety of BT524 in part I of the study. In addition, the hemostatic efficacy, surrogate efficacy, and safety of single and/or repetitive administrations for on-demand prophylaxis (ODP) and/or on-demand treatment (ODT) of bleeding events (i.e., surgical procedure, spontaneous or post-traumatic severe bleeding) will be investigated in part II of the study. Surrogate efficacy of single (part I) and/or repetitive administrations of BT524 (part II) will be evaluated by the determination of the maximum clot firmness (MCF).

In spite of the extension of the ongoing phase I/II study 984 to a phase I/III pivotal study and the expansion of the patient number of part II by 10 additional patients the parameter 'clinical response' will stay as a secondary endpoint. In a Scientific Advice meeting the PPD) confirmed 'clinical response' being an appropriate efficacy endpoint and recommended to keep the efficacy evaluation as secondary endpoint having PK/PD as primary endpoint for the whole study (part I and part II).

8 ETHICAL AND REGULATORY CONSIDERATIONS

This clinical study protocol and any amendments will be submitted to a properly constituted Independent Ethics Committee (IEC) / Institutional Review Board (IRB) and/or Regulatory Authorities, in agreement with applicable regulatory requirements, for formal approval of the study conduct. A copy of these approvals must be submitted to Biotest before initiation of the clinical study and each site needs to keep a copy of these documents.

Changes to the clinical study protocol must be made in the form of an amendment that has the prior written approval of Biotest and – as applicable – of the appropriate IEC/IRB and regulatory authority.

The clinical study will be performed according to the legal requirements of the national law/s of the participating country/ies taking into account the principles of Good Clinical Practice (GCP) and the ethical principles that guided development of the Declaration of Helsinki.

A Paediatric Investigational Plan application for agreement on data needed on paediatric age groups in congenital fibrinogen deficiency, as well as on the planned study design and the investigation procedure in this age group was submitted to EMA in June 2016. The planned inclusion and treatment of children 0 to < 6 years into the ongoing study 984 was described in detail. The positive opinion of the Paediatric Committee on the agreement of the Paediatric Investigation Plan (EMA-001931-PIP01-16) was obtained in March 2017 and the extension of the ongoing study 984 was introduced within protocol amendment No 4.

9 STUDY DESIGN

The present study is designed as a prospective, 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*.

As shown in Table 2 the study is divided into two study parts (part I and part II), briefly described in the following:

Table 2: 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**
20 patients (≥ 6 years) **3 patients (< 6 years)** **In total:** **n = 23 patients (part I)**	all patients who have completed part I : 20 patients (≥ 6 years) and 3 patients (< 6 years) ⇨ additional patients without PK/PD : at least 10 patients (≥ 6 years) and at least 3 patients < 6 years **In total: 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 the 14 day single-dose PD, and the evaluation of the maximum clot firmness (MCF) as a surrogate efficacy parameter. Moreover, initial safety will be investigated.

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 **section 11.1.5**).

Safety will be assessed by physical examination (including ECG), vital signs, routine lab parameters, adverse events, development of fibrinogen antibodies and coagulation activation monitoring.

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 post-traumatic 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 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 enrolled in part II (ODP/ODT) without PK/PD assessment (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).

All study subjects will be offered to extend their study participation (in part II) until the last enrolled subject (of the additional subjects directly enrolled in part II) has finished study part II (12 months).

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 post-operatively, re-bleedings), requirement of other fibrinogen-containing products (fresh frozen plasma, cryoprecipitate) and 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.**

10 INVESTIGATIONAL MEDICINAL PRODUCT

10.1 Investigational Medicinal Product BT524

10.1.1 Description of Investigational Medicinal Product BT524

The Investigational Medical Product (IMP) BT524 is a lyophilized, heat-treated fibrinogen concentrate manufactured from human plasma. CCI CCI . The manufacturing process also includes CCI CCI

BT524 is presented as a single-use glass vial of 100 ml with a nominal content of 1 g of lyophilisate (powder for solution for injection/ infusion). The lyophilisate is to be reconstituted under aseptic conditions with 50 ml of water for injections using an appropriate transfer device or syringe.

The vial is to be swirled gently until the product is fully dissolved. After reconstitution, the solution should be almost colorless and clear to slightly opalescent. Reconstituted products should be inspected visually for particulates and discoloration prior to administration. Do not use solutions that are cloudy or contain deposits.

Substance code: BT524
Active ingredient: Fibrinogen concentrate from human plasma
Dosage form Powder for solution for injection/infusion
Content: 1 g
Concentration: 20 mg/ml after reconstitution with 50 ml water for injections
Container: 100 ml glass vial with rubber stopper
Manufacturer: PPD

Batch number and expiry date are given in the applicable certificate of analysis (COA).

10.1.2 Packaging and Labeling

A single container (100 ml glass bottle with rubber stopper) of BT524 contains 1 g fibrinogen, lyophilisate. The labeling of BT524 will be performed according to local requirements. A sample label will be contained in the Trial Master File (TMF).

10.1.3 Storage Conditions

BT524 is to be stored in a cabinet or other enclosure which is security locked.
Generally access should be restricted to the investigator and authorized personnel.
CCI
The temperature has to be documented on a temperature log.

11 STUDY TREATMENT

11.1 Dosage Regimen

BT524 is available as lyophilized powder to be reconstituted in water for injections.

The content of each vial of BT524 is to be reconstituted with 50 ml water for injections resulting in a nominal final concentration of 20 mg/ml. After reconstitution, the solution is recommended to be used immediately. Any unused solution must be discarded because of risk of bacterial contamination.

The total dose, the infusion rate, and the batch and vial numbers of each infusion of BT524 must be recorded in the eCRF (electronic Case Report Form) and the drug accountability log. The dose per kilogram BW will be calculated.

11.1.1 Dosage and Administration

The study is divided into two study parts with a fixed dose of BT524 to be administered for the pharmacokinetic assessment (part I) and variable, *individually tailored* dose regimens in the extended ODP/ ODT part of the study (part II).

Part I

Dosage for the Assessment of the Pharmacokinetics/ Pharmacodynamics of BT524

Each patient fulfilling the inclusion/ exclusion criteria is to receive a fixed dose of 70 mg BT524 per kilogram BW via a single intravenous infusion for the assessment of the pharmacokinetics/ pharmacodynamics of BT524 (see Table 3).

Adults (18 to 75 years), Children/Adolescents Group I and Group II (≥ 6 years):

BT524 is to be administered intravenously (IV) via an infusion pump with an infusion rate of 5 ml/min (part I) corresponding to a maximum infusion rate of 100 mg/min. BT524 is to be administered preferably in the forearm vein. Other administration routes are only allowed after approval from the sponsor.

Pre-school Children Group III (2 to < 6 years), Newborns/Infants and Toddlers Group IV (0 days to < 2 years):

BT524 is to be administered intravenously (IV) via an infusion pump with an adapted infusion rate below 5 ml/min (100 mg/minute) according to age, BW, and medical condition at the discretion of the treating physician of the patient (for further details please refer to Appendix 20.1).

Table 3: Pharmacokinetics: Dose, Target Level, Mode of Administration and Infusion Rate of BT524

	Dose of BT524	Target Level	No. of Doses	MOA	Infusion Rate
Pharmacokinetics					
	70 mg/kg BW	—	single	IV	5 ml/min* < 5 ml/min** (< 100 mg/ml)

BW: body weight; IV: intravenous; min: minute; MOA: mode of administration
* for Adults and Children/Adolescents Group I and Group II (≥ 6 years).
** for Pre-school Children Group III and Newborns/Infants and Toddlers Group IV (< 6 years)

For the assessment of the pharmacokinetics/ pharmacodynamics the total dose will be individually calculated on each patient's BW taking into account the actual activity of BT524 of the batch used as specified in the **COA** as Fibrinogen activity (Precipitation). The corresponding volume to the calculated total dose of BT524 is to be administered according to the following example.

For example: A patient with a BW of 60 kg is to receive a total dose of 4,200 mg BT524 (m). The actual Fibrinogen activity (Precipitation) for the batch used is ~19 g/l according to COA. The volume to be administered is 221.05 ml. Duration of infusion is 44.21 minutes.

$$\mathbf{V_{inf.}} = \frac{\text{m (mg)}}{\text{c (mg/ml)}} = \frac{\text{4,200 mg}}{\text{19 mg/ml}} = \underline{\mathbf{221.05\ ml}}$$

Detailed information regarding the prevention of potential risks associated with the administration of BT524 is given in **section 11.7**.

Part II

On-demand Prophylaxis and On-demand Treatment

In part II, patients will receive BT524 for *on-demand prophylaxis* (ODP) and/or *on-demand treatment* (ODT) in case of bleeding events (i.e., surgical procedure, spontaneous or post-traumatic severe bleeding). With respect to ODP and/or ODT, the dosage, frequency of administration and duration of the substitution therapy with BT524 is *individually tailored,* to be adapted on the severity of the hemostatic disorder, the location and extent of the surgical procedure/ spontaneous bleed and the patient's clinical condition.

Adults (18 to 75 years), Children/Adolescents Group I and Group II (≥ 6 years):

BT524 is to be administered intravenously (IV) with a maximum infusion rate of 100 mg/min.

Pre-school Children Group III (2 to < 6 years), Newborns/Infants and Toddlers Group IV (0 days to < 2 years):

BT524 is to be administered intravenously (IV) via an infusion pump with an adapted infusion rate below 5 ml/min (100 mg/minute) according to age, BW, and medical condition at the discretion of the treating physician of the patient (for further details please refer to Appendix 20.1).

BT524 is to be administered preferably in the forearm vein. Alternatively, BT524 can be administered through a central venous line or a peripherally inserted central catheter (PICC) in case of elective surgeries. Other administration routes are only allowed after approval from the sponsor.

Guidance for On-demand Prophylaxis (ODP) and On-demand Treatment (ODT)

Unless valid information on the recovery rate for BT524 is available, the dosage regimen for surgical interventions and spontaneous bleedings will target (functional) fibrinogen levels recommended by the Core SmPC for Human Fibrinogen Products. Hence, the dosage, the amount and frequency of BT524 administration should be calculated on an individual patient basis by regular measurement of plasma fibrinogen activity levels and continuous monitoring of the clinical condition of the patient and - if applicable – on other replacement therapies used. Guidance for on-demand prophylaxis and/or on-demand treatment with BT524 in case of surgical interventions or spontaneous bleeding is given in Table 4.

Table 4: Guidance for On-demand Prophylaxis and/ or On-demand Treatment

Target levels recommended by the Core SmPC for Human Fibrinogen Products

	Dose of BT524	**Target Level**	**No. of Doses**	**MOA**	**Infusion Rate**
Surgical intervention					
On-demand prophylaxis (ODP)	variable*	1 g/l**	as required	IV	max 100 mg/min
On-demand treatment (ODT)	variable*	1 g/l** maintained until hemostasis is secure	as required	IV	max 100 mg/min
		> 0.5 g/l** until wound healing is complete			
Spontaneous bleeding					
On-demand treatment (ODT)	variable*	—	as required	IV	max 100 mg/min

IV: intravenous; max: maximum; min: minute; MOA: mode of administration

Values given are guidance only, and higher or lower levels and increased frequency of administration may be necessary.

* adapted on the severity, location and extent of bleeding, and the patient's clinical condition

** depending on the severity of the event fibrinogen levels may be raised in individual cases to a maximum of 1.5 g/l at the discretion of the investigator.

Calculation of Doses for On-demand Prophylaxis (ODP) and On-demand Treatment (ODT) by recovery rate of BT524

Once valid information on the recovery rate of BT524 is available, the doses of BT524 to be administered for surgical procedure or treatment of a bleeding episode should be calculated according to the following formula given by the Core SmPC for Human Fibrinogen Products:

Dose (g) =[desired levels (g/l) – baseline level (g/l)] x 1/recovery (g/l / g/kg) x BW (kg).

11.1.2 Compliance with Dosage Regimens

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, the assessment of plasma concentrations of BT524 may also serve as an adherence measure.

11.1.3 Dose Justification

Therapeutic target levels of fibrinogen of at least 1 - 1.5 g/l are recommended for the prevention and treatment of congenital fibrinogen deficiency (Peyvandi et al. 2006, Manco-Johnson et al. 2009); however, others recommend target levels > 1 g/l for spontaneous bleeding and > 0.5 g/l until the bleeding surface is completely healed (Core SmPC for Human Fibrinogen Products, 2009/2015); (EMA 2009, Tziomalos et al. 2009, EMA (Committee for Medicinal Products for Human Use) 2015).

The dose to be administered for the assessment of the pharmacokinetics of BT524 is 70 mg per kg BW. The doses as well as the mode of administration and the infusion rates planned for BT524 in the present study are based on the results of preclinical studies with BT524 in comparison to Haemocomplettan. This applies in particular to the safety pharmacology (influence on core battery, Harbauer rabbit model, see Investigator's Brochure, **section 5.3**) and toxicology (thrombogenicity, Wessler model, see Investigator's Brochure, **section 5.4.1**) as well as primary (clottable protein, Clauss assay) and secondary pharmacodynamics (fib-tem, maximum clot firmness) (see Investigator's Brochure, **section 5.1**).
All preclinical testing resulted in comparability between BT524 and Haemocomplettan. Therefore, published PK data (Manco-Johnson et al. 2009) and product information from a commercially available human fibrinogen concentrate (RiaSTAP Full Prescribing Information, March 2010 (CSL Behring 2010), which is identical to Haemocomplettan (Manco-Johnson et al. 2009, CSL Behring 2015) have been taken into consideration.

For the first patients to be treated in part II, product-specific information on recovery might not be available. For these patients guidance on on-demand prophylaxis and/or on-demand treatment with BT524 in case of surgical intervention or spontaneous bleeding is provided. This guidance complies with the dosage recommendations of the Core SmPC for Human Fibrinogen Products. Once valid information on the recovery rate of BT524 is available the recommended formula of the Core SmPC is to be used to calculate the dosage for the target level desired.

11.1.4 Treatment of Overdosage

In order to avoid overdosage in patients with congenital afibrinogenemia or severe congenital hypofibrinogenemia, regular monitoring of the plasma level of fibrinogen during therapy is indicated.

In case of overdosage, the risk of development of thromboembolic complications is enhanced (Core SmPC for Human Fibrinogen Products, 2009/2015). Please refer to Section 11.7.

11.1.5 Enrolment Procedures

With respect to safety, the following study-specific enrolment procedures are implemented in study part I:

The first five of the approximately 20 patients planned are to be recruited consecutively taken into account a dosing-free safety interval of 7 days between each patient.

The dosing-free safety interval of two expected biological half-lives of BT524 (according to the Core SmPC of Human Fibrinogen: $t_{1/2}$ = 3-4 days) is considered to be sufficient for the detection of immediate (i.e., hypersensitivity) and later adverse effects (i.e., thrombosis).

Subsequently, patients 6 to 20 are allowed to be treated simultaneously, if applicable.

The first 10 of the approximately 20 patients planned are to be adults (aged 18 to 75 years). Patients 11 to 20 are allowed to be 6 to 75 years of age. A Data Monitoring Committee (DMC) has been established to assess the available adult safety- and PK-data prior to the enrolment of any children (≥ 6 years) and adolescents into the study. Each patient is to be hospitalized until PK follow-up day 2 to ensure a close monitoring of the safety parameters and potential adverse effects.

Planned enrolment of children and adolescents:

Patients 6 to 10 may then be treated simultaneously; again there will be a 7-day dosing-free safety interval after the 10th adult patient. After completion of patient 10, a DMC will review the available safety data prior to the enrolment of any children and adolescents into the study. Patients 11 to 20 are also allowed to be treated simultaneously, if applicable.

Subsequently, after the first 20 patients of ≥ 6 to ≤ 75 years finished part I, at least 3 additional paediatric patients < 6 years of age are planned to be enrolled in the study part I. Prior to enrolment of any children < 6 years of age a DMC will review and assess all available safety and PK/PD data from adults and children ≥ 6 years including data of at least 3 children ≥ 6 to < 12 years and of at least 3 adolescents ≥ 12 to < 18 years.

With respect to safety, the following study-specific enrolment procedures are implemented in study part II:

All patients included in part I will be eligible for participation in part II.

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

Subsequently, after the first 20 patients of ≥ 6 to ≤ 75 years finished part I, at least 3 additional paediatric patients < 6 years of age are planned to be enrolled in the study part II without PK/PD assessment in study part I. Prior to enrolment of any children < 6 years of age a DMC will review and assess all available safety and PK/PD data from adults and children ≥ 6 years including data of at least 3 children ≥ 6 to < 12 years and of at least 3 adolescents ≥ 12 to < 18 years. In total, approximately 36 patients are planned to be treated in this study: approximately 23 patients in part I and II, at least 10 additional patients ≥ 6 years and at least 3 paediatric patients < 6 years in part II without PK/PD assessment of part I.

11.2 Randomization Code

Not applicable. As this is an open-label study design patients will not be randomized.

11.3 Assignment of Patient Identification

Screening identification

For the coherent assignment of the study documents all patients having signed the informed consent and having entered the screening period will receive a screening number prior to the first dosing of BT524. The screening number is composed of an 'S' followed by a four digit number (e.g., S0101 or S1204) of which the first two digits define the investigational site and the last two digits the patient screened at the corresponding site. Screening numbers are assigned consecutively per site. Screening numbers are assigned once only and will not be replaced i.e., in case of a screening failure.

Patient identification

In addition to the screening number, a patient number will be assigned if the patient fulfils the eligibility criteria (inclusion/ exclusion criteria) and is to receive BT524.

The patient number comprises a four digit number of which the first two digits define the investigational site and the last two digits the patient enrolled at the corresponding site. Patient numbers are assigned consecutively per site. Patient numbers are assigned unique and will not be replaced e.g., in case of a patient prematurely withdrawn.

11.4 Drug Accountability

The IMP will be supplied to the investigator or a local pharmacy at the time of site initiation under the assumption that all required regulatory documents are in place. The investigator or his/her designee should maintain records that document adequately that the study participants were provided the doses specified in the protocol and reconcile all IMPs received for the study. The investigator has to ensure that consignments of IMPs are received correctly by a competent person and that the IMP is safely and appropriately handled and stored.

Before the IMP is returned or destroyed, the investigator or designee is obliged to keep sufficient documentation of the delivery, use, and destruction or return of unused, used or partially used packages of IMP. The documentation must include dates, quantities, patient numbers, batch numbers or other identification numbers, and expiry dates.

The investigator must allow the monitor to perform drug reconciliation. The entries in the eCRF as well as the documentation kept in the Investigator Site File will be compared with the returned and residual IMPs, with clarification of any discrepancies or inconsistencies.

11.5 Previous and Concomitant Medication or Treatment

All previous medication and treatment in the previous 3 months prior to the administration of BT524 are to be recorded in the 'Previous and Concomitant medications' section of the eCRF.

Concomitant medication therapeutically required and *not interacting relevantly with the coagulation system* is allowed, as long as it is kept stable during the study. If a change in concomitant medication is necessary during the study, it is the responsibility of the investigator to ensure that details regarding the medication are recorded in full in the eCRF (i.e., identity of all medications, dosage and route of administration, frequency, duration of administration, and indication for use) at each visit.

11.6 Prohibited Medication or Treatment

Blood donation or comparable blood loss within 60 days prior to infusion of BT524 for the pharmacokinetic assessment is not allowed.

Any concomitant medication *interacting relevantly with the coagulation system* such as

- fibrinogen concentrates other than BT524 (for prophylaxis or on-demand treatment)
- fresh frozen plasma
- cryoprecipitate
- low molecular weight heparin or unfractioned heparin
- factor Xa inhibitors (e.g., rivaroxaban, apixaban)
- factor IIa inhibitors (e.g., dabigatran)
- PY12 inhibitors (e.g., clopidogrel, prasugrel, ticagrelor) etc.
- and other blood or plasma derivatives

is prohibited 2 weeks prior to infusion of BT524 and within the study unless required by an emergency situation (major surgeries or major bleeding events that requires respective medication).

In case prohibited medication had to be administered for emergency situations details of the event, reason for intake, product administered, and the dosage must be recorded accurately in the eCRF at the corresponding visit. Moreover, in case fresh frozen plasma, cryoprecipitate or other blood or plasma derivatives had to be administered the virus safety measures on the product must be recorded.

11.7 Risks and Precautions

Transmissible agents

Despite standard measures (i.e., selection of donors, screening of individual donations and plasma pools for specific markers of infection, and effective manufacturing steps for inactivation/ removal of viruses) to prevent infections resulting from the use of medicinal products prepared from human blood or plasma, the possibility of transmitting infective agents cannot be totally excluded. This also applies to unknown or emerging viruses and other pathogens.

The manufacturing measures taken are considered effective for enveloped viruses such as HIV, HBV and HCV, for the non-enveloped viruses HAV and parvovirus B19, and prions.

Hypersensitivity reactions

All plasma or plasma-derived human products may lead to allergic or anaphylactic reactions. These might also be induced by BT524, by the active substance or any of the excipients of the medicinal product. With an authorized fibrinogen concentrate

allergic like/ anaphylactic like reactions such as generalized urticaria, erythema, drop in blood pressure, dyspnoea, and/or body temperature increase were observed in rare cases. If allergic or anaphylactic-type reactions occur, the infusion must be stopped immediately. In case of anaphylactic shock, standard medical treatment for shock must be applied (Core SmPC for Human Fibrinogen Products, 2009/2015).

Thus, due to the risk of potential allergic or anaphylactic reactions, the initial administration of BT524 should, according to the treating physician's judgment, be performed under medical supervision where proper medical care for allergic or anaphylactic reactions can be provided.

Thromboembolic episodes

There is a risk of thrombosis when patients with congenital fibrinogen deficiency are treated with human fibrinogen particularly with high dose or repeated dosing (Core SmPC for Human Fibrinogen Products, 2009/2015]; (de Moerloose et al. 2010, EMA (Committee for Medicinal Products for Human Use) 2015). Thus, patients given human fibrinogen should be observed closely for signs or symptoms of thrombosis.

Prothrombin fragments F_{1+2}, TAT, and D-dimer are monitored regularly to detect a hypercoagulable status.

An (transient) increase in body temperature may occur (Core SmPC for Human Fibrinogen Products, 2009/2015).

Overdosage

Regular monitoring of the plasma level of fibrinogen during treatment is indicated to avoid overdosage. In case of overdosage, the risk of development of thromboembolic complications is enhanced.

12 STUDY POPULATION

12.1 Study Population, Diagnosis and Number of Study Participants

In view of the limited number of patients, a total of approximately 36 patients with congenital afibrinogenemia or severe congenital hypofibrinogenemia are planned to be treated within this study: approximately 20 patients ≥ 6 to ≤ 75 years and at least 3 additional patients 0 to < 6 years in part I and II, at least 10 additional patients ≥ 6 years and at least 3 patients < 6 years in part II without PK/PD assessment of part I. Eligibility is defined by the inclusion and exclusion criteria as described below.

12.1.1 Gender Distribution

There are no gender-based enrolment restrictions applicable for the study i.e., male and female patients are intended to be included.

Since men and women might suffer from congenital afibrinogenemia or severe congenital hypofibrinogenemia, patients of both genders should be included into the study. Equitable inclusion of both genders in research is important to ensure that both receive a proportionate share of benefits of research and that neither bears a disproportionate burden.

Women of childbearing potential are allowed to participate when using reliable/ effective contraceptive method(s) during the study and at least one month after the last

administration of study drug. However, pregnant women are to be excluded (see general exclusion criterion 18).

12.1.2 Children and adolescents

Children and adolescents (≥ 6 years) will be enrolled only after completion of dosing and the associated 7-day dosing-free safety interval of the first 10 adult patients enrolled into the study and after the DMC has reviewed the data from these 10 adult patients. The measures taken to minimize risk for children and adolescents enrolled in the study are described in section 13.5.4.

Subsequently, after the first 20 patients of ≥ 6 to ≤ 75 years finished part I, three additional paediatric patients < 6 years of age are planned to be enrolled in the study part I and subsequently in the part II.

Prior to enrolment of any children < 6 years into the study a DMC will review and assess all available safety and PK/PD data from adults and children ≥ 6 years enrolled in the study so far (including data of least 3 children ≥ 6 to < 12 years and 3 adolescents ≥ 12 to < 18 years).

At least 3 additional patients < 6 years will be enrolled in part II (ODT/ODP) without PK/PD assessments (part I).

12.2 Inclusion Criteria

Only patients meeting all of the following inclusion criteria will be considered for study inclusion:

Inclusion Criteria	Rationale	Screening
1. Known congenital afibrinogenemia or severe congenital hypofibrinogenemia	medical	X
2. Plasma fibrinogen activity ≤ 0.5 g/l and antigen ≤ 0.5 g/l	medical	X
3. Male or female	administrative	X
4. Age 0 to 75 years, with the first ten patients will be 18 years or older	administrative	X
5. Presumed to be compliant with the study procedures and to terminate the study as scheduled	Administrative / medical	X
6. Willing and able to be hospitalized for 3 days for the pharmacokinetic assessment (if applicable)	administrative / medical	X
7. Willing and able to be hospitalized - if required - in case of interventions (e.g., surgical procedures, major bleeds)	administrative / medical	X
8. Written informed consent by the patient, his/her parents or by the patient's legal / authorized representative as applicable	administrative	X

12.3 Exclusion Criteria

Patients having any of the following general exclusion criteria, either at screening (pre-visit) or at enrolment (visit 1) are to be excluded from the study:

Exclusion Criteria	Rationale	Screening
1. Known congenital dysfibrinogenemia	medical	X
2. Known bleeding disorder other than congenital fibrinogen deficiency	medical	X
3. History of esophageal variceal bleeding	medical	X
4. Known presence or history of venous/arterial thrombosis or thromboembolic event (TEE) in the preceding 6 months	Medical	X
5. Known presence or history of fibrinogen inhibitory antibodies	medical	X
6. Known presence or history of hypersensitivity to human fibrinogen or human plasma proteins e.g., immunoglobulins, vaccines or hypersensitivity to any of the excipients.	medical	X
7. Known positive serology for HIV-1 and HIV-2	medical	X
8. Clinically relevant biochemical or hematological findings (except due to underlying disease or emergency bleeding) outside the normal range (at the investigator's discretion)	medical	X
9. Clinically relevant pathological findings in physical examination including ECG	medical	X
10. Treatment with any fibrinogen concentrate and/or fibrinogen-containing product within 2 weeks prior to infusion of BT524	medical	X
11. Concomitant medication interacting relevantly with the coagulation system (e.g., low molecular weight heparin, unfractioned heparin, factor Xa inhibitors, factor IIa inhibitors or PY12 inhibitors) within 2 weeks prior to infusion of BT524	medical	X
12. Recent vaccination within 3 weeks prior to infusion (only applicable for patients in PK part I)	medical	X
13. BW below 22 kg for patients ≥ 6 years (only applicable for patients in PK part I); BW below the 5th percentile of the normal range for children (refers to local standards*)	medical	X
14. End stage disease	medical	X
15. Abuse of drugs	medical	X
16. Unable to understand and follow the study requirements (refers to the patient, his/her parents or to the patient's legal / authorized representative as applicable)	administrative	X
17. Participation in another interventional clinical study within 30 days before entering the study or during the study	administrative	X

Exclusion Criteria	Rationale	Screening
18. Pregnant/ nursing woman, or woman of childbearing potential not using reliable/ effective contraceptive method(s) during the study and at least one month after the last administration of study drug (e.g., oral/ injectable/ implantable/ insertable/ topical hormonal contraceptives, intrauterine devices, female sterilization, partner's vasectomy or condoms)	medical	X
19. Any other condition that, in the investigator's judgment, could have an impact on patient's safety or study results	administrative /medical	X

(*Please refer to Appendix 20.1)

Pharmacokinetics (PK)

In addition to the **general exclusion** criteria mentioned above, patients meeting any of the following **PK-specific exclusion criteria** at enrolment are to be excluded from the pharmacokinetic assessment. Patient enrolment is to be postponed until no PK exclusion criterion applies.

PK-Specific Exclusion Criteria	Rationale	Screening
20. Elective surgery during the 14 day PK blood sampling period	medical	X
21. Acute infection	medical	X
22. Clinically relevant increase or decrease in body temperature	medical	X
23. Actively bleeding or anticipated bleeding (including female menorrhea) at the time point of or within 7 days prior to infusion of BT524	medical	X
24. Surgery within 7 days prior to infusion of BT524	medical	X
25. Immobilization within 7 days prior to infusion of BT524	medical	X
26. Intake of alcohol or significantly increased intake of caffeine containing products within 24 hours prior to infusion of BT524	Medical	X
27. Blood donation or comparable blood loss within 60 days prior to infusion of BT524	medical	X
28. Excessive physical exercise (extreme sports activities, sauna) within 72 hours prior to infusion of BT524	medical	X

12.4 Study Participants Withdrawal Criteria and Procedures

The participation of an individual study participant may be terminated prematurely for reasons such as:

a) Withdrawal of written informed consent

b) Withdrawal due to study participant's own request (e.g. personal reasons)

c) Adverse reactions during or upon administration of the investigational medicinal product
d) Occurrence of pregnancy
e) Lack of study compliance
f) Any other condition which in the opinion of the investigator no longer permits a safe participation in the study

A study participant and/or his parents or legally acceptable representative is/are entitled to discontinue participation in the clinical study at their own request at any time without stating a reason.

The investigator can terminate a patient's participation in the study at any time if continuation could lead to disadvantages for the study participant which cannot be justified by the investigator.

The reason for withdrawal of the study participant must be documented by the investigator together with all data collected until the day of premature study termination including laboratory results and assessment of adverse events. All examinations foreseen for the patient's last study visit (e.g., safety visit) should be performed.

In case a patient withdraws due to an adverse event or serious adverse event please follow the instructions given in **section 14.6 o**f this protocol.

12.5 Postponement of Enrolment for PK Assessment (Part I) and During ODP/ODT (PART II)

The administration of BT524 for any event (PK assessment, ODP, ODT) of an individual study participant must be postponed for reasons such as:

a) Required treatment with any medication known or suspected to interfere with the investigational medicinal product within the PK assessment period of 14 days
b) Treatment with any fibrinogen concentrate and/or fibrinogen-containing product within two weeks prior to infusion of BT524
c) Treatment with medication interacting relevantly with the coagulation system (e.g., low molecular weight heparin, unfractioned heparin, factor Xa inhibitors, factor IIa inhibitors or PY12 inhibitors) within two weeks of the respective product prior to infusion of BT524

12.6 Study Participants' Information

The study participant and/or - if applicable - legally acceptable representative will be informed about the study according to the requirements of GCP and the legal requirements of the country in which the patient is recruited.

The study, its objectives, possible benefits and risks, and its consequences will be verbally explained to the study participant and/or his/her legally acceptable representative. Moreover, the study participant and/or legally acceptable representative is/are provided with written information about the study. Sufficient time will be allowed for the information to be read and for questions to be asked. Attention should be paid to any signs of undue distress in paediatric subjects who are unable to clearly indicate their distress (ICH Harmonised Tripartite Guideline; E11 Step 4, 2000). The study participant and/or legally acceptable representative must be told that refusal to participate in the study does not cause any disadvantages to their treatment;

similarly, withdrawal of written informed consent is possible at any time, without stating a reason and without prejudice to further medical management.

Study participants and/or legally acceptable representative should be informed and should agree that medical data may be reviewed by authorized persons during monitoring and during an audit or an inspection by the appointed regulatory authority or ethics committee, but that personal data will be treated with absolute confidentiality.

Upon request, the study participant and/or legally acceptable representative must be granted access to the insurance terms and conditions.

Any new and relevant information that evolves during the course of the study concerning the investigational medicinal product, alternative treatments, or the benefit/risk ratio will be communicated to the study participant and/or legally acceptable representative.

The study participant's and/or legally acceptable representative's written informed consent will be filed at the investigator's site.

12.7 Declaration of Informed Consent

The study participant and/or - if applicable - legally acceptable representative must give written consent to participate in the study by signing and personally dating the informed consent form. Informed consent to the proposed data handling and to data inspection must also be documented in written form. Written informed consent must be obtained from each study participant or legally acceptable representative before any study-related procedures are performed. A duplicate of the signed and dated written informed consent form must be handed over to the study participant and/or – if applicable - legally acceptable representative.

13 COURSE OF THE STUDY

13.1 Visit Schedule

The study flowcharts (see **section 3** Flowcharts of Study**)** provide tabular overviews on the visit dates and the assessments to be performed at each visit in the respective patient subgroup. Patients are assigned to the subgroups according to their age and BW: Adults (18 to 75 years), Children/Adolescents Group I (6 years or older) with BW above 43 kg, Children/Adolescents Group II (6 years or older) with BW ≤ 43 kg, Pre-school Children Group III (2 to < 6 years), and Newborns/Infants and Toddlers Group IV (0 days to < 2 years). Detailed description on the measures and methods to be used for the assessments are given in **section 14**.

13.1.1 Visit Types and Detailed Visit Schedules for the Assessment of the Pharmacokinetics/Pharmacodynamics of BT524 (**PART I**)

13.1.1.1 Visit Types

The following visit types are planned for study part I.

- ***Screening visit:***

  The patient known to suffer from congenital afibrinogenemia or severe congenital hypofibrinogenemia and having signed informed consent to participate in the study

will have a *screening visit* (day -17 to day -1) to confirm eligibility for the study. The assessments as depicted in the flowchart for *screening visit* have to be performed.

- ***PK Dosing day 0:***

  The patient considered to be eligible will enter study part I. After inclusion and exclusion criteria have been re-checked, and blood samples for predose measurements collected, the patient will receive a fixed single intravenous infusion of BT524 (at 70 mg per kg BW) for the assessment of the PK/PD of BT524. The subgroup specific assessments as depicted in the flowchart for *PK dosing day 0* have to be performed (see section 3.1 Flowchart of Study - Adults, section 3.2 Flowchart of Study - Children/Adolescents Group I, section 3.3 Flowchart of Study - Children/Adolescents Group II, section 3.4 Flowchart of Study - Pre-school Children Group III and section 3.5 Flowchart of Study - Newborns/Infants and Toddlers Group IV).

- ***PK Follow-up day 1 and Follow-up day 2:***

  Patient will be hospitalized until day 2 and will be closely monitored. The subgroup specific assessments as depicted in the respective flowchart for *PK follow-up day 1 and PK follow-up day 2* have to be performed.

- ***PK Follow-up days 4, 7, 10, and 14:***

  Patient will have regular site visits on the *PK follow-up days 4, 7, 10, and 14*. The subgroup specific assessments as depicted in the respective flowchart for *PK follow-up days 4, 7, 10, and 14* have to be performed.

- ***PK Safety visit:***

  In part I a *safety visit* is to be conducted on day 49±4 after the administration of BT524. The subgroup specific assessments as depicted in the respective flowchart for PK Safety visit have to be performed.

  Exception: In case a patient experiences a bleeding event and is to receive at least one administration of BT524 within this time interval of 49±4 days, the *safety visit* of the PK/PD assessment on that Day 49 can be omitted. In this case, the respective dosing day 0 and the *safety visit* on day 49±4 after the (last) administration of BT524 for the bleeding event will serve as the safety visit related to part I. The safety visit is also to be performed for each patient prematurely withdrawn from study participation due to any reason.

13.1.1.2 Detailed Visit Schedules

The following procedures are planned for study part I.

Screening Visit (day -17 to day -1):

After having obtained Informed consent (patient and/or legal representative) the following assessments are to be performed for all subjects unless otherwise specified:

- Inclusion / exclusion criteria
- Medical history
- Plasma concentration of Fibrinogen antigen is to be done by enzyme-linked immunosorbant assay (ELISA) *locally*
  - only in Adults and Children/Adolescents Group I and II (≥ 6 years)
- Plasma concentration of Fibrinogen antigen is to be done *by nephelometry centrally*

- Plasma activity of Fibrinogen (Clauss assay) is to be done *locally*
  - only in Adults and Children/Adolescents Group I and II (≥ 6 years)
- Plasma activity of Fibrinogen (Clauss assay) is to be done *centrally*
- Fibrinogen inhibitory antibodies: to be done *locally* (by available method e.g., correction test of thrombin time)
- Coagulation activation: PT(INR), aPTT, TAT, F_{1+2}, D-dimer, to be done *locally or centrally* (depending on local availability of validated test systems)
  - only in Adults and Children/Adolescents Group I and II (≥ 6 years)
- Safety laboratory to be done *locally*
  - in Adults and Children/Adolescents Group I and II (≥ 6 years)
  - ⇨ Hematology (RBC, WBC, platelet count, hemoglobin, hematocrit)
  - ⇨ Biochemistry (ASAT, ALAT, creatinine, and urea)
- Safety laboratory to be done *locally*
  - in Pre-school Children Group III and in Newborns/Infants and Toddlers Group IV
  - ⇨ Biochemistry (ASAT, ALAT, creatinine, urea, γ-GT, AP, total bilirubin, potassium, sodium, calcium, chloride)
- Urine analysis (pH, blood, WBC, protein, glucose, ketone bodies, nitrite, bilirubin, urobilinogen)
- Vital signs (pulse, blood pressure, body temperature)
- Physical examination
- Electrocardiogram (ECG)
- Ultrasonography of lower limbs (according to study specific ultrasonography manual)
- Pregnancy test (urine) - only in females of childbearing potential
- Concomitant disease / concomitant medication
- Assessment of risk and burden (paediatric patients)

PK Dosing Day 0:

The patient will be hospitalized

- Check/re-check of inclusion / exclusion criteria
- Single IV infusion of BT524 (at 70 mg/kg BW)
- PK assessment:
  - ⇨ Plasma concentration of fibrinogen antigen (nephelometry), to be done centrally
  - ⇨ Plasma concentration of fibrinogen activity (Clauss assay), to be done centrally

  Time points for both fibrinogen antigen and fibrinogen activity as following:
  - Adults (18 - 75 years) and Children/Adolescents Group I (≥ 6 years, BW > 43 kg): pre-dose, immediately at the end of infusion, and 0.5, 1, 2, 4, and 8 hours post-end of infusion

  - Children/Adolescents Group II (≥ 6 years, BW ≤ 43 kg): pre-dose, immediately at the end of infusion, and 1 and 4 hours post-end of infusion
  - Pre-school Children Group III (2 to < 6 years): pre-dose, immediately at the end of infusion, and 1 and 12 hours post-end of infusion
  - Newborns/Infants and Toddlers Group IV (0 days to < 2 years): pre-dose, immediately at the end of infusion, and 4 h* post-end of infusion (*only in infants and toddlers, at the discretion of the investigator considering the exact clinical situation of the patient)
- Maximum clot firmness (MCF) by Fib-tem S of ROTEM:
  - Adults (18 - 75 years) and Children/Adolescents Group I and Group II (≥ 6 years): pre-dose, 1 and 8 hours post-end of infusion, to be done *centrally and locally* (if possible)
  - Pre-school Children Group III (2 to < 6 years): pre-dose, and 1 hour post-end of infusion, to be done *centrally*
  - Newborns/Infants and Toddlers Group IV (0 days to < 2 years): pre-dose, and immediately at the of infusion, to be done *centrally*
- Fibrinogen inhibitory antibodies: pre-dose, to be done centrally
  - only in Adults and Children/Adolescents Group I and II (≥ 6 years)
- Coagulation activation: PT(INR), aPTT, TAT, F_{1+2}, D-dimer, to be done *locally or centrally* (depending on local availability of validated test systems):
  - Adults (18 - 75 years): pre-dose and 1, 4, and 8 hours post-end of infusion
  - Children/Adolescents Group I and Group II (≥ 6 years): pre-dose, 4 and 8 hours post-end of infusion
  - Pre-school Children Group III (2 to < 6 years): pre-dose, and 1 hour post-end of infusion
  - Newborns/Infants and Toddlers Group IV (0 days to < 2 years): pre-dose and immediately at the of infusion
- Safety laboratory: pre-dose, to be done *locally*
  - ⇨ Hematology (RBC, WBC, platelet count, hemoglobin, hematocrit)
- Safety laboratory: pre-dose, to be done *locally*
  - only in Adults and Children/Adolescents Group I and II (≥ 6 years)
  - ⇨ Biochemistry (ASAT, ALAT, γ-GT, AP, total bilirubin, creatinine, urea, potassium, sodium, calcium, and chloride)
  - ⇨ Urine analysis (pH, blood, WBC, protein, glucose, ketone bodies, nitrite, bilirubin, urobilinogen)
- Immunoglobulin E (IgE):
  - Adults and Children/Adolescents Group I and Group II (≥ 6 years): pre-dose, to be done *centrally*
  - Pre-school Children Group III (2 to < 6 years) and Newborns/Infants and Toddlers Group IV (0 days to < 2 years): only in case of any suspected hypersensitivity/ allergy/ anaphylaxis, to be done centrally
- Viral safety: analysis pre-dose, collection of retention sample

- Vital signs (pulse, blood pressure, body temperature): pre-dose, 0.5 hours after start of infusion, and 0.5, 1, 2, 4, and 8 hours post-end of infusion
- Physical examination: pre-dose and 2 hours post-end of infusion
- ECG 6 hours post-end of infusion
- Ultrasonography of lower limbs (according to study specific ultrasonography manual): whenever a thrombosis or TEE is suspected
- Pregnancy test (urine): pre-dose - only in females of childbearing potential
- Adverse events
- Concomitant disease / concomitant medication
- Assessment of risk and burden (paediatric patients)

PK Follow-up Day 1:

The patient will be hospitalized.

- PK assessment:
  - ⇨ Plasma concentration of fibrinogen antigen (nephelometry), to be done centrally
  - ⇨ Plasma concentration of fibrinogen activity (Clauss assay), to be done centrally
    - Adults (18 - 75 years) and Children/Adolescents Group I and Group II (≥ 6 years): 24 hours post-end of infusion
    - Pre-school Children Group III (2 to < 6 years): no assessment
    - Infants and Toddlers Group IV (28 days to < 2 years): 24 hours post-end of infusion
    - Newborns Group IV (0 days to 27 days): no assessment
- Coagulation activation: PT(INR), aPTT, TAT, F_{1+2}, D-dimer, to be done *locally or centrally* (depending on local availability of validated test systems)
    - Adults (18 - 75 years) and Children/Adolescents Group I and Group II (≥ 6 years): follow-up Day 1
    - Pre-school Children Group III (2 to < 6 years): no assessment
    - Infants and Toddlers Group IV (28 days to < 2 years): follow-up Day 1 (24 hours post-end of infusion)
    - Newborns Group IV (0 days to 27 days): no assessment
- Safety laboratory: to be done locally
  - ⇨ Hematology (RBC, WBC, platelet count, hemoglobin, hematocrit) and
  - ⇨ Biochemistry (ASAT, ALAT, creatinine, and urea)
    - Adults (18 - 75 years) and Children/Adolescents Group I and Group II (≥ 6 years): follow-up Day 1
    - Pre-school Children Group III (2 to < 6 years): no assessment
    - Infants and Toddlers Group IV (28 days to < 2 years): follow-up Day 1 (24 hours post-end of infusion)
    - Newborns Group IV (0 days to 27 days): no assessment
- IgE: only in case of any suspected hypersensitivity/ allergy/ anaphylaxis, to be done centrally

- Vital signs (pulse, blood pressure, body temperature)
- Physical examination
- ECG
- Ultrasonography of lower limbs (according to study specific ultrasonography manual): whenever a thrombosis or TEE is suspected
- Adverse events
- Concomitant disease / concomitant medication
- Assessment of risk and burden (paediatric patients)

PK Follow-up Day 2:

Last day of hospitalization.

- PK assessment:
  - ⇨ Plasma concentration of fibrinogen antigen (nephelometry), to be done *centrally*
  - ⇨ Plasma concentration of fibrinogen activity (Clauss assay), to be done *centrally*
    - Adults (18 - 75 years) and Children/Adolescents Group I (≥ 6 years): 48 hours post-end of infusion
    - Children/Adolescents Group II (≥ 6 years): no assessment
    - Pre-school Children Group III (2 to < 6 years): 48 hours post-end of infusion
    - Newborns/Infants and Toddlers Group IV (0 days to < 2 years): no assessment
- Coagulation activation: PT(INR), aPTT, TAT, F_{1+2}, D-dimer, to be done *locally or centrally* (depending on local availability of validated test systems):
  - Adults (18 - 75 years): follow-up Day 2
  - Children/Adolescents Group I and Group II (≥ 6 years): no assessment
  - Pre-school Children Group III (2 to < 6 years): follow-up Day 2
  - Newborns/Infants and Toddlers Group IV (0 days to < 2 years): no assessment
- Safety laboratory: to be done *locally:*
  - ⇨ Hematology (RBC, WBC, platelet count, hemoglobin, hematocrit)
  - ⇨ Biochemistry (ASAT, ALAT, γ-GT, AP, total bilirubin, creatinine, urea, potassium, sodium, calcium, and chloride)
  - ⇨ Urine analysis (pH, blood, WBC, protein, glucose, ketone bodies, nitrite, bilirubin, urobilinogen)
    - Adults (18 - 75 years) and Children/Adolescents Group I and Group II (≥ 6 years): follow-up Day 2
    - Pre-school Children Group III (2 to < 6 years): follow-up Day 2
    - Newborns/Infants and Toddlers Group IV (0 days to < 2 years): no assessment
- IgE: only in case of any suspected hypersensitivity/ allergy/ anaphylaxis, to be done *centrally*

- Vital signs (pulse, blood pressure, body temperature)
- Physical examination
- Ultrasonography of lower limbs (according to study specific ultrasonography manual): whenever a thrombosis or TEE is suspected
- Adverse events
- Concomitant disease / concomitant medication
- Assessment of risk and burden (paediatric patients)

END OF REGULAR HOSPITALIZATION

PK Follow-up Day 4:

Visit at the site.

- PK assessment: 96 hours post-end of infusion
  - only in Adults and Children/Adolescents Group I and II (≥ 6 years)
  - ⇨ Plasma concentration of fibrinogen antigen (nephelometry), to be done centrally
  - ⇨ Plasma concentration of fibrinogen activity (Clauss assay), to be done centrally
- Coagulation activation: PT(INR), aPTT, TAT, F_{1+2}, D-dimer, to be done *locally or centrally* (depending on local availability of validated test systems)
  - only in Adults
- Safety laboratory: to be done *locally*
  - only in Adults
  - ⇨ Hematology (RBC, WBC, platelet count, hemoglobin, hematocrit)
  - ⇨ Biochemistry (ASAT, ALAT, creatinine, and urea)
- IgE: only in case of any suspected hypersensitivity/ allergy/ anaphylaxis, to be done centrally
- Vital signs (pulse, blood pressure, body temperature)
- Physical examination
- Ultrasonography of lower limbs (according to study specific ultrasonography manual): whenever a thrombosis or TEE is suspected
- Adverse events
- Concomitant disease / concomitant medication
- Assessment of risk and burden (paediatric patients)

PK Follow-up Day 7:

Visit at the site.

- PK assessment: 168 hours post-end of infusion
  - only in Adults and Children/Adolescents Group I and II (≥ 6 years)
  - ⇨ Plasma concentration of fibrinogen antigen (nephelometry), to be done centrally
  - ⇨ Plasma concentration of fibrinogen activity (Clauss assay), to be done centrally

- Coagulation activation: PT(INR), aPTT, TAT, F_{1+2}, D-dimer, to be done *locally or centrally* (depending on local availability of validated test systems)
    - only in Adults and Children/Adolescents Group I and II (≥ 6 years)
- Safety laboratory: to be done locally
    - only in Adults and Children/Adolescents Group I and Group II (≥ 6 years)
    - ⇨ Hematology (RBC, WBC, platelet count, hemoglobin, hematocrit)
    - ⇨ Biochemistry (ASAT, ALAT, creatinine, and urea)
- IgE: only in case of any suspected hypersensitivity/ allergy/ anaphylaxis, to be done *centrally*
- Vital signs (pulse, blood pressure, body temperature)
- Physical examination
- Ultrasonography of lower limbs (according to study specific ultrasonography manual): whenever a thrombosis or TEE is suspected
- Adverse events
- Concomitant disease / concomitant medication
- Assessment of risk and burden (paediatric patients)

PK Follow-up Day 10:

Visit at the site.

- PK assessment: 240 hours post-end of infusion
    - only in Adults and Children/Adolescents Group I and II (≥ 6 years)
    - ⇨ Plasma concentration of fibrinogen antigen (nephelometry), to be done centrally
    - ⇨ Plasma concentration of fibrinogen activity (Clauss assay), to be done centrally
- Coagulation activation: PT(INR), aPTT, TAT, F_{1+2}, D-dimer, to be done *locally or centrally* (depending on local availability of validated test systems)
    - only in Adults
- Safety laboratory: to be done *locally*
    - only in Adults
    - ⇨ Hematology (RBC, WBC, platelet count, hemoglobin, hematocrit)
    - ⇨ Biochemistry (ASAT, ALAT, creatinine, and urea)
- IgE: only in case of any suspected hypersensitivity/ allergy/ anaphylaxis, to be done centrally
- Vital signs (pulse, blood pressure, body temperature)
- Physical examination
- Ultrasonography of lower limbs (according to study specific ultrasonography manual): whenever a thrombosis or TEE is suspected
- Adverse events
- Concomitant disease / concomitant medication
- Assessment of risk and burden (paediatric patients)

PK Follow-up Day 14:

Visit at the site.

- PK assessment: 336 hours post-end of infusion
  - only in Adults and Children/Adolescents Group I (≥ 6 years, BW > 43 kg)
  - ⇨ Plasma concentration of fibrinogen antigen (nephelometry) to be done centrally
  - ⇨ Plasma concentration of fibrinogen activity (Clauss assay), to be done centrally
- Coagulation activation: PT(INR), aPTT, TAT, F_{1+2}, D-dimer, to be done *locally or centrally* (depending on local availability of validated test systems)
  - only in Adults and Children/Adolescents Group I and Group II (≥ 6 years)
- Safety laboratory: to be done locally
  - only in Adults and Children/Adolescents Group I and Group II (≥ 6 years)
  - ⇨ Hematology (RBC, WBC, platelet count, hemoglobin, hematocrit)
  - ⇨ Biochemistry (ASAT, ALAT, γ-GT, AP, total bilirubin, creatinine, urea, potassium, sodium, calcium, and chloride)
  - ⇨ Urine analysis (pH, blood, WBC, protein, glucose, ketone bodies, nitrite, bilirubin, urobilinogen)
- IgE: only in case of any suspected hypersensitivity/ allergy/ anaphylaxis, to be done centrally
- Vital signs (pulse, blood pressure, body temperature)
- Physical examination
- Ultrasonography of lower limbs (according to study specific ultrasonography manual)
- Pregnancy test (urine) - only in females of childbearing potential
- Adverse events
- Concomitant disease / concomitant medication
- Assessment of risk and burden (paediatric patients)

END OF PK/PD ASSESSMENT/SAMPLING PERIOD

Safety Visit (Day 49±4):

Visit at the site; also to be performed for each patient prematurely withdrawn from study participation due to any reason.

- Fibrinogen inhibitory antibodies: to be done locally (by available method e.g., correction test of thrombin time)
- Coagulation activation: PT(INR), aPTT, TAT, F_{1+2}, D-dimer, to be done locally or centrally (depending on local availability of validated test systems) ⇨ only in Adults
- Viral safety: collection of retention sample
- IgE: only in case of any suspected hypersensitivity/ allergy/anaphylaxis, to be done centrally
- Vital signs (pulse, blood pressure, body temperature)
- Physical examination

- Adverse events
- Concomitant disease / concomitant medication
- Assessment of risk and burden (paediatric patients)

13.1.2 Bleeding Events, Visit Types and Detailed Visit Schedules for On-demand Prophylaxis/On-demand Treatment with BT524 (**PART II**)

PART II

At discretion of the investigator, patients with no major safety complications in part I will continue in study part II. At least 10 additional patients ≥ 6 to ≤ 75 years and at least 3 additional patients < 6 years without PK/PD assessment of part I will be treated in part II.

In **part II**, a variety of singular events of different types, severity, and BT524-dosing regimens for **ON-DEMAND PROPHYLAXIS/ ON-DEMAND TREATMENT** is expected.

The following types of events and procedures in various combinations are possible:

- Minor non-surgical bleeding event
- Major non-surgical bleeding event
- Spontaneous bleeding event
- Elective bleeding event: an event that is planned e.g., surgery
- Hospitalization: patient needs to stay overnight at hospital
- No Hospitalization: patient will be treated with BT524 at site and will leave without overnight stay

13.1.2.1 Visit Types for Bleeding Events (Without Hospitalization)

In study part II, the following visit types are planned for bleeding events for which a hospitalization of the patient is not required.

- ***Screening visit (only for additional patients not treated within PK/PD part I):***

  The patient known to suffer from congenital afibrinogenemia or severe congenital hypofibrinogenemia and having signed informed consent to participate in the study will have a *screening visit* to confirm eligibility for the study. The assessments as depicted in the flowchart for *screening visit (see 3.6.1)* have to be performed.

- ***Dosing Day 0 – Pre-dose:***

  The patient experiencing any bleeding and considered to be eligible for on-demand prophylaxis/on-demand treatment with BT524 for this bleeding event will enter study part II. After having re-checked the inclusion and exclusion criteria, the assessments regarding safety as depicted in the flowchart for *dosing day 0 - pre-dose* have to be performed.

- ***Dosing Day 0 – Post-End of Infusion:***

  The patient will receive a single dose or repetitive doses of BT524 which is/are individually tailored depending on the type and severity of this particular event. The assessments regarding efficacy and safety as depicted in the flowchart for *dosing day 0 - post-end of infusion* have to be performed.

- ***Follow-up Days 1, 2, 5, and 10:***

  Since the patient will not be hospitalized, follow-up telephone contacts to the patient by the investigator regarding potential adverse events and concomitant disease/ concomitant medication are to be performed for each case on the *follow-up days 1, 2, 5, and 10*.

- ***Optional Visit:***

  An *optional visit* might be conducted at any time within 3 weeks after discharge at the discretion of the investigator. The assessments regarding safety as depicted in the flowchart for the *optional visit* have to be performed.

- ***Safety Visit:***

  A *safety visit* is to be conducted on day 49±4 after the (last) administration of BT524 for this bleeding event.

  <u>*Exception:*</u> In case a patient experiences a further bleeding and is to receive at least one administration of BT524 within this time interval of 49±4 days, the *safety visit* related to the preceding bleeding event can be omitted. In this case, the respective dosing day 0 and the *safety visit* on day 49±4 after the (last) administration of BT524 related to the current bleeding event will also serve as the safety visit related to the preceding event.
  The safety visit is also to be performed for each patient prematurely withdrawn for any reason.

13.1.2.2 Detailed Visit Schedules or Bleeding Events (<u>Without</u> Hospitalization)

The following visit types with respective procedures are planned in study part II for each bleeding event for which hospitalization of the patient is <u>not</u> required.

- ***Screening Visit (only for additional patients not treated within PK/PD part I):***

After having obtained Informed consent (patient and/or legal representative) the following assessments are to be performed:

- Inclusion / exclusion criteria
- Medical history
- Plasma concentration of Fibrinogen antigen is to be done *by nephelometry centrally*
- Plasma activity of Fibrinogen (Clauss assay) is to be done *centrally*
- Fibrinogen inhibitory antibodies: to be done *locally* (by available method e.g., correction test of thrombin time)
- Coagulation activation: PT(INR), aPTT, TAT, F_{1+2}, D-dimer, to be done *locally or centrally* (depending on local availability of validated test systems)
  - <u>only in Adults and Children/Adolescents Group I and Group II (≥ 6 years)</u>
- Safety laboratory: to be done *locally*
  - <u>only in Adults and Children/Adolescents Group I and Group II (≥ 6 years)</u>

  ⇨ Hematology (RBC, WBC, platelet count, hemoglobin, hematocrit)
- Safety laboratory: to be done *locally*

  ⇨ Biochemistry (ASAT, ALAT, creatinine, urea, γ-GT, AP, total bilirubin, potassium, sodium, calcium, chloride)

  - ⇨ Urine analysis (pH, blood, WBC, protein, glucose, ketone bodies, nitrite, bilirubin, urobilinogen)
- Vital signs (pulse, blood pressure, body temperature)
- Physical examination
- Electrocardiogram (ECG)
- Ultrasonography of lower limbs (according to study specific ultrasonography manual)
- Pregnancy test (urine) - only in females of childbearing potential
- Concomitant disease / concomitant medication
- Assessment of risk and burden (paediatric patients)

Dosing Day 0 – Pre-dose:

The patient will **not** be hospitalized.

- Re-check of inclusion / exclusion criteria
- Documentation of the type of the event (e.g., spontaneous bleeding, surgery)
- Fibrinogen inhibitory antibodies: only if the patient received fibrinogen since last test.
  If applicable, to be done *locally* (by available method e.g., correction test of thrombin time).
- **Single or repetitive IV infusion(s) of BT524 for ODP/ ODT** (according to **Table 4** or according to the formula given by the Core SmPC for Human Fibrinogen Products once valid information on the recovery rate of BT524 is available)
- Plasma concentration of fibrinogen activity (Clauss assay): to be done *locally and centrally*
- Maximum clot firmness (MCF) by Fib-tem S of ROTEM): to be done *centrally, and locally* (if possible)
- Coagulation activation: PT(INR), aPTT, TAT, F_{1+2}, D-dimer, to be done *locally or centrally* (depending on local availability of validated test systems)
- Safety Laboratory: to be done *locally*
  - ⇨ Hematology (RBC, WBC, platelet count, hemoglobin, hematocrit)
- Safety Laboratory: to be done *locally*
    - o only in Adults and Children/Adolescents Group I and Group II (≥ 6 years):
  - ⇨ Biochemistry (ASAT, ALAT, γ-GT, AP, total bilirubin, creatinine, urea, potassium, sodium, calcium, and chloride)
  - ⇨ Urine analysis (pH, blood, WBC, protein, glucose, ketone bodies, nitrite, bilirubin, urobilinogen)
- Viral safety: collection of retention sample
- Ultrasonography of lower limbs (according to study specific ultrasonography manual)
- Vital signs (pulse, blood pressure, body temperature)
- Physical examination
- Pregnancy test (urine) - only in females of childbearing potential

- Adverse events
- Concomitant disease / concomitant medication
- Assessment of risk and burden (paediatric patients)

Dosing Day 0 – Post-End of Infusion:

The patient will not be hospitalized.

- Plasma concentration of fibrinogen activity (Clauss assay): 1 hour post-end of infusion and as required, to be done *locally and centrally*
- Maximum clot firmness (MCF) by Fib-tem S of ROTEM: 1 hour post-end of infusion and as required, to be done *centrally, and locally* (if possible)
- Coagulation activation: PT(INR), aPTT, TAT, F_{1+2}, D-dimer: before discharge, to be done *locally or centrally* (depending on local availability of validated test systems)
- Safety laboratory: before discharge, to be done *locally*
  - ⇨ Hematology (RBC, WBC, platelet count, hemoglobin, hematocrit)
  - ⇨ Biochemistry (ASAT, ALAT, γ-GT, AP, total bilirubin, creatinine, urea, potassium, sodium, calcium, and chloride)
  - ⇨ Urine analysis (pH, blood, WBC, protein, glucose, ketone bodies, nitrite, bilirubin, urobilinogen)
- Ultrasonography of lower limbs (according to study specific ultrasonography manual) and of any other suspected site: whenever a thrombosis or TEE is suspected
- Vital signs (pulse, blood pressure, body temperature): 0.5 hours after start of infusion, 0.5 hours post-end of infusion, and before discharge
- Physical examination: before discharge
- Adverse events
- Concomitant disease / concomitant medication
- Assessment of risk and burden (paediatric patients)

Follow-up Days 1, 2, 5, and 10:

Phone contacts by the investigator to the patient regarding

- Adverse events
- Concomitant disease / concomitant medication
- Assessment of risk and burden (paediatric patients)

Optional Visit:

At the discretion of the investigator the patient may have an optional visit at any time within three weeks after discharge.

- Coagulation activation: PT(INR), aPTT, TAT, F_{1+2}, D-dimer, to be done *locally or centrally* (depending on local availability of validated test systems)
- Safety laboratory: to be done *locally*
  - o <u>in Children Group III and IV only if required</u>
  - ⇨ Hematology (RBC, WBC, platelet count, hemoglobin, hematocrit)

- ⇨ Biochemistry (ASAT, ALAT, γ-GT, AP, total bilirubin, creatinine, urea, potassium, sodium, calcium, and chloride)
- ⇨ Urine analysis (pH, blood, WBC, protein, glucose, ketone bodies, nitrite, bilirubin, urobilinogen)

- Ultrasonography examination of lower limbs (according to study specific ultrasonography manual) and of any other suspected site: whenever a thrombosis or TEE is suspected
- Vital signs (pulse, blood pressure, body temperature)
- Physical examination
- Pregnancy test (urine) - only in females of childbearing potential
- Adverse events
- Concomitant disease / concomitant medication
- Assessment of risk and burden (paediatric patients)

Safety Visit (Day 49±4):

Visit at the site; also to be performed for each patient prematurely withdrawn from study participation due to any reason.

- Fibrinogen inhibitory antibodies: to be done *locally* (by available method e.g., correction test of thrombin time)
- Coagulation activation: PT(INR), aPTT, TAT, F_{1+2}, D-dimer, to be done *locally or centrally* (depending on local availability of validated test systems)
  - only in Adults and Children/Adolescents Group I and Group II (≥ 6 years)
- Virus safety: collection of retention sample
- Ultrasonography of lower limbs (according to study specific ultrasonography manual) and of any other suspected site: whenever a thrombosis or TEE is suspected
- Vital signs (pulse, blood pressure, body temperature)
- Physical examination
- Pregnancy test (urine) - only in females of childbearing potential
- Adverse events
- Concomitant disease / concomitant medication
- Assessment of risk and burden (paediatric patients)

13.1.2.3 Visit Types for Surgery or Bleeding Events (With Hospitalization)

In study part II, the following visit types are planned for bleeding events for which a hospitalization of the patient is required.

- ***Screening visit (for additional patients not treated within PK/PD part I):***

  The patient known to suffer from congenital afibrinogenemia or severe congenital hypofibrinogenemia and having signed informed consent to participate in the study will have a *screening visit* to confirm eligibility for the study. The assessments as depicted in the flowchart for *screening visit* have to be performed.

- ***Dosing Day 0 – Pre-dose:***

  The patient experiencing any bleeding and considered to be eligible for on-demand prophylaxis/on-demand treatment with BT524 for this bleeding event requiring hospitalization will enter study part II. After having re-checked inclusion and exclusion criteria the patient will receive a single dose or repetitive doses of BT524 which is/are individually tailored depending on the type and severity of this particular event. The assessments regarding safety as depicted in the flowchart for *dosing day 0 - pre-dose* have to be performed.

- ***Dosing Day 0 – Post-End of Infusion:***

  The assessments regarding efficacy and safety of BT524 as depicted in the flowchart for *dosing day 0 - post-end of infusion* have to be performed.

- ***Follow-up Day 1 (24 h Post-End of Infusion):***

  The patient will be closely monitored regarding efficacy and safety of BT524. The assessments regarding efficacy and safety as depicted in the flowchart for *24 hours after the end of last infusion* have to be performed.

- ***Follow-up Day 2 until Day Before Hospital Discharge:***

  The patient will be monitored regarding safety of BT524 on the *follow-up day 2 until the day before hospital discharge*. The assessments regarding safety as depicted in the flowchart for *from day 2 until the day before discharge (if applicable)* have to be performed.

- ***Day of Hospital Discharge (if Different than 24 h Post-End of Infusion):***

  On the *day of hospital discharge* the patient will have final assessments regarding safety of BT524. The assessments regarding safety as depicted in the flowchart for the *discharge day* have to be performed.

- ***Optional Visit:***

  After hospital discharge, an *optional visit* might be conducted at any time before day 49 at discretion of the investigator. The assessments regarding safety as depicted in the flowchart for the *optional visit* have to be performed.

- ***Safety Visit:***

  A *safety visit* is to be conducted on day 49±4 after the (last) administration of BT524 for this bleeding event.

  Exception: In case a patient experiences a further bleeding and is to receive at least one administration of BT524 within this time interval of 49±4 days, the *safety visit* related to the preceding bleeding event can be omitted. In this case, the respective dosing day 0 and the *safety visit* on day 49±4 after the (last) administration of BT524 related to the current bleeding event will also serve as the safety visit related to the preceding event.
  The safety visit is also to be performed for each patient prematurely withdrawn from study participation for any reason.

13.1.2.4 Detailed Visit Schedules for Bleeding Events (With Hospitalization)

The following visit types with respective procedures are planned in study part II for each bleeding event for which hospitalization of the patient is required.

- ***Screening Visit (only for additional patients not treated within PK/PD part I):***

After having obtained Informed consent (patient and/or legal representative) the following assessments are to be performed:

- Inclusion / exclusion criteria
- Medical history
- Plasma concentration of Fibrinogen antigen is to be done by nephelometry *centrally*
- Plasma activity of Fibrinogen (Clauss assay) is to be done *locally and centrally*
- Fibrinogen inhibitory antibodies: to be done *locally* (by available method e.g., correction test of thrombin time)
- Coagulation activation: PT(INR), aPTT, TAT, F_{1+2}, D-dimer, to be done *locally or centrally* (depending on local availability of validated test systems)
    - only in Adults and Children/Adolescents Group I and Group II (≥ 6 years)
- Safety laboratory: to be done *locally*
    - only in Adults and Children/Adolescents Group I and Group II (≥ 6 years)
    - ⇨ Hematology (RBC, WBC, platelet count, hemoglobin, hematocrit)
- Safety laboratory: to be done *locally*
    - ⇨ Biochemistry (ASAT, ALAT, creatinine, urea, γ-GT, AP, total bilirubin, potassium, sodium, calcium, chloride)
    - ⇨ Urine analysis (pH, blood, WBC, protein, glucose, ketone bodies, nitrite, bilirubin, urobilinogen)
- Vital signs (pulse, blood pressure, body temperature)
- Physical examination
- Electrocardiogram (ECG)
- Ultrasonography of lower limbs (according to study specific ultrasonography manual)
- Pregnancy test (urine) - only in females of childbearing potential
- Concomitant disease / concomitant medication
- Assessment of risk and burden (paediatric patients)

Dosing Day 0 – Pre-dose

The patient will be hospitalized.

- Re-check of inclusion / exclusion criteria
- Documentation of the type of the event (e.g., spontaneous bleeding, surgery)
- **Single or repetitive IV infusion(s) of BT524 for ODP/ ODT** (according to **Table 4** or according to the formula given by the Core SmPC for Human Fibrinogen Products once valid information on the recovery rate of BT524 is available)
- Plasma concentration of fibrinogen activity (Clauss assay), to be done *locally and centrally*
- Maximum clot firmness (MCF) by Fib-tem S of ROTEM: to be done *centrally, and locally (if possible)*

- Fibrinogen inhibitory antibodies: only if the patient received fibrinogen since last test.
  If applicable, to be done *locally* (by available method e.g., correction test of thrombin time)
- Coagulation activation: PT(INR), aPTT, TAT, F_{1+2}, D-dimer, to be done *locally or centrally* (depending on local availability of validated test systems)
- Safety laboratory: to be done *locally*
  - ⇨ Hematology (RBC, WBC, platelet count, hemoglobin, hematocrit)
- Safety Laboratory: to be done *locally*
  - only in Adults and Children/Adolescents Group I and Group II (≥ 6 years)
  - ⇨ Biochemistry (ASAT, ALAT, γ-GT, AP, total bilirubin, creatinine, urea, potassium, sodium, calcium, and chloride)
  - ⇨ Urine analysis (pH, blood, WBC, protein, glucose, ketone bodies, nitrite, bilirubin, urobilinogen)
- Viral safety: collection of retention sample
- Vital signs (pulse, blood pressure, body temperature)
- Ultrasonography of lower limbs (according to study specific ultrasonography manual)
- Physical examination
- Pregnancy test (urine) - only in females of childbearing potential
- Adverse events
- Concomitant disease / concomitant medication
- Assessment of risk and burden (paediatric patients)

Dosing Day 0 – Post-End of Infusion

The patient will be hospitalized.

- Plasma concentration of fibrinogen activity (Clauss assay): 1 hour post-end of infusion and as required, to be done *locally and centrally*
- Maximum clot firmness (MCF) by Fib-tem S of ROTEM: 1 hour post-end of infusion and as required, to be done *centrally, and locally (if possible)*
- Coagulation activation: PT(INR), aPTT, TAT, F_{1+2}, D-dimer: to be done *locally or centrally* (depending on local availability of validated test systems)
  - Adults (18 - 75 years) and Children/Adolescents Group I and Group II (≥ 6 years): 1 hour post-end of infusion and as required
  - Pre-school Children Group III (2 to < 6 years): as required
  - Newborns/Infants and Toddlers Group IV (0 days to < 2 years): as required
- Safety laboratory: to be done *locally,* as required,
  - ⇨ Hematology (RBC, WBC, platelet count, hemoglobin, hematocrit)
  - ⇨ Biochemistry (ASAT, ALAT, γ-GT, AP, total bilirubin, creatinine, urea, potassium, sodium, calcium, and chloride)
  - ⇨ Urine analysis (pH, blood, WBC, protein, glucose, ketone bodies, nitrite, bilirubin, urobilinogen)

- Ultrasonography of lower limbs (according to study specific ultrasonography manual) and of any other suspected site: whenever a thrombosis or TEE is suspected
- Vital signs (pulse, blood pressure, body temperature): 0.5 hours after start of infusion, 0.5 hours post-end of infusion, and 4 hours post-end of infusion or as appropriate
- Adverse events
- Concomitant disease / concomitant medication
- Assessment of risk and burden (paediatric patients)

Follow-up Day 1 (24 h Post-End of Infusion)

The patient will be hospitalized.

- Coagulation activation: PT(INR), aPTT, TAT, F_{1+2}, D-dimer, to be done *locally or centrally* (depending on local availability of validated test systems)
- Safety laboratory: to be done *locally*
  - ⇨ Hematology (RBC, WBC, platelet count, hemoglobin, hematocrit)
  - ⇨ Biochemistry (ASAT, ALAT, γ-GT, AP, total bilirubin, creatinine, urea, potassium, sodium, calcium, and chloride)
  - ⇨ Urine analysis (pH, blood, WBC, protein, glucose, ketone bodies, nitrite, bilirubin, urobilinogen)
    - o <u>in Adults (18 - 75 years) and Children/Adolescents Group I and Group II (≥ 6 years):</u> as required, but at least to be done once after last infusion of BT524 and before discharge
    - o <u>Pre-school Children Group III (2 to < 6 years):</u> 24 h post end of last infusion
    - o <u>Newborns/Infants and Toddlers Group IV (0 days to < 2 years):</u> 24 h post end of last infusion
- Ultrasonography of lower limbs (according to study specific ultrasonography manual) and of any other suspected site: whenever a thrombosis or TEE is suspected
- Vital signs (pulse, blood pressure, body temperature)
- Physical examination
- Adverse events
- Concomitant disease / concomitant medication
- Assessment of risk and burden (paediatric patients)

Follow-up Day 2 until Day before Hospital Discharge (if applicable):

The patient will be hospitalized.

- Coagulation activation: PT(INR), aPTT, TAT, F_{1+2}, D-dimer: as required, to be done *locally or centrally* (depending on local availability of validated test systems)
- Safety laboratory: as required, to be done *locally*
  - ⇨ Hematology (RBC, WBC, platelet count, hemoglobin, hematocrit)

- ⇨ Biochemistry (ASAT, ALAT, γ-GT, AP, total bilirubin, creatinine, urea, potassium, sodium, calcium, and chloride)
- ⇨ Urine analysis (pH, blood, WBC, protein, glucose, ketone bodies, nitrite, bilirubin, urobilinogen)

- Ultrasonography of lower limbs (according to study specific ultrasonography manual) and of any other suspected site: whenever a thrombosis or TEE is suspected
- Vital signs: as required
- Adverse events
- Concomitant disease / concomitant medication
- Assessment of risk and burden (paediatric patients)

Day of Hospital Discharge (if Different than 24 h Post-End of Infusion):

The patient will be discharged from hospital.

- Coagulation activation: PT(INR), aPTT, TAT, F_{1+2}, D-dimer, to be done *locally or centrally*
- Safety laboratory: as required, to be done locally
  - ⇨ Hematology (RBC, WBC, platelet count, hemoglobin, hematocrit)
  - ⇨ Biochemistry (ASAT, ALAT, γ-GT, AP, total bilirubin, creatinine, urea, potassium, sodium, calcium, and chloride)
  - ⇨ Urine analysis (pH, blood, WBC, protein, glucose, ketone bodies, nitrite, bilirubin, urobilinogen)
- Ultrasonography of lower limbs (according to study specific ultrasonography manual) and of any other suspected site: whenever a thrombosis or TEE is suspected
- Vital signs
- Physical examination
- Adverse events
- Concomitant disease / concomitant medication
- Assessment of risk and burden (paediatric patients)

Optional Visit

After hospital discharge, an *optional visit* might be conducted at any time before day 49 at discretion of the investigator.

- Coagulation activation: PT(INR), aPTT, TAT, F_{1+2}, D-dimer, to be done *locally or centrally*
- Safety laboratory: as required, to be done *locally*
  - ⇨ Hematology (RBC, WBC, platelet count, hemoglobin, hematocrit)
  - ⇨ Biochemistry (ASAT, ALAT, γ-GT, AP, total bilirubin, creatinine, urea, potassium, sodium, calcium, and chloride)
  - ⇨ Urine analysis (pH, blood, WBC, protein, glucose, ketone bodies, nitrite, bilirubin, urobilinogen)

- Ultrasonography examination of lower limbs (according to study specific ultrasonography manual) and of any other suspected site: whenever a thrombosis or TEE is suspected
- Vital signs (pulse, blood pressure, body temperature)
- Physical examination
- Pregnancy test (urine) - only in females of childbearing potential
- Adverse events
- Concomitant disease / concomitant medication
- Assessment of risk and burden (paediatric patients)

Safety Visit (*Day* 49±4)

Visit at the site; also to be performed for each patient prematurely withdrawn from study participation due to any reason.

- Fibrinogen inhibitory antibody: to be done *locally* (by available method e.g., correction test of thrombin time)
- Coagulation activation: PT(INR), aPTT, TAT, F_{1+2}, D-dimer, to be done *locally or centrally*
    - only in Adults and Children/Adolescents Group I and Group II (≥ 6 years)
- Ultrasonography examination of lower limbs (according to study specific ultrasonography manual) and of any other suspected site: whenever a thrombosis or TEE is suspected
- Viral safety: collection of retention sample
- Vital signs (pulse, blood pressure, body temperature)
- Physical examination
- Pregnancy test (urine) - only in females of childbearing potential
- Adverse events
- Concomitant disease / concomitant medication
- Assessment of risk and burden (paediatric patients)

13.2 Duration of the Study

First Patient in	Adults: 20-Mar-2013 Children/Adolescents (≥ 6 to < 18 years): 09-Nov-2014 Children < 6 years: Q2/2018 *(planned)*
Last Patient Last Visit *(planned)*	Q1/2020

Individual Study Participant

Study part I comprises of 14 days (including hospitalization until day 2) for the assessment of the pharmacokinetics/ pharmacodynamics of BT524 and the conduct of the safety visit (i.e., day 49±4 after the administration of BT524). Regular duration of individual study participation for eligible screened patients in part I is approximately 1.5 months. Maximum duration of individual study participation in part I is up to 66±4 days.

Duration of study part II is variable for the individual patient. For the last patient included it comprises of a minimum of 12 months period for optional on-demand prophylaxis and/or on-demand treatment including the conduct of the safety visit (i.e., day 49±4 after the last administration of BT524).

All study subjects will be offered to extend their study participation (in part II) until the last enrolled subject (of the additional patients without PK/PD assessment) has finished study part II. This implicates that probably the total duration of individual study participation in both study parts will be more than 15.5 months.

In case the patient experiences a bleeding event at the very end of his/her individual study participation even including the last day of month 12, regular individual study duration in part II is extended at maximum until day 49±4 after the administration of BT524 for the conduct of the safety visit for this very last event.

13.2.1 End of Study

The end of study will be defined as the Last Visit of the Last Study Participant (= LPLV (Last Patient Last Visit).

13.3 Criteria for Premature Termination

13.3.1 Premature Termination of the Entire Clinical Study

The study as a whole may be stopped by Biotest after consultation with the Coordinating Investigator if there are reasons for which continuation of study is no longer justified, such as:

a) Unacceptable delay of study completion
b) Low recruitment rate
c) A large number of study participants with premature termination
d) Changed benefit-risk ratio according to the efficacy and/or safety results from this or parallel studies
e) Recommendation by the DMC (please refer to section 14.3)

Stopping rule

The DMC is expected to review all safety relevant information for each participating subject individually with the purpose to identify safety issues that are pertinent to the decision whether a) the study can be continued as intended and/or b) whether the safety relevant methods and procedures need to be adjusted.

These decisions will be based on the in-depth review of all individual safety pertinent information by qualified experts; their resulting recommendations will be guided by following considerations:

a. Occurrence of any fatal serious adverse event for which a causal relationship to the investigational medication is reasonably possible (i.e. SAR whether unexpected or not)
b. Occurrence of any non-fatal serious adverse event for which a causal relationship to the investigational medication is reasonably possible (i.e. SAR whether unexpected or not) that is life-threatening or results in persistent or significant disability or incapacity

c. Occurrence of any non-fatal adverse event for which a causal relationship to the investigational medication is reasonably possible (i.e. SAR whether unexpected or not) and that is medically significant since it put the trial participant at risk for an outcome as specified under a) or b) above if no intervention had been undertaken
d. Occurrence of non-serious adverse reactions (AR whether unexpected or not) of severe intensity in more than 1/3 of the trial exposed patients
e. Occurrence of non-serious non-severe adverse reactions (AR whether unexpected or not) that cause severe bother and inconvenience (in terms of duration and intensity) in more than 1/3 of the trial exposed patients.

In the event of any of the above, the DMC will also review possibly contributing factors unrelated to the trial medication in order to identify ways to reduce the risk of such complications significantly by adapting the trial's methods (eligibility criteria, trial test procedures, schedule, etc.).

In the event of any of the above, the DMC will recommend to stop the study if the risk for the reoccurrence of such event(s) cannot be reduced to a significant extent by adapting the trial's methods.

In case of premature termination of the entire study, the sponsor has to notify the appropriate regulatory authorities within 15 days.

13.3.2 Premature Termination of an Individual Study Site

The study may be stopped at an individual study site for reasons such as:

a) Low recruitment rate
b) Lack of co-operation
c) Severe deviations from study protocol
d) Manipulation of study data
e) Violation of other ethical or legal principles.

13.4 Treatment and Care after the End of the Study

For patients having finished the study and for all patients who drop out prematurely, it is the responsibility of the investigator to choose adequate therapeutic measures.

13.5 Benefit-Risk Evaluation

13.5.1 Benefit

It is to be expected that patients with congenital fibrinogen deficiency e.g. a- and hypofibrinogenemia have a benefit from the single BT524 PK infusion due to the reduction of their bleeding risk (e.g. induced by [minor] trauma) for a period of approximately 1 to 2 weeks. In addition in part II the on-demand prophylaxis is expected to prevent bleeding during e.g. tooth extractions, surgical procedures etc. The on-demand treatment will be applied to stop any bleeding that may occur during the course of the study.

In part I, the main character of this study is non-therapeutic (evaluation of PK, safety and tolerability data). Part II adds the benefits of treatment and prophylaxis for the participating patients. Moreover, the study patients contribute to the evaluation of a clinically needed, important therapy option to the benefit of future patients to be treated with BT524.

13.5.2 Foreseeable Risk and Discomfort Related to BT524

Adverse drug reactions (ADRs) to be expected with BT524

In study 984, BT524 is applied to humans for the first time. BT524 is a highly purified fibrinogen concentrate manufactured by Biotest from human plasma.

Data on experience in humans is not yet available specifically for BT524. An EMA **"Guideline on Core SmPC for Human Fibrinogen Products (EMEA/CHMP/BPWP/691754/2013 Rev 1)"** is in place dated 23-July-2015. This guideline is applicable to BT524 and comprises the following data on foreseeable risks with human fibrinogen.

- **Section 4.3 Contraindications**

Section 4.3 Contraindications names *"Hypersensitivity to the active substance or to any of the excipients"* and *"[Product specific for products containing heparin:] <Known allergy to heparin or history of heparin induced thrombocytopenia type II.>".*

As BT524 does not contain heparin, the second point does not apply to BT524. With regard to the contraindication hypersensitivity, this point is addressed in the exclusion criteria (see general exclusion criterion 6).

- **Section 4.4 Special warnings and precautions for use**

Section 4.4 Special warnings and precautions for use states:

(1) *"There is a risk of thrombosis when patients, with either congenital or acquired deficiency, are treated with human fibrinogen particularly with high dose or repeated dosing. Patients given human fibrinogen should be observed closely for signs or symptoms of thrombosis.*
In patients with a history of coronary heart disease or myocardial infarction, in patients with liver disease, in peri- or post-operative patients, in neonates, or in patients at risk of thromboembolic events or disseminated intravascular coagulation, the potential benefit of treatment with human plasma fibrinogen should be weighed against the risk of thromboembolic complications. Caution and close monitoring should also be performed.

(2) Acquired hypofibrinogenaemia is associated with low plasma concentrations of all coagulation factors (not only fibrinogen) and inhibitors and so treatment with blood products containing coagulation factors should be considered. Careful monitoring of the coagulation system is necessary.

(3) If allergic or anaphylactic-type reactions occur, the injection/infusion should be stopped immediately. In case of anaphylactic shock, standard medical treatment for shock should be implemented.

(4) [Product specific for products containing heparin:]
<Interference with clotting tests>
When performing clotting tests which are sensitive to heparin in patients receiving high doses of human fibrinogen, the heparin as a constituent of the administered product must be taken into account.

(5) [The text to be inserted here for transmissible agents should be in accordance with the current version of the guideline on the Warning on Transmissible Agents in SmPCs and Package Leaflets for plasma-derived medicinal products (EMA/CHMP/BWP/360642/2010 rev. 1) (EMA 2011).]

When medicines are made from human blood or plasma, certain measures are put in place to prevent infections being passed on to patients. These include:

- *careful selection of blood and plasma donors to make sure those at risk of carrying infections are excluded,*
- *the testing of each donation and pools of plasma for signs of virus/infections,*
- *the inclusion of steps in the processing of the blood or plasma that can inactivate or remove viruses.*

Despite these measures, when medicines prepared from human blood or plasma are administered, the possibility of passing on infection cannot be totally excluded. This also applies to any unknown or emerging viruses or other types of infections.
The measures taken are considered effective for enveloped viruses such as HIV, HBV and HCV and for the non-enveloped viruses HAV and parvovirus B19.

It is strongly recommended that every time you receive a dose of BT524 the name and batch number of the product are recorded in order to maintain a record of the batches used.

In the case of replacement therapy with coagulation factors in other congenital deficiencies, antibody reactions have been observed, but there is currently no data with fibrinogen".

With regard to the special warnings and precautions for use, the first paragraph on thromboembolic events is addressed in several exclusion criteria (e.g. see exclusion criteria 4).

The risk of thromboembolic events is addressed in several exclusion criteria (e.g. Known bleeding disorders other than congenital fibrinogen deficiency, history of esophageal variceal bleeding, known presence or history of venous/arterial thrombosis or thromboembolic events in the preceding 6 months). It is also closely followed up throughout the study, by ultrasonography of lower limbs as well as determination of coagulation activation parameters, and by more routinely follow-up of the patient (vital signs, physical exams, adverse events, etc.)

The second paragraph of section 4.4 applies to acquired hypofibrinogenemia only and does therefore not apply to the study population of study 984.

The study population of study 984 is limited to patients with congenital a- or severe hypofibrinogenemia as a homologous model population for patients with fibrinogen deficiency. This model population was chosen because it allows the generation of a representative PK profile in fibrinogen deficient plasma with a minimization of any interferences and heterogenicity as opposed to PK sampling in patients with acquired fibrinogen deficiency.

The third paragraph on allergic or anaphylactic type reactions is addressed in the exclusion criterion 6.

The fourth paragraph is only applicable to heparin containing products. BT524 does not contain heparin.

The fifth paragraph addresses the risk of transmissible agents in plasma derived medicinal products. This risk is minimized in the production process (see also **section 10.1**). Additionally, virology sample are taken pre-treatment and a virus safety follow-up visit is planned on day 49±4 to confirm that no seroconversion has occurred within study 984.

The last, sixth paragraph on antibody reactions is again addressed in the exclusion criteria (Known presence or history of fibrinogen inhibitory antibodies). The risk of development of antibodies exists in theory and this will be monitored during the present study.

- **4.8 Undesirable effects**

The following table of known adverse drug reactions with human fibrinogen is provided by the EMA guideline:

Table 5: Known Adverse Drug Reactions with Human Fibrinogen

MedDRA Standard System Organ Class	Undesirable effects	Frequency
Immune system disorders:	Allergic or anaphylactic-type reactions	
Vascular disorders:	Thromboembolic episodes (including myocardial infarction and pulmonary embolism (see **section 4.4**)	
General disorders and administration site conditions:	Increase in body temperature	

According to EMA Guideline

In addition, the risk of transmissible agents in plasma-derived medicinal products is addressed [see **section 4.4 of "Guideline on Core SmPC for Human Fibrinogen Products (EMEA/CHMP/BPWP/ 691754/2013 Rev 1)"**].

As described above, these potential risks are addressed in the respective exclusion criteria, e.g. "Known presence or history of hypersensitivity to human fibrinogen or human plasma proteins e.g., immunoglobulins, vaccines" as this predisposition may imply an increased risk for allergic or anaphylactic-type reactions as well as for hypersensitivity reactions (with in body temperature as one potential symptom) and "Known presence or history of venous/arterial thrombosis/thromboembolic events in the preceding 6 months".

13.5.3 Risk minimization measures for all study participants

Although risks cannot entirely be excluded, they are to be minimized by the following established measures:

- By the careful selection of the patients as reflected in the inclusion and exclusion criteria.
- By the close surveillance of patients throughout the study (ultra-sonography examination of lower limbs and of any other suspected site, as well as close follow-up of coagulation activation parameters, and regular evaluation of viral safety and of development of antibodies).
- By routine and frequent patients follow-up procedures (including physical examination, assessment of vital signs, and adverse event reporting).
- By the implementation of the stopping rule procedures as outlined in Section 13.3.1.
- By the implementation of a DMC. A DMC has been established in order to review the first ten adult patients' data before inclusion of children and

adolescents. The DMC is to ensure the safety of all study participants but in particular with regard to the inclusion of children and adolescents.

13.5.4 Risk minimization measures regarding the enrolment and treatment of children and adolescents

The anticipated risks to paediatric patients in Study 984 are considered comparable with those that adult patients may encounter from administration of BT524 and which are listed in Table 5: allergic or anaphylactic-type reactions, thromboembolic events, increase in body temperature, and a theoretical risk of transmissible agents from plasma-derived medicinal products. No additional risks for children and adolescents have been identified so far.

Although risks for children and adolescents cannot entirely be excluded, they can be minimized by the following additionally implemented measures:

- By assessment of individual risk and burden in paediatric patients by the investigator at every visit.
- By the adaptation of the treatment to medical requirements and dosing according to the subject's BW.
- By the timing of the inclusion of children and adolescents: Children and adolescents will not be enrolled until after completion of dosing and the associated 7-day dosing-free safety interval of the first 10 adult patients enrolled into the study and after the DMC has reviewed the data from these 10 patients.

13.5.5 Reduction of Pharmacokinetics blood sampling volume and time points in Paediatric Patients

Blood sampling time points in paediatric patients were selected to ensure a reliable estimate of the product's pharmacokinetics as a valid basis for comparison with other fibrinogen products and as a valid basis for dose selection in paediatric patients other than a simple adjustment to BW.

A total of 13 blood samplings pre- and post-infusion are performed in adult patients and in children and adolescents with BW > 43 kg, requiring a total of 252 ml of blood in adults.

In children and adolescents with a BW of ≤ 43 kg, the number of blood samplings pre- and post-infusion is reduced to 8 over a period of 10 days, with longer time intervals between each sampling and the next.

In addition, the amount of blood was reduced to lower the burden on children and adolescents and avoid additional risks. The total volume needed in the PK part I of the study does not exceed 173.3 ml in children and adolescents with a BW ≤ 43 kg and 203.3 ml in children and adolescents with a BW above 43 kg.

In very young paediatric patients a further reduced sampling scheme will be applied. This includes sparse sampling with 5 PK sampling time points for children between 2 to < 6 years, a minimal sampling with 3 PK samples for the infants and toddlers and only two PK sampling time points for newborns. Time points have been selected trough an optimal design to support best the derived PK information. The volume of blood to be drawn is reduced as much as possible by procedures adopted for the paediatric age group, using for example paediatric tubes and plasma micro-sampling.

The number of sampling time points for paediatric patients and the reduced amount of blood drawn are the minimal necessary number needed to meet the study's PK objectives.

13.5.6 Justification of Risk and Burden in Paediatric Patients

The participation of children and adolescents in the preliminary pharmacokinetic and safety part of Study 984 will allow an understanding of each included child and adolescent profile in terms of fibrinogen deficiency characteristics (antigen level is rarely assessed), and in terms of response to administration of fibrinogen concentrate. Only in this way the study can yield a tangible benefit while ensuring a reliable estimate of the product's pharmacokinetics.

Furthermore, children and adolescents with fibrinogen deficiency are a target population that may benefit from BT542 administration, especially for treatment of trauma-related bleedings (frequently expected in childhood) and for prevention of surgery-related bleedings. Dental care is also frequently needed before 18 years of age, and in Egypt, Lebanon and Tunisia (where Study 984 is also conducted), a number of male children undergo circumcision before the age of 10.

Risks and the burden in paediatric patients have been reduced as far as possible by the described measures, and the assessed risks and burden appear to be justified by the expected benefits. The risk and burden for each paediatric patient in the study will be assessed by the investigator at each visit.

13.5.7 Other Sources of Possible Risk and Discomfort

Puncture of a vein and/or placement of indwelling catheters for blood withdrawal may cause pain and occasionally results in hematoma, thrombosis or thrombophlebitis.

Discomfort may be caused by any study procedure such as pre- and post-study examinations (including drug and virological HIV tests) and sampling (blood, urine).

13.5.8 Summary of Possible Risk and Discomfort

The anticipated risks all study participants (adults and paediatric patients) may encounter from administration of single/ multiple dose(s) of BT524 are allergic or anaphylactic-type reactions, thromboembolic events, an increase in body temperature, and the theoretical risk of transmissible agents from plasma-derived medicinal products.

During this hospitalization period possible allergic or anaphylactic-type reactions as well as thromboembolic events are likely to be detected early and can be treated adequately and timely to minimize any medium- or long-term risks.

Moreover, patients will be advised to walk and not to immobilize themselves to minimize the risk for thrombosis.

Overall the risk benefit profile of this study is regarded as favorable. This conclusion is based on the fact that Fibrinogen concentrates have shown to be safe, well-tolerated (Henselmans et al. 1999, Fenger-Eriksen et al. 2009) and to rapidly restore and maintain hemostasis in patients with congenital as well as acquired fibrinogen deficiencies in different indications (e.g., obstetrics, cardiovascular surgery). All available investigations for BT524 indicate an expected benefit risk profile comparable

to the long available marketed fibrinogen concentrates and a safety profile that is in line with the available EMA Core SmPC.

14 ASSESSMENT OF PRIMARY AND SECONDARY OBJECTIVES AND CRITERIA FOR EVALUATION

14.1 Pharmacokinetics

The primary objective of this study is the assessment of 14 day single-dose pharmacokinetics of BT524 following IV infusion of 70 mg/kg BW (**PART I)**.

14.1.1 Specification of Pharmacokinetic Parameters

For evaluation of the pharmacokinetics (PK) of BT524 the plasma concentration of fibrinogen antigen (nephelometry) will be determined at several time points during the 14 day sampling period (see **section 14.4.3.1**).

The exact time (actual time) post-end of infusion at which the actual samples were collected and their corresponding precise values are to be considered for PK analyses.

Pharmacokinetics of BT524 will be evaluated by means of standard formulae using a statistical software package. The pharmacokinetic parameters to be evaluated comprise:

- Terminal Elimination Half-life ($t_{1/2}$) for fibrinogen antigen
- Time to reach Maximum Concentration (t_{max})
- Maximum Concentration (C_{max})
- Area Under the Concentration-Time Curve (AUC) calculated to the last measured concentration (AUC(0-t)) and extrapolated to infinity (AUC(0-inf)
- Clearance (CL)
- Mean Residence Time (MRT)
- Volume of Distribution (V_{ss})
- Incremental Recovery (IR)
- Classical in vivo recovery (IVR)

PK parameters will be derived from time-concentration profiles using adapted methodology (non-compartmental analysis, compartment analysis, or population modeling, as appropriate/ required).

14.2 Pharmacodynamics

The 14 day single-dose pharmacodynamics of BT524 following IV infusion of 70 mg/kg BW is a **secondary objective** of this study (**PART I**).

14.2.1 Specification of Pharmacodynamic Parameters

For evaluation of the pharmacodynamics (PD) of BT524 the plasma concentration of fibrinogen activity (Clauss assay) will be determined at several time points during the 14 day sampling period (see **section 14.4.3.1**).

The exact time post-end of infusion at which the actual samples were collected and their corresponding precise values are to be considered for PD analyses.

Pharmacodynamics of BT524 will be evaluated by means of standard formulae using a statistical software package. The pharmaco-dynamic parameters to be evaluated comprise:

- Terminal Elimination Half-life ($t_{1/2}$) for fibrinogen activity
- Time to reach Maximum Concentration (t_{max})
- Maximum Concentration (C_{max})
- Area Under the Concentration-Time Curve (AUC) calculated to the last measured concentration (AUC(0-t)) and extrapolated to infinity (AUC(0-inf)
- Clearance (CL)
- Mean Residence Time (MRT)
- Volume of Distribution (Vss).
- Incremental Recovery (IR)
- Classical in vivo recovery (IVR)

Those parameters will be derived using adapted methodology, non-compartmental analysis, compartment analysis, or population modeling, as appropriate/ required.

14.3 Data Monitoring Committee (DMC)

The DMC has been constituted by members who have expertise in the field of hematology/hemostaseology and/or investigation and/or experience in the proper conduct of clinical studies, and/or statistical knowledge, and who do not have any limiting conflicts of interest (i.e., financial, intellectual, professional or regulatory).

The main aim of the DMC is to ensure the safety of the study participants in particular with regard to the inclusion of children and adolescents (< 18 years). Children and adolescents (≥ 6 to < 18 years) will not be enrolled until after completion of dosing and the associated 7-day dosing-free safety interval of the first 10 adult patients enrolled into the study and after the DMC has duly reviewed these data sets.

In addition, the DMC will perform a second mandatory data review after the last patient has finished the PK safety visit and respective data are available.

Subsequently, after the first 20 patients of ≥ 6 to ≤ 75 years finished part I, at least 3 additional paediatric patients < 6 years of age are planned to be enrolled in the study part I and at least 3 additional patients < 6 years of age are planned to be enrolled directly in the study part II without PK/PD assessment in part I. Prior to enrolment of any children < 6 years of age the DMC will review and assess all available safety and PK/PD data from adults and children ≥ 6 years enrolled in the study so far (including data of least 3 children ≥ 6 to < 12 years and of at least 3 adolescents ≥ 12 to < 18 years).

The DMC will be fully established before enrolment of any children and adolescents into the study so that it can respond to any safety signal identified in adult patients.

The DMC can also make other recommendations to the Sponsor concerning termination of the trial based on the assessment of the likelihood to reach a tangible benefit without exposing trial participants to undue risk and inconvenience.
For details on stopping rule please refer to section 13.3.1.

In addition, the extent and timing of the pharmacokinetic profiling will be observed, including the between-subject variability of the data, the smoothness of the disposition curves, and the likelihood to capture the disposition profile with the smallest possible blood sampling load.

The DMC will remain in office until completion of the end-of-trial visit in the last patient.

The proceedings of the DMC will be governed by a separate charter.

14.4 Efficacy

Within the study surrogate efficacy will be assessed in both parts whereas clinical endpoints will be assessed **in part II** only.

14.4.1 Specification of Surrogate Efficacy Parameter

Maximum clot firmness (MCF, mm) addresses the clot integrity and will be measured by rotational thromboelastometry. MCF serves as a surrogate endpoint.

In Part I MCF pre-dose and at 1 and 8 hours post-end of each IV infusion will be compared and correlation between MCF and fibrinogen activity pre-dose and at 1 and 8 hours post-end of each IV infusion will be assessed (in Adults and Children/Adolescents Group I and Group II (≥ 6 years).

In Pre-school Children Group III (2 to < 6 years) MCF will be compared pre-dose and at 1 hour post-end of each IV infusion and correlation between MCF and fibrinogen activity pre-dose and at 1 hour post-end of each IV infusion will be assessed.

In Newborns (0 days to 27 days) and in Infants and Toddlers (28 days to < 2 years), Group IV, MCF will be compared pre-dose and at the end of each IV infusion and correlation between MCF and fibrinogen activity pre-dose and at the end of each IV infusion will be assessed.

In Part II MCF will be compared pre-dose and at 1 hour post-end of each IV infusion and correlation between MCF and fibrinogen activity pre-dose and at 1 hour post-end of each IV infusion will be assessed.

14.4.2 Specifications of Clinical Efficacy Parameters

PART II

Efficacy of BT524 will be assessed as **secondary objectives**.

The following efficacy parameters will be assessed after each bleeding event:

- Overall **hemostatic 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"
- Total loss of blood (e.g., intra- and postoperatively, re-bleedings), if applicable
- Units of other fibrinogen-containing products infused besides BT524 e.g., fresh frozen plasma or cryoprecipitate
- Units of transfusion products infused, e.g., allogenic or autologous blood (packed red blood cells, fresh whole blood), platelets
- Consumption of BT524 (doses per kilogram BW required pre-, intra- or post-operatively for effective treatment)

The following efficacy parameter will be assessed after wound healing is expected to be completed:

- Quality of wound healing, if applicable

With respect to the evaluation of efficacy, patients with multiple events are to be considered as *individual cases* in a primary analysis.

14.4.3 Methods for Assessing, Recording and Analyzing Pharmacokinetic Parameters

14.4.3.1 Determination of Fibrinogen Antigen

PART I

For evaluation of the primary endpoint, the 14 day pharmacokinetics of BT524, the plasma concentration of fibrinogen antigen will be determined at several time points during the 14 day sampling period.

Fibrinogen antigen will be determined quantitatively by means of nephelometry (detection limit of 0.03 mg/l).

Plasma samples are to be collected:

In Adults and Children/Adolescents Group I (≥ 6 years and BW > 43 kg): on PK dosing day 0 pre-dose, immediately at the end of BT524 IV infusion, at 0.5, 1, 2, 4, 8, 24, 48, 96, 168, 240, and at 336 hours post-end of infusion;

In Children/Adolescents Group II (≥ 6 years and BW ≤ 43 kg): on PK dosing day 0 pre-dose, immediately at the end of BT524 IV infusion, at 1, 4, 24, 96, 168, and at 240 hours post-end of infusion;

In Pre-school Children Group III (2 to < 6 years): on PK dosing day 0 pre-dose, immediately at the end of BT524 IV infusion, at 1, 12, and 48 hours post-end of infusion;

In Infants and Toddlers (28 days to < 2 years): on PK dosing day 0 pre-dose, immediately at the end of BT524 IV infusion, and 24 hours post-end of infusion;

In Newborns (0 days to 27 days): on PK dosing day 0 pre-dose, immediately at the end of BT524 IV infusion; (see **sections** 3.1 to 3.5).

It is very important to record the exact time post-end of infusion at which the actual samples were collected and to consider their corresponding precise values for the PK analyses.

Plasma concentration of fibrinogen antigen will be determined locally (by ELISA) and centrally (by nephelometry) at screening, at all other timepoints only at the central laboratory. Sample collection and processing are described in the laboratory manual.

14.4.4 Methods for Assessing, Recording and Analyzing Pharmacodynamic Parameters

14.4.4.1 Determination of Fibrinogen Activity

PART I

For evaluation of the pharmacodynamics (PD) of BT524 the plasma concentration of fibrinogen activity will be determined at several time points during the 14 day sampling period.

Fibrinogen activity (functional) will be determined by means of the Clauss assay (detection limit of 0.2 g/l) (Clauss 1957, Palareti and Maccaferri 1990).

Plasma samples are to be collected:

In Adults and in Children/Adolescents Group I (≥ 6 years and BW > 43 kg): on PK dosing day 0 pre-dose, immediately at the end of BT524 IV infusion, at 0.5, 1, 2, 4, 8, 24, 48, 96, 168, 240, and at 336 hours post-end of infusion;

In Children/Adolescents Group II (≥ 6 years and BW ≤ 43 kg): on PK dosing day 0 pre-dose, immediately at the end of BT524 IV infusion, at 1, 4, 24, 96, 168, and at 240 hours post-end of infusion;

In Pre-school Children Group III (2 to < 6 years): on PK dosing day 0 pre-dose, immediately at the end of BT524 IV infusion, at 1, 12, and 48 hours post-end of infusion;

In Infants and Toddlers (28 days to < 2 years): on PK dosing day 0 pre-dose, immediately at the end of BT524 IV infusion, 4* and 24 hours post-end of infusion (*only at the discretion of investigator considering the exact clinical situation of the patient);

In Newborns (0 days to 27 days): on PK dosing day 0 pre-dose, immediately at the end of BT524 IV infusion; (see **sections** 3.1 to 3.5).

The exact time post-end of infusion at which the actual samples were collected and their corresponding precise values are to be considered for PD analyses.

Plasma concentration of fibrinogen activity will be determined locally and centrally at screening, all other timepoints only at the central laboratory. Sample collection and processing are described in the laboratory manual.

14.4.5 Methods for Assessing, Recording and Analyzing Efficacy Parameters

14.4.5.1 Method for Assessing, Recording and Analyzing Surrogate Efficacy Parameter

14.4.5.2.1 *Maximum Clot Firmness (MCF) by Fib-tem S of ROTEM Device*

Hemostatic efficacy of BT524 serves as a surrogate efficacy (secondary endpoint) and will be investigated by the determination of the Maximum Clot Firmness (MCF, mm) measured by rotational thromboelastometry. MCF as a *surrogate efficacy parameter* likely to predict clinical benefit was accepted by the FDA for the conditional approval of the fibrinogen concentrate RiaSTAP in 2009.

PART I

In part I, MCF is to be determined in Adults and Children/Adolescents Group I and Group II (≥ 6 years) on PK dosing day 0 pre-dose, at 1 and 8 hours post-end of BT524 IV infusion.

In Pre-school Children Group III (2 to < 6 years) MCF is to be determined on PK dosing day 0 pre-dose and at 1 hour post-end of BT524 IV infusion.

In Newborns and in Infants and Toddlers Group IV (0 days to < 2 years) MCF is to be determined on PK dosing day 0 pre-dose and immediately at the end of BT524 IV infusion (see study flowchart for pharmacokinetics, **sections** 3.1 **to** 3.5). MCF pre-dose value will be compared to the post-dose MCF values.

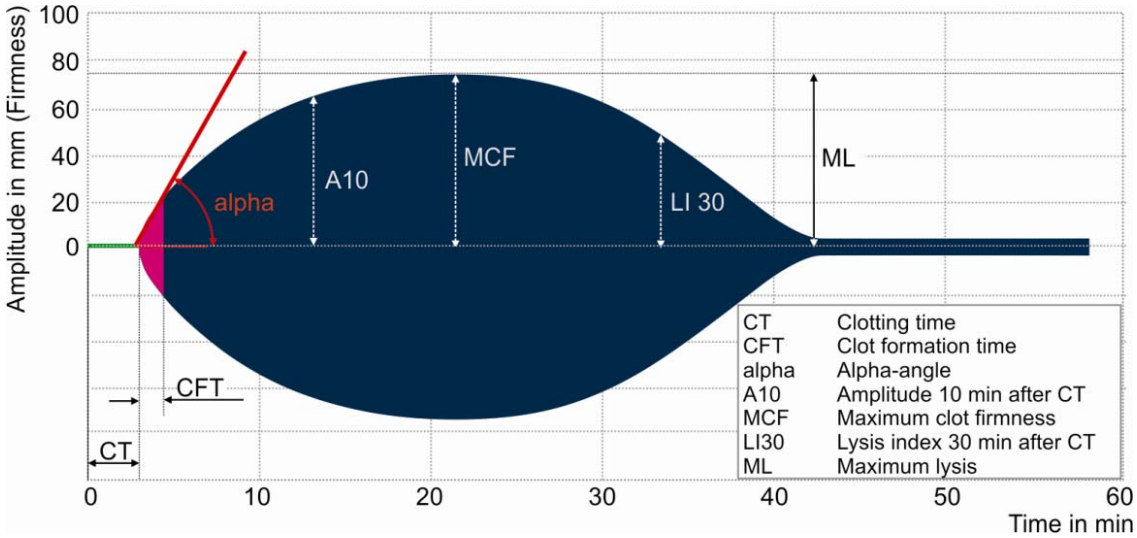
PART II

In part II, MCF is to be determined for each administration of BT524 (if applicable) pre-dose, at 1 hour and as required post-end of BT524 IV infusion (see **sections 3.1 to 3.6**). MCF pre-dose value will be compared to the post-dose MCF values.

MCF will be determined locally from whole blood or at the central laboratory by means of the Fib-tem S assay (tissue factor activation and platelet inhibition), a ready-to-use ROTEM® (rotational thromboelastometry) system reagent (PPD) which allows the assessment of the fibrinogen level and the quality of the fibrin polymerization in citrated blood by inhibiting the platelets.

Fib-tem S measures the viscoelastic properties of the clot and provides information on the speed of coagulation initiation, kinetics of clot growth (MCF, mm), clot strength, and breakdown (Lang et al. 2009). **Figure 1** shows an example of the ROTEM readout of citrated normal blood.

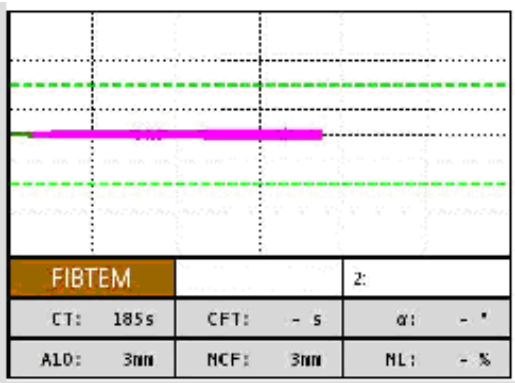
Figure 1: ROTEM Readout of Citrated Normal Blood



The ROTEM® analyses: FibTEM® test (fibrin clot obtained by platelet inhibition with cytochalasin D). The clotting time (CT (seconds)) represents the time from the start of the test until a clot firmness of 2 mm is detected; maximum clot firmness (MCF (mm)) represents the total amplitude of the clot (Schochl et al. 2010).

In the ROTEM read out of Fib-tem S test expected reference (normal range) values for the amplitude of MCF are 9-25 mm for fibrinogen levels (PPD). In patients with congenital afibrinogenemia or severe congenital hypofibrinogenemia the MCF would not be measurable (refer to Figure 2):

Figure 2: Fib-tem S Readout in Afibrinogenemia



Sample collection and processing are described in the laboratory manual.

14.4.5.2 Methods for Assessing, Recording and Analyzing Clinical Efficacy Parameters

14.4.5.2.1 *Investigator Assessment on Overall Hemostatic Response to Treatment with BT524*

PART I

No clinical parameters will be evaluated.

PART II

The investigator is asked to classify any bleeding event (spontaneous bleeding, surgery, post traumatic bleeding) post-dose as minor or major (please refer to Appendix 20.3 *Recommendation for the 'Assessment of Bleeding Events'*). For each surgical procedure as well as for each treated bleed, the investigator will classify the overall hemostatic response to treatment with BT524 according to a 4 point scale as "none", "moderate", "good" or "excellent". The overall assessment is to be performed at the day of hospital discharge (if applicable) or at the end of the treated bleeding event.

14.4.5.2.2 *Loss of Blood*

PART I

No clinical parameters will be evaluated.

PART II

For each surgical procedure total loss of blood (e.g., intra- and postoperatively, re-bleedings) will be evaluated - if applicable - or at least estimated as far as possible. In addition, loss of blood is to be rated by the investigator according to the following classifications

- loss of blood is lower than expected for the procedure performed
- loss of blood is within the expected range for the procedure performed
- loss of blood is higher than expected for the procedure performed

14.4.5.2.3 *Consumption of Alternative Fibrinogen-containing Products*

PART I

No clinical parameters will be evaluated.

PART II

Units of other fibrinogen-containing products such as fresh frozen plasma, cryoprecipitate or alternative commercially available fibrinogen concentrates given to counteract hemodynamic instability will be documented and evaluated for each bleeding event (e.g., surgical intervention).

14.4.5.2.4 *Consumption of Transfusion Products*

PART I

No clinical parameters will be evaluated.

PART II

Units of transfusion products (allogenic or autologous blood [packed red blood cells, fresh whole blood], platelets) given to counteract hemodynamic instability will be documented and evaluated for each bleeding event (e.g., surgical intervention).

14.4.5.2.5 *Consumption of BT524*

PART I

Consumption of BT524 (dose per kilogram BW and total dose) will be calculated.

PART II

Consumption of BT524 (dose per kilogram BW, dose per infusion and total dose) required pre-, intra- or post-operatively for effective treatment will be calculated.

14.4.5.2.6 *Wound Healing*

PART I

No clinical parameters will be evaluated.

PART II

Quality of wound healing will be assessed in part II only if applicable.

14.5 Safety

14.5.1 Specification of Safety Parameter(s) and Timing

The following safety parameters are described in the following sections:

- ECG
- Adverse events
- Development of fibrinogen antibodies
- Vital signs e.g., blood pressure, heart rate, body temperature
- Physical examination
- Clinical laboratory parameters of

Hematology:
RBC, WBC, platelet count, hemoglobin, and hematocrit

Biochemistry:
Aspartate aminotransferase, alanine aminotransferase, γ-glutamintransferase, alkaline phosphatase, total bilirubin, creatinine, urea, potassium, sodium, calcium, chloride

- *Markers of coagulation activation:*
  PT(INR), aPTT, TAT, F_{1+2}, D-dimer
  Urine Analysis:
  pH, blood, WBC, protein, glucose, ketone bodies, nitrite, bilirubin, urobilinogen
- Virus safety

14.5.1.1 Adverse Events

Safety issues will be addressed by occurrence, frequency, nature, and severity of adverse events (AEs).

The number of AEs will be documented including safety laboratory parameters reported as adverse events.

The patients are asked about AEs during the infusion and since the last visit. The patients will furthermore be explicitly inquired with regard to their well-being by 'non-leading' questions at each visit.

14.5.1.2 Physical Examination and Vital Signs

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.

Time points for the assessment of physical examinations are given in the study flow charts (see **section 3.1** to 3.6).

PART I

Physical examinations are to be performed at screening visit, on dosing day 0 pre-dose and at 2 hours post-end of BT524 IV infusion, and on the follow-up days 1, 2, 4, 7, 10, and 14 post-infusion, and at the safety visit.

PART II

On-demand prophylaxis/ on-demand treatment

- Without hospitalization: physical examinations are to be performed at screening visit (only for additional patients without participation in PK/PD part I) and at dosing day pre-dose of BT524 IV infusion and before discharge, at the optional visit and the safety visit.
- With hospitalization: physical examinations are to be performed at screening visit (only for additional patients without participation in PK/PD part I) and at each dosing day pre-dose of BT524 IV infusion, at 24 hours after the end of last infusion, on the day of hospital discharge, at the optional visit and the safety visit.

In addition to the scheduled physical examinations symptom directed physical examination will be conducted whenever necessary.

For all changes assessed to be clinically relevant an AE form must be completed.

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)

Time points for the assessment of vital signs are given in the study flow charts (see **section 3**).

PART I

Vital signs are to be performed at screening visit, on PK dosing day 0 pre-dose of BT524 IV infusion and at 0.5 hours after start of infusion, and at 0.5, 1, 2, 4, 8 hours post-end of infusion, and on the follow-up days 1, 2, 4, 7, 10, and 14 post-infusion, and at the safety visit (see study flowchart for pharmacokinetics, **sections 3.1** - 3.5).

PART II

On-demand prophylaxis/ on-demand treatment

- Without hospitalization: vital signs are to be performed at screening visit (only for additional patients without participation in PK/PD part I) and on the dosing day pre-dose of BT524 IV infusion, 0.5 hours after start of infusion, at 0.5 hours post-end of infusion, before discharge, and at the optional visit and the safety visit.
- With hospitalization: vital signs are to be performed at screening visit (only for additional patients without participation in PK/PD part I) and at each dosing day pre-dose of BT524 IV infusion, 0.5 hours after start of infusion, at 0.5 and 4 hours post-end of infusion, at 24 hours after the end of last infusion, from day 2 until the day before hospital discharge whenever required, on the day of hospital discharge, at the optional visit, and the safety visit.

14.5.1.3 Coagulation Parameters

The following safety coagulation parameters will be investigated:

- Prothrombin time (PT) / International normalized ratio (INR)
  PT is a measure of the integrity of the extrinsic and final common pathways of the procoagulant cascade. PT presents the time for patient plasma to clot after the addition of calcium and thromboplastin as an activator of the extrinsic pathway. Therefore, deficiencies or inhibitors of clotting factors within the extrinsic (factor VII) and final common pathways (factors V, X, II, I [fibrinogen]) result in prolongation of the PT.
  The INR is a mathematical conversion of a patient's PT that accounts for the sensitivity of thromboplastin used by factoring in the international sensitivity index (ISI) values supplied by its manufacturer PT (Kamal et al. 2007).

- Activated partial thromboplastin time (aPTT)
  aPTT measures the integrity of the intrinsic and final common pathways of the coagulation cascade and represents the time for patient plasma to clot after the addition of phospholipid (intrinsic pathway activator) and calcium (Kamal et al, 2007).

- Thrombin-antithrombin III complex (TAT)
  TATs develop during the inactivation of thrombin – the central enzyme of the coagulation system – via complexion with anti-thrombin. TATs are also an indirect measure of thrombin generation. In combination with F_{1+2}

hypercoagulable status can be detected (Wagner and Dati 2008).

- Prothrombin fragments 1 and 2 (F_{1+2})
  During the activation process of prothrombin to thrombin F_{1+2} are split off and represent an indirect measure of thrombin generation. They are useful to detect and follow-up hypocoagulable status (Wagner and Dati 2008).

- D-dimer
  D-dimer is a fibrin degradation product (or FDP), a small protein fragment present in the blood after a blood clot is degraded by fibrinolysis. D-dimer contains two crosslinked D fragments of the fibrinogen protein. D-dimers are produced when fibrin is cleaved by plasmin. The presence of D-dimer may be used to assist with the diagnosis of DIC, Deep Venous Thrombosis (DVT) or Pulmonary Embolism (PE).

Time points for the assessment of coagulation parameters are given in the study flow charts (see **section 3**). Coagulation parameters are to be determined locally or centrally.

PART I

Coagulation parameters are to be determined:

- In Adults (18 to 75 years): at screening visit, on PK dosing day 0 pre-dose of BT524 IV infusion and at 1, 4, and 8 hours post-end of infusion. Additional determinations are to be performed on the follow-up days 1, 2, 4, 7, 10, and 14 post-infusion and at the safety visit.

- In Children/Adolescents Group I and Group II (6 to < 18 years): at screening visit, on PK dosing day 0 pre-dose of BT524 IV infusion and at 4 and 8 hours post-end of infusion. Additional determinations are to be performed on the follow-up days 1, 7, and 14 post-infusion.

- In Pre-school Children Group III (2 to < 6 years): on PK dosing day 0 pre-dose of BT524 IV infusion and at 1 hour post-end of infusion. Additional determinations are to be performed on the follow-up day 2 post-infusion.

- In Infants and Toddlers (28 days to < 2 years): on PK dosing day 0 pre-dose of BT524 IV infusion, immediately at the end of infusion, and 24 hours post-end of infusion;

- In Newborns Group IV (0 days to 27 days): on PK dosing day 0 pre-dose of BT524 IV infusion and immediately at the end of infusion.

PART II

On-demand prophylaxis/ on-demand treatment

- Without hospitalization: coagulation parameters are to be assessed at screening visit (only for additional patients without participation in PK/PD part I) and on the dosing day pre-dose of BT524 IV infusion, before discharge, and at each optional and safety visit.

- With hospitalization: coagulation parameters are to be assessed at screening visit (only for additional patients without participation in PK/PD part I) and on the dosing day pre-dose of BT524 IV infusion, at 1 hour post-end of infusion and as required, at 24 hours after the end of infusion, from day 2 until the day before

hospital discharge as required, on the day of hospital discharge, and at each optional and safety visit.

14.5.1.4 Determination of Fibrinogen inhibitory antibodies

The routine determination of antibodies directed against fibrinogen epitopes leading to inhibition of fibrinogen activity will be done locally at the screening visit and at the PK safety visit (day 49 +/- 4).

PART I

- In Adults: at screening visit, on PK dosing day 0 pre-dose of BT524 IV infusion and at the safety visit (day 49 +/- 4).
- In Children/Adolescents Group I and Group II: at screening visit, on PK dosing day 0 pre-dose of BT524 IV infusion and at the safety visit (day 49 +/- 4).
- In Pre-school Children Group III: at screening visit (locally and centrally) and at the safety visit (day 49 +/- 4).
- In Newborns/Infants and Toddlers Group IV: at screening visit (locally and centrally) and at the safety visit (day 49 +/- 4).

PART II

- Fibrinogen inhibitory antibodies are to be assessed at screening visit (only for additional patients without participation in PK/PD part I) and at the safety visit (day 49 +/- 4).
- Furthermore the investigators can decide to undertake further determinations during the clinical trial pre-dose of BT524 IV infusion depending on the clinical course of the patient and suspicion of Fibrinogen inhibitor development of the individual patient.

The development of Fibrinogen inhibitory antibodies has to be reported as serious adverse event (SAE).

Patients who have developed Fibrinogen inhibitor antibodies have to be withdrawn from the study and standard treatment or prophylaxis of bleeding has to be initiated by the investigator / treating physician.

14.5.1.5 Safety Laboratory

The following safety laboratory parameters will be determined:

Hematology
- RBC
- WBC
- Platelet count
- Hemoglobin
- Hematocrit

Clinical chemistry
- aspartate aminotransferase
- alanine aminotransferase
- γ-glutamyltransferase

- alkaline phosphatase
- total bilirubin
- creatinine
- urea
- potassium
- sodium
- calcium
- chloride

Urinalysis
- pH
- Qualitative investigation for
  - pH
  - blood
  - white blood cells
  - protein
  - glucose
  - ketone bodies
  - nitrite
  - bilirubin
  - urobilinogen

Time points for the assessment of safety laboratory parameters are given in the study flow charts (see **section 3**).

PART I

In part I, safety laboratory parameters are to be determined:

- In Adults: at screening visit, on PK dosing day 0 pre-dose of BT524 IV infusion, and on the follow-up days 1, 2, 4, 7, 10, and 14 post-infusion (see study flowchart for pharmacokinetics, **section 3.1**).
- In Children/Adolescents Group I and Group II: at screening visit, on PK dosing day 0 pre-dose of BT524 IV infusion, and on the follow-up days 1, 2, 7, and 14 post-infusion (see study flowchart for pharmacokinetics, **section 3.2 and 3.3**).
- In Pre-school Children Group III: at screening visit, on PK dosing day 0 pre-dose of BT524 IV infusion, and on the follow-up day 2 post-infusion (see study flowchart for pharmacokinetics, **section 3.4**).
- In Newborns/Infants and Toddlers Group IV: at screening visit (biochemistry and urine analysis), and on PK dosing day 0 pre-dose of BT524 IV infusion (hematology). Additional determinations (hematology and biochemistry) on the follow-up day 1 (24 hours post-infusion) are to be performed only in infants and toddlers (see study flowchart for pharmacokinetics, **section 3.5**).

PART II

On-demand prophylaxis/ on-demand treatment
- Without hospitalization: safety laboratory parameters are to be determined at screening visit (only for additional patients without participation in PK/PD part I) and on the dosing day 0 pre-dose of BT524 IV infusion, before discharge, and at each optional visit as required.

- With hospitalization: safety laboratory parameters are to be determined at screening visit (only for additional patients without participation in PK/PD part I) and on the dosing day 0 pre-dose of BT524 IV infusion and as required post-end of infusion, at 24 hours post-end of infusion as required, from day 2 until the day before hospital discharge as required, on the day of hospital discharge as required, and at each optional visit as required. In all cases, they are to be determined at least once after the last infusion of BT542 and before discharge.

Safety laboratory parameters will be determined at the local laboratory. Details on collection, processing and handling of blood samples are described in the laboratory manual.

All safety laboratory blood and urine samples will be tested on an ongoing basis and will be destroyed after successful analysis.

14.5.1.6 Determination of Immunoglobulin Classes in Case of Anaphylaxis and/or Inhibitor Development

Immunglobulin E is to be determined in Adults and Children/Adolescents Group I and Group II (≥ 6 years) on PK dosing day 0 pre-dose of BT524 IV infusion. In any patient developing anaphylaxis and/or inhibitors to fibrinogen, data on IgE against fibrinogen will be determined and recorded.

14.5.1.7 Ultrasonography Imaging

The ultrasonography is an imaging technique used in the study to visualize thromboembolic events (e.g., deep vein thrombosis). Detailed instruction on the performance of the ultrasonography will be provided in the ultrasonography guidance manual.

PART I

In part I, ultrasonography imaging will be performed at screening visit, during the 14 day pharmacokinetic sampling period assessment whenever a thrombosis or TEE is suspected, and on follow-up day 14 (see study flowcharts for pharmacokinetics, **section 3**).

PART II

On-demand prophylaxis/ on-demand treatment

- Without hospitalization: ultrasonography imaging are to be performed at screening visit (only for additional patients without participation in PK/PD part I) and on the dosing day pre-dose, post-end of infusion whenever a thromboembolic event is suspected, and at the safety visit if a thrombosis or TEE is suspected.
- With hospitalization: ultrasonography imaging are to be performed at screening visit (only for additional patients without participation in PK/PD part I) and on the dosing day pre-dose and from post-end of infusion until day of hospital discharge whenever a thrombosis or TEE is suspected.

14.5.1.8 Electrocardiogram (ECG)

PART I

Standard ECG assessments are to be performed at screening visit, on PK dosing day 0, 6 hours post-end of BT524 IV infusion, and on follow-up day 1 (see study flowcharts for pharmacokinetics, **section 3**). The ECG print outs are signed by the investigator (= source document) and placed in the patient's chart.

PART II

Standard ECG assessments are to be performed at screening visit only for additional patients without participation in PK/PD part I.

14.5.1.9 Pregnancy Test

PART I

In all women of childbearing potential a negative pregnancy test (test sample either from urine) must be available at screening visit, on PK dosing day 0 pre-dose of BT524 IV infusion and on the follow-up day 14 (see study flowchart for pharmacokinetics, **section 3**).

PART II

In part II, a pregnancy test (urine) must be confirmed negative before each elective surgery and/or bleeding event on screening visit (only for additional patients without participation in PK/PD part I) and on dosing day 0 pre-dose. At each optional visit and at the safety visit (in case of a prematurely withdrawn from study participation) a further pregnancy test (urine) will be performed.

14.5.1.10 Viral Safety

Several pre- and post-dose serum samples (5 ml each) are to be taken from each patient participating in the study. The samples are to be collected and stored at -70 °C for possible future testing. Sample collection and processing are described in the laboratory manual.

PART I

A serum sample is to be drawn on PK dosing day 0 pre-dose of the BT524 IV infusion for analysis, and as retention sample. At the safety visit, a serum sample is to be drawn as retention sample (day 49±4 after the administration of BT524).

PART II

On-demand prophylaxis/ on-demand treatment

- Without hospitalization: a serum sample is to be drawn on dosing day pre-dose and at each safety visit (day 49±4 after the last administration of BT524).
- With hospitalization: a serum sample is to be drawn on dosing day pre-dose and at each safety visit (day 49±4 after the last administration of BT524).

14.5.1.11 Retention Samples

All retention samples collected for local or central determination or for possible future testing (e.g., suspected transmission of an infective agent) will be destroyed after successful analysis, if applicable and finalization of the study report. This applies also for laboratory samples described in the efficacy chapter (refer to **sections 14.4.3.1** and **14.4.5**).

14.5.1.12 Assessment of Risk and Burden in Newborns, Infants and Toddlers, Children and Adolescents

At each study visit the investigator will assess and document whether the risk and burden imposed on each paediatric patient (0 to < 18 years) by participation in the study are acceptable. This has to be documented on a separate form.

14.5.2 Methods for Assessing, Recording and Analyzing Safety Parameter(s)

All laboratory results have to be evaluated in the eCRF according to the following pattern:

a) outside reference range but not clinically relevant (e.g. due to already known conditions, due to sampling conditions, only marginal deviation, due to underlying diseases in the study population)
b) outside reference range and clinically relevant.

Laboratory values which are outside the reference range and assessed as clinically relevant have to be controlled and documented as adverse events if they occur for the first time after administration of investigational medicinal product BT524.

If abnormal laboratory values are signs of an adverse event (e.g. an infection) that has already been reported during the present study, this has to be stated but the respective abnormal laboratory value does not constitute a separate adverse event.

14.6 Adverse Events

14.6.1 Definitions

Adverse Event (AE)

Any unfavorable or unintended sign, symptom, or disease that appears or worsens in a patient or clinical investigation subject during the period of observation in a clinical study. The AE may be any of the following:

- A new illness
- An exacerbation of a sign or symptom or the underlying condition under treatment or of a concomitant illness
- Unrelated to participation in the clinical study or an effect of the study medication or comparator drug
- A combination of one or more of the above factors

No causal relationship with the study medication is implied by the use of the term "adverse event".

Planned or elective surgical or invasive procedures for pre-existing conditions that have not worsened are not AEs.

However, any complication that occurs during a planned or elective surgery is an AE. Conditions leading to unplanned surgical procedures may be AEs.

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 from the time the subject/patient receives his/her first dose of study drug until his/her last study visit will be considered a treatment emergent AE (TEAE).

Immediately Reportable Adverse Event (IRAE)

Immediately reportable AEs (IRAEs) are AEs that must be reported to the Sponsor within 24 hours of the study site being informed of the IRAE.

Immediately reportable AEs include

- All Serious Adverse Events (SAEs)
- All AESIs
- AEs that result in a patient's withdrawal from the study (including TEE, fibrinogen inhibitory antibody, suspected allergic reaction)
- Pregnancy

Serious adverse event (SAE)

An SAE is any untoward medical occurrence or effect that at any dose:

- Results in death,
    - *death is an outcome of an AE and not an AE itself. All deaths, regardless of cause or relationship must be reported for patients on study.*
- Is life-threatening,
    - *life-threatening means that the patient was at immediate risk of death from the event as it occurred. This does not include an event that might have led to death if it were more severe.*
- Requires hospitalization or prolongation of existing hospitalization,
    - *complications that occur during hospitalizations are AEs. However, if a complication prolongs hospitalization or requires new hospitalization, it is an SAE. In-patient hospitalization means the patient has been formally admitted to a hospital for medical reasons, for any length of time, which may or may not be overnight. It does not include presentation and care within an emergency department. If a patient experiences an AE during dosing and remains in hospital until the AE resolves, this is not considered an SAE unless the investigator considers that the event would have required hospitalization*
- Results in persistent or significant disability or incapacity,
- Is a congenital anomaly or birth defect, or
- Is another medically important condition

An important medical event that is not immediately life threatening or will result in death or hospitalization, but which may jeopardize the patient or may require medical intervention to prevent one of the outcomes listed above, should be reported as “serious” as well.

Medical and scientific judgment should be exercised in deciding whether a case is serious.

“Occurring at any dose” does not imply that the patient is receiving study drug at the time of the event.

Adverse Event of Special Interest (AESI)

An AE of special interest (serious or non-serious) is one of scientific and medical concern specific to the sponsor's IMP or development program, for which ongoing monitoring and immediate communication by the investigator to the sponsor may be appropriate. Such events may require further investigation in order to characterize and understand them. Reporting / Notifying requirements are detailed in section 14.6.4.

The following AEs have been defined as AESI for this study: Thrombosis or TEE, and suspicion of transmission of infective agents (viral safety).

Severity of Adverse Event:

Refers to the extent to which an AE affects the patient's daily activities. Severity will be categorized according to the criteria shown in Table 6.

Table 6: Severity of Adverse Event

Mild:	The AE does not interfere with the patient's routine activities.
Moderate:	The AE interferes with the patient's daily routine, but usual routine activities can still be carried out.
Severe:	The AE results in the inability to perform routine activities.

The term "severity" is used to describe the intensity of an event. This is not the same as "serious". Seriousness, not severity, serves as the guide for defining regulatory reporting obligations. The highest severity grade attained should be reported, for AEs with divergent severities.

Causality of Adverse Event:

Refers to the relationship of the AE to study drug. Causality will be categorized according to the following criteria:

Not related:

AEs for which a reasonable explanation for an alternative cause is considered plausible e.g., no study drug taken, plausible clinical alternative like accidental injury, expected progression of underlying or concomitant disease, pharmacologically incompatible temporal relationship, intercurrent illness.

Related:

AEs for which a reasonably possible clinical and/or pharmacological relationship to study drug cannot be excluded e.g., lacking plausible alternatives.

14.6.2 Recording Adverse Events

In this study adverse events will be recorded electronically in the eCRF.

Period:

- **Patient Enrolment to the First Administration of Study Drug:** Non-treatment emergent AEs will be recorded from the time when the patient is enrolled into the study (date of signature of the informed consent) until first administration of study drug.

- **After Administration of Study Drug until respective 49 day visit (Part I and Part II):** All TEAEs will be recorded.
- **In-between individual 49 day periods or after last 49 day visit:** Any serious treatment emergent AE considered to be related to the study medication by the investigator will be recorded.

If an AE (serious or not) started after administration of study drug but did not end before the 49 day visit, the investigator should make a reasonable effort to establish the outcome and the end date. If this is not possible, the outcome recorded at the 49 day visit will be assumed to be the final outcome.

If an event stops and later restarts, all the occurrences must be reported. AEs assessed as related to study medication by the investigator and all SAEs must be followed up until resolution.

The investigator should attempt to establish a diagnosis of the event based on signs, symptoms and/or other clinical information. In such cases, the diagnosis should be documented as the AE and/or SAE and not the individual signs/symptoms. Signs/ symptoms should be documented only if a diagnosis cannot be established. If a diagnosis is accompanied by unusual symptoms, the diagnosis itself and the symptoms have to be reported separately.

In addition to the definition as given, the following special types of events should be recorded:

- Laboratory values that are outside the normal range and if, in the opinion of the investigator, these values represent a clinically relevant change versus pre-treatment values are also defined as AEs.
  If abnormal laboratory values are signs of an AE (e.g. an infection) that has already been recorded, the respective abnormal laboratory value does not constitute a separate AE. Wherever reasonable the reporting investigator will use the clinical term rather than the laboratory term (e.g., anemia versus low hemoglobin value).

14.6.2.1 Responsibilities of Investigator

AE data should be obtained through observation of the patient, from any information volunteered by the patient, or through patient questioning. The general type of question asked could be similar to: “Do you have any health problems?” or “Have you had any health problems since your last clinic visit?”

AEs are to be documented/ recorded accurately and completely on the AE pages of the respective eCRF and in the patient's source data.

All non-treatment emergent AEs will be recorded. During an individual 49 day period all TEAEs are to be recorded. In between individual 49 day periods or after last 49 day visit all serious TEAE considered to be related to the study medication by the investigator will be recorded.

This is true even if the study drug was not administered according to the study protocol.

For conditions leading to unplanned surgical procedures the underlying condition, should be documented as an AE, but not the procedure.

All known information regarding IRAEs must be recorded on the AE log of the eCRF **within 24 hours** of the study center being informed of the IRAE. For IRAEs, all other eCRF pages must be updated or completed as necessary. Electronic CRFs that must be completed for all IRAEs are: patient identification, study drug accountability, demographics, medical history, and concomitant medication. This information must be completed within 24 hours of the study center being informed of the IRAE.

For all IRAEs where important or relevant information is missing, active follow-up should be undertaken.

If for the further evaluation of an AE additional information is required by Biotest's Corporate Drug Safety department, then a representative of the sponsor must be granted access to the medical records. A respective statement has to be integrated in the written informed consent form to ensure adequate assessment of all AEs. Investigators also have the duty to assist in the elucidation of cases and if requested to provide a final written opinion.

- **Follow-up of Adverse Events**
  Adverse events should be followed up to determine the outcome.

  AEs that are serious or severe or considered related to the study medication or study procedures must be followed up by the investigator until the AE is resolved or resolved with sequelae, and until all queries related to the AE have been clarified. If the subject had an AE with fatal outcome, an autopsy report should be provided if possible.

  If AEs that are serious or severe or considered related to study medication or study procedures are ongoing at the time of the subject's last study visit, or if the subject has clinically relevant laboratory parameter abnormalities at the last study visit, one or more safety follow-up visit should be scheduled for those subjects. The investigator should set the interval to the additional Safety follow-up visit according to his/her medical judgment. Follow-up activities should be continued until the investigator considers it medically justifiable to stop further follow-up.

  All other AEs must be followed up by the investigator until the AE is resolved or resolved with sequelae or the end of the period of observation (= last study visit), whichever comes first.

  The investigator should respond to any queries raised by the sponsor in relation to adverse events, including provision of supporting documentation for SAEs or other IRAEs (e.g. ECG data, laboratory results, hospital summary, autopsy report) within the requested timeline. In case of fatal or life-threatening SAEs the sponsor may request urgent clarification within one calendar day. In general, if for AEs requiring immediate reporting from investigator to sponsor (IRAE/SAE) follow-up information becomes available, this must be reported to the sponsor **within 24 h** of becoming aware of this information (i.e. the same timeframe as for initial IRAE/SAE reports). Any supporting documents have to be identified by the patient number, and personal data (e.g. subject name, address or phone number) obliterated prior to sending to the sponsor. For details on reporting IRAE/SAE see section 14.6.4.

  Adverse event data in the CRF must be updated accordingly when follow-up information is received.

All efforts to collect follow-up information must be documented in the subject's source data.

Subjects who were treated with the study medication but did not complete the study as per protocol, should receive all the examinations and investigations scheduled for the last study visit. The investigator should make all efforts to contact subjects lost to follow-up and document the attempts in the subject's source data.

14.6.2.2 Responsibilities of Sponsor

For purposes of safety analyses all AEs will be recorded in the clinical database. To ensure the basis for expedited and periodic notification of authorities, IRAEs will be additionally recorded in the drug safety database of the sponsor.

14.6.3 Evaluation of Adverse Events

14.6.3.1 Responsibilities of Investigator

To permit standardized assessment of AEs, the investigator will evaluate amongst others the seriousness, severity and causality of each AE using the AE pages of the eCRF.

The seriousness, severity and causality of each AE will be evaluated by the investigator in accordance with the definitions in **section 14.6.1.**

Causality of AE:

For all AEs a causality assessment must be provided, even if based on preliminary data, and documented on AE page of the eCRF.

14.6.3.2 Responsibilities of Sponsor

The causality assessment given by the investigator will not be downgraded by the sponsor. If the sponsor disagrees with the investigator's causality assessment, both the opinion of the investigator and the sponsor will be recorded.

14.6.4 Notifying of Adverse Events

14.6.4.1 Responsibilities of Investigator

In this study AEs will be reported electronically from the site to the sponsor using the eCRF.

All known information regarding IRAEs (SAEs, AESIs, pregnancy, and AEs leading to withdrawal) must be recorded on the AE log of the eCRF **within 24 hours** of the site learning of the event (see also section 14.6.2.1).

In case the electronic system is not function 24 hours, SAE paper forms will be provided to be used in the case of an IRAE. The paper forms will also need to be faxed or e-mailed to the sponsor within 24 hours of the site learning of the AE.

<u>Adverse Event Reporting Contact:</u>

For questions regarding IRAEs, or to provide information that cannot be provided electronically via the eCRF, or to notify the sponsor of an IRAE in the event of technical failure, the investigator should contact:

Biotest AG – Department Corporate Drug Safety
Fax: +49 6103 / 801 - 854
E-mail: **Error! Hyperlink reference not valid.**drugsafety@biotest.com

Any requested supporting documentation (e.g., discharge summary, ECG, laboratory results, autopsy report) should be sent to the sponsor's Corporate Drug Safety department using the contact details provided above.

Prior to forwarding any personal data for safety reporting reasons, it needs to be ensured that the documents are coded in a way that keeps patient's identity confidential (e.g., by using the patient's identification code, randomization number).

If required, the investigator is responsible for informing local IECs/IRBs of safety reports in compliance with applicable regulatory requirements. Copies of all correspondence relating to reporting of any safety reports to the EC/IRB should be maintained in the Investigator Site File / Regulatory Binder.

14.6.4.2 Responsibilities of Sponsor

Biotest's Corporate Drug Safety department is responsible for fulfilling all obligations regarding notification of Regulatory Authorities and IECs/ IRBs according to applicable regulatory requirements (expedited and periodic reporting, e.g. serious unexpected suspected adverse reactions, Development Safety Update Report). In addition, the sponsor will be responsible for information of investigators according to the current legislation.

14.6.4.3 Pregnancy Reporting

In the unlikely event that a woman becomes pregnant during the study this is reported within 24 hours of the site learning of the situation using the "Drug Exposure via Parent Report Form" paper form and the contact details as above. The investigator should make any reasonable effort to follow-up the pregnancy until birth of the child; and will report all outcomes associated with the pregnancy to the sponsor.

14.6.4.4 Investigational Product Complaints

Complaints associated with the investigational medicinal product must be recorded in the eCRF and reported to the sponsor **within 24 hours** of the investigator becoming aware of the IMP complaint, using the “Investigational Medicinal Product Complaint” report form. In case of corresponding AEs related to suspected quality defects, the AEs have to be entered in the respective eCRF pages (AE page/ IRAE page).

Any complaint samples should be provided to the sponsor upon request.

15 STATISTICS

The statistical planning and evaluation of the study will be carried out by a qualified statistician in accordance with the ICH-guidelines and adequate biostatistical SOPs. A detailed Statistical Analysis Plan (SAP) will be prepared at the latest before data base lock.

15.1 Calculation of Sample Size

The primary objectives of this study are key PK parameters. For the PK parameters no formal sample size calculation is 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 (maximal clot firmness), 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 in the study population consisting of patients with congenital fibrinogen deficiency (i.e., a- or severe hypofibrinogenemia) prior to BT524 treatment and 1 hour after treatment will be measured by Fib-tem S of ROTEM.

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 $\alpha = 0.05$ (2-sided) significance level.

15.2 Statistical Methods

The statistical planning and evaluation of the study will be carried out by a qualified statistician in accordance with the ICH-guidelines and adequate biostatistical SOPs. A more detailed description of the statistical analysis will be provided in the SAP. The SAP is to be finalized and approved prior to database lock.

All analyses of this open-label study will be performed on the intent-to-treat (ITT) as well as the per protocol (PP) population. ITT population will include all patients who received at least any portion of BT524. The PP population will include all patients who received at least 90 % of the planned total dose of BT524, met all inclusion and no exclusion criteria, complied with the protocol procedures and had no major deviations impacting on study analysis.

Statistical tests will be performed descriptively. 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 p-value less than 0.05 will be considered statistically significant.

Only descriptive analyses will be performed to compare the efficacy results of study 984 with the results from published clinical trials (Manco-Johnson 2009 and Peyvandi 2006).

15.2.1 Populations for Analysis

Four study populations will be defined for analysis:

Part I PK/PD

Intent-to-treat population (ITT) / Full Analysis Set (FAS)
All patients, who received any portion of BT524, are part of the ITT population.

Per protocol population (PP)
The PP population consists of all patients of the ITT population, who will have received at least 90 % of the planned total dose of BT524, met all inclusion criteria and none of the exclusion criteria and won't have received any alternative fibrinogen-containing blood product during the specimen collection phase (until day 14).

The PP population will exclude all patients of the ITT population who finish the study with major protocol deviations (e.g. patients who have received any fibrinogen concentrate and/or fibrinogen-containing product within two weeks prior to infusion of BT524) or who terminate the study prematurely due to an event which could be possibly related to the study medication. Classification of protocol deviations as major or minor will be agreed upon between sponsor and study statistician prior to the database lock.

Pharmacokinetic per protocol population (PK PP)
The PK PP population consists of all patients of the PP population of the part I, who will have provided PK data.

Safety population
The safety population comprises of all patients who were exposed to BT524 (equal to ITT).

Part II ODP/ODT
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; in addition efficacy analysis for bleeding events and surgical interventions will be analyzed as repeated measurements per subject in the ITT and PP populations.

15.2.2 General Methodology

All data collected will be analyzed using appropriate descriptive statistical methods using SAS® version 9.2 or higher for the production of all tables, listings and figures and for the statistical analysis. 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.

Data will be summarized with respect to demographic and baseline characteristics, efficacy and safety observations and measurements.

Tabulations will be presented for each parameter and will be sorted by age group and gender, if applicable. Generally, for presentation overall totals of the cohort will be provided.

15.2.3 Demographic Data and Other Baseline Characteristics

Assessments made at screening visit and at PK Dosing Day 0 (pre-dose) will be summarized for the total of the sample (all patients enrolled) and by the sample of patients treated with BT524 using descriptive statistical methods only. These assessments will include demographic and other relevant baseline characteristics (medical history, physical examination, previous or concomitant medication, vital signs, etc.). 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.

15.2.4 Primary Objective

The following standard PK parameters of BT524/fibrinogen will be derived from plasma antigen concentration data measured at each documented time point using adequate PK analysis software:

- Terminal Elimination Half-life ($t_{1/2}$) for fibrinogen antigen
- Time to reach Maximum Concentration (t_{max})
- Maximum Concentration (C_{max})
- Area Under the Concentration-Time Curve (AUC) calculated to the last measured concentration (AUC(0-t)) and extrapolated to infinity (AUC(0-inf)
- Clearance (CL)
- Mean Residence Time (MRT)
- Volume of Distribution (V_{ss})
- Incremental Recovery (IR)
- Classical in vivo recovery (IVR)

A more detailed algorithm/software used for the calculation of the PK parameters will be provided in the statistical analysis plan.

Descriptive statistical methods will be employed to show the distribution of each parameter in the whole population and within each subgroup. Further population PK modelling analysis will be investigated to allow analysis of the sparse sampling data obtained in the children < 6 years and the research of influence of covariate on the PK behavior.

Similar approach will be used for the analysis of the fibrinogen activity.

15.2.5 Efficacy Analysis

Secondary Objectives

Descriptive statistical methods will be employed for all secondary variables of efficacy. Details will be given in the statistical analysis plan.

Part I

For analysis of PD, the same software will be used to determine the respective parameters with fibrinogen activity data.

Surrogate efficacy parameter MCF, assessed by fib-tem S, will be evaluated by a one sample t-test (pre-/post-comparison) and presented in a tabular format and/or graphical format. This analysis will be confirmatory for the 1 hour post-end of infusion assessment.

Part II

Efficacy will be evaluated based on ODP and/or ODT of bleeding events (i.e. surgical procedures, spontaneous or post- traumatic severe bleeding). Response will be assessed by the investigator by means of a 4 point scale (‘none’, ‘moderate’, ’good’, and ’excellent’). Response rates will be presented with 95 % confidence intervals both considering each event as an individual case and considering events as repeated measurements within the same patient, if applicable (e.g. by General estimation equations with intra-subject correlation structure). Additionally, type of surgery, loss of blood intra- and postoperatively, quality of wound healing, units of other fibrinogen-containing products, and units of transfusion products will be considered. Moreover,

the consumption of BT524 required for effective treatment (bleeding events; pre-, intra-, post-operatively) will be calculated. Furthermore, MCF as a surrogate efficacy parameter will be evaluated also in part II of the study (non-confirmatory).

Details will be described in the statistical analysis plan.

15.2.6 Safety Analysis

Adverse events (AEs) will be coded by means of the MedDRA® dictionary. Incidence rates (i.e. number and percentage of affected patients) will be calculated for the coding levels *system organ class* and *preferred term*. Further analyses of AEs will focus on seriousness, intensity, causal relationship to study medication, and outcome. Serious adverse events (SAEs) will be displayed in detail.

Safety laboratory assessments will be categorized with respect to the laboratory specific reference ranges as normal/abnormal. Abnormal values will be further classified with respect to clinical relevance. Changes over time will be described by means of “shift-tables”.

Safety analysis will be based on the safety population.

Descriptive methods will be applied for all variables of safety. Details will be provided in the statistical analysis plan.

15.2.7 Further Statistical Issues

A detailed description of statistical analyses will be provided in the SAP which will be finalized prior to data base closure.

In case of missing efficacy data (e.g. due to premature discontinuation) the last-observation-carried-forward (LOCF) principle will be applied, if appropriate.

16 DATA MANAGEMENT

16.1 Data Collection

Study data will be directly entered via eCRF into the study database on a central server by authorized investigator and/or study personnel. Automatic and manual queries according to the data validation plan will be generated by the data management department and sent through the EDC (electronic data capture) system for clarification to the investigator. Corrections will be entered directly into the system. This procedure will be repeated until all queries are solved. All query forms are linked to the eCRF in the EDC system.

The complete data management (data capture, data entry, data validation, checks on plausibility, query handling, data editing after entry, coding, data base closure, etc.) will be defined in advance within a data handling plan/ data management plan together with a description of the personnel responsible for data entry performance and controlling and specific data handling procedures.

The final data will be transported to the SAS-system for subsequent data analyses in accordance with the statistical analysis plan.

MedDRA will be used for coding of Adverse Events. Concomitant medication will be coded of the **A**(natomical) **T**(herapeutical **C**(hemical)-code, levels 2-5. For coding of concomitant diseases, MedDRA will be used, too.

16.2 Correction of Data

All corrections and changes of original data are recorded in an audit trail including all former and present values. The audit trail records all changes made, the reason for change, at what time they were done and by whom. The audit trail cannot be changed. The Investigator is obliged to keep the database up-to-date at all times, i.e., data are to be entered by the Investigator preferably on the same day as the respective patient contact. Only the authorized investigator and/or study personnel can change data.

16.3 Data Handling

Data cleaning and coding will be carried out by data managers and qualified persons for medical coding, respectively. After data entry by authorized investigator and/or study personnel and source data verification, logical and numerical plausibility checks will be performed. All study specific data management procedures will be described in the data management plan and data validation checks specification.

16.3.1 Deviations from the Study Protocol

Deviations from the protocol will be judged during the study and/or when an individual patient's eCRF is completed and monitored.

Before closure of the data base, responsible persons will decide which patients have to be considered as major/minor protocol violators (as defined in the statistical analysis plan) in the statistical analysis.

17 QUALITY CONTROL AND QUALITY ASSURANCE

17.1 Study Initiation Activities

The investigator(s) will be informed about objectives and methods of the study, the inclusion and exclusion criteria, the time-schedule, and the applied procedures by means of a pre-study visit by the monitor (if necessary), an investigators' meeting prior to start of the study, and during the site-initiation visit by the monitor.

17.2 Training of Site Staff

The Principal Investigator needs to ensure that all persons assisting with the clinical study are adequately informed about the protocol, the IMP and their study related duties and functions. Furthermore the Principal Investigator is requested to maintain a list of appropriately qualified persons to whom the investigator has delegated significant study-related duties.

17.3 Documentation and Filing

<u>eCRF-System</u>
For present clinical study the EDC system AptivAdvantage will be used for online data entry, data validation and data management.

All data to be recorded according to this study protocol must be documented in the eCRF. The investigator will be instructed how to complete the eCRF. For each patient a separate eCRF record will be created and completed. For the selected patient record

the study number, the screening number and patient number will be displayed in the eCRF. The Investigator must ensure that the patient's pseudonymity will be maintained.

Entries in the eCRF must only be made by the Investigator or persons authorized by the investigator. A list of all persons who are allowed to make entries in the eCRF must be available at each study site.

Corrections to case report forms may only be carried out by persons listed on the site signature and delegation log.

The investigator must verify that all data entries in the eCRF are accurate and correct.

Entries are to be checked against appropriate source documentation by the monitor.
An archiving CD or DVD with the PDFs containing all study data or study data of the specific site will be sent to Biotest and the Investigator respectively.

List of study participants (patient identification log)
The investigator is asked to keep a confidential list of names of all patients participating in the study, giving reference to the patients' records. With the help of this list it must be possible to identify the patients and their medical records. In addition, the investigator is asked to keep a list of all patients screened on a screening log to document identification of patients who entered pre-study screening. In case of non-eligibility a reason is to be provided.

Source data
Source data is all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical study necessary for the reconstruction and evaluation of the study. Source data are contained in source documents which comprise clinical documentation, data, and records (e.g., hospital records, clinical and office charts, laboratory notes, memoranda, patients' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, patient files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical study).

Investigator Site File / Regulatory Binder
Before site initiation the CRO will provide an Investigator Site File / Regulatory Binder to each study site. The investigator site file will include essential documents as defined by the ICH GCP guideline and applicable local requirements.

The investigator will be responsible for the continual update and maintenance of the investigator site file, which will be periodically reviewed by the monitor(s). In case of an audit by the sponsor or an inspection by the Regulatory Authorities these documents will be reviewed.

All study related documents are to be archived and stored according to legal requirements.

Prior to destruction the investigator will contact Biotest AG for approval and conformation of such.

17.4 Monitoring

The monitor is responsible for checking the quality of data and adherence to the study protocol and to legal and ethical requirements according to local laws and GCP.

The interval between monitoring visits will be dependent on the recruitment rate and the complexity of the study. Source data verification is an essential part of the monitoring process and the investigator must grant direct access to the study participants' source data. The extent and nature of monitoring will be described in detail within the monitoring plan.

17.5 Audits and Inspections

Audits will be performed according to the corresponding audit program, including the possibility that a member of the sponsor's quality assurance function may arrange to visit the investigator in order to audit the performance of the study at the study site, as well as all study documents originating there. Audits may also be performed by contract auditors. In this case, the sponsor's quality assurance function will agree with the contract auditor regarding the timing and extent of the audit(s). In case of audits at the investigational site, the monitor will usually accompany the auditor(s).

Inspections by regulatory authority representatives and IECs/IRBs are possible at any time, even after the end of study. The investigator is to notify the sponsor immediately of any such inspection. The investigator and institution will permit study-related monitoring, audits, reviews by the IEC/IRB and/or Regulatory Authorities, and will allow direct access to source data and source documents for monitoring, audits, and inspections.

17.6 Archiving

After evaluation and reporting of the study data, all documents relating to the study will be kept in the archives of the sponsor and the study site(s) according to applicable regulatory requirements.

18 GENERAL REGULATIONS, AGREEMENTS AND ORGANISATIONAL PROCEDURES

18.1 Study Administrative Structure

Details for the study administrative structure are kept as a separate list filed in the TMF.

18.2 Written Agreements

A written agreement will be set up between Biotest and each investigator setting out any arrangements on delegation and distribution of tasks and obligations and, if appropriate, on financial matters.

18.3 Insurance/Liability

In accordance with the relevant national regulations, the sponsor has taken out patient liability insurance for all patients who have given their consent to the clinical study. The study participants are insured against injury caused by study medication or participation. The study participants will be informed about the insurance and their own responsibilities and duties.

The insurance company issuing the policy is defined by the Insurance Certificate for Clinical Trials for the respective county. This certificate will comply with the country-specific legal requirements.

18.4 Investigator's Brochure (IB)

The investigator will be informed about current knowledge concerning the study medication through an IB for this study. All investigators will be informed immediately about relevant new information available.

18.5 Amendments to the Protocol

Changes to the Clinical Study Protocol must be made in the form of an amendment that has the prior written approval of Biotest and – as applicable – of the appropriate IEC/IRB and regulatory authority.

Amendments, submission(s) and approvals(s) will be distributed to the concerned study site(s).

Amendments in order to eliminate immediate hazard to patients may be implemented before the approval of the ethics committee and/or Regulatory Authorities after consultation with Biotest.

In the event that a significant deviation from the protocol is anticipated based on the patients status, or occurs during the protocol due to an accident or mistake, the investigator or his/her designee must contact the sponsor at the earliest possible time. This will allow an early joint decision to be made as to whether or not the patient should continue in the study. This decision will be documented by both the investigator and sponsor.

18.6 Confidentiality

The objectives and contents of this clinical study as well as its results are to be treated as confidential and may not be made accessible to third parties.

18.7 Final Report and Publication

For each study an integrated final report according to ICH-requirements will be produced. At the end of the study the sponsor will provide the competent authority and IEC/IRB with a summary of the clinical study report within 6 months after the end of the study, where required.

It is generally recommended that the results of clinical studies be presented at congresses and symposia and/or published in scientific journals. Prior to their publication, all results of medical tests with the sponsor's products, and/or publications

or lecture manuscripts concerning such results, should be reviewed and discussed by the coordinating investigator and the sponsor by mutual agreement.

Each investigator is obligated to keep data pertaining to the study secret. He/she must consult with the sponsor before any study data are published.

The legitimate interests of the sponsor, such as acquiring optimum patent protection, coordinating submissions to the health authorities or coordination with other studies in the same field that are underway, protection of confidential data and information, etc. will be given due consideration by all partners involved.

For the present study, the pharmacokinetics of BT524 will be analyzed and reported in a separate report before the finalization of the study.

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20 APPENDICES

Appendix 20.1

Dosage for Newborns, infants and children

The dose should be determined according to the BW and the clinical need.

The reconstituted solution of BT524 should be administered intravenously (IV) via an infusion pump with an adapted infusion rate below 5 ml/min based on the age of the paediatric patient.

A recommendation for infusion rates of BT524 in the paediatric population is presented in the table below. Nevertheless, selection of the infusion rate remains principally at the discretion of the treating paediatrician (investigator) considering the exact clinical situation of the patient.

Table: Recommended infusion rates of BT524 in the paediatric population

Age Group	Infusion rate ml/min[§]	Infusion rate ml/h[§]
Adults	5.0	300.0
12 to <18 years	5.0	300.0
6 to <12 years	5.0	300.0
4 to <6 years	1.0	60.0
2 to <4 years	0.75	45.0
3 months to <2 years	0.30	18.0
28 days to <3 months	0.30	18.0
Newborns (0 to 27 days)	0.10	6.0

[§] *Fibrinogen solution at 20mg/ml.*

Appendix 20.2

Growth charts for children and adolescents

Pediatric growth charts consist of a series of percentile curves that illustrate the distribution of selected body measurements in children and adolescents. Pediatric growth charts are tools that contribute to forming an overall clinical impression for the child being measured. Growth charts are not intended to be used as a sole diagnostic instrument.

Growth is not only a result of nutrition but also a result of inherited factors. Ethnicity can influence a child's growth patterns, and so some countries have their own growth charts. However, the World Health Organization's (WHO) growth charts are used most often and considered the standard around the world.

The WHO Child Growth Standards (World Health Organization 2018, World Health Organization 2018)

The following web sites present growth reference data for children and adolescents:

WHO Weight-for-age GIRLS Birth to 13 weeks (percentiles)

WHO Weight-for-age GIRLS Birth to 5 years (percentiles)

WHO Weight-for-age GIRLS 5 to 10 years (percentiles)

WHO Weight-for-age BOYS Birth to 13 weeks (percentiles)

WHO Weight-for-age BOYS Birth to 5 years (percentiles)

WHO Weight-for-age BOYS 5 to 10 years (percentiles)

Appendix 20.3

Recommendation for the 'Assessment of Bleeding Events'

Type of event (post traumatic bleeding / surgery / spontaneous bleeding)	**Event description**	**Assessment of event** (major / minor)
post traumatic bleeding	subcutaneous hematoma	minor
post traumatic bleeding	small injury	minor
post traumatic bleeding	hemarthrosis / joint bleed / bone bleed / muscular bleed / synovectomy	minor or **major** (depending on extent of event)
spontaneous bleeding	bone cyst bleed / intra medullar bleed	minor
spontaneous bleeding	rectorrhagia / anal fissures	minor or **major** (depending on extent of event)
spontaneous bleeding	muscular hematoma	minor or **major** (depending on extent of event)
spontaneous bleeding	hemoperitoneum	**major**
spontaneous bleeding	intracerebral bleeding	**major**
spontaneous bleeding	spontaneous hemarthrosis	**major**
surgery	circumcision	minor
surgery	gingival bleeding / gingivitis	minor
surgery	dental surgery 1-2 teeth (dental implant / dental extraction / implant replacement / root canal treatment)	minor
surgery	dental surgery ≥ 3 teeth (dental implant / dental extraction / implant replacement / root canal treatment)	**major**
surgery	major surgery, e.g. splenectomy, appendectomy	**major**