Clinical Study Protocol

Title: A randomized, active-controlled, multicenter, phase III study investigating efficacy and safety of intra-operative use of BT524 (human fibrinogen concentrate) in subjects undergoing major spinal or abdominal surgery (AdFIrst)

Short Title: AdFIrst - Adjusted Fibrinogen replacement strategy

Clinical Phase:	III
Version incl. date:	Final 4.0 of 04-DEC-2019
EudraCT Number:	2017-001163-20
Study No.:	995

Sponsor

PPD

Coordinating Investigator

PPD

Overview of Amendments integrated in the protocol text of Version 4.0 of 04-DEC-2019

Amendment No / CSP Version	Date	Sections concerned	Rationale
1 / CSP V2.0	26-APR-2018	Signature Page, Synopsis, 2, 3, 4, 6, 7, 8, 9, 10	Introduction of a new Biostatistician. Update with clarification of wording, corrections and formatting. Revision of the protocol to eliminate inconsistencies between different protocol sections.
1 / CSP V2.0	26-APR-2018	Flowchart, 3, 7, 9	Clarification regarding the time-period between screening and baseline and the need of repeated assessments and diagnostic tests at these visits.
1 / CSP V2.0	26-APR-2018	Synopsis, 4	Incomplete exclusion criterion 4 was complemented.
1 / CSP V2.0	26-APR-2018	3	Clarification of treatment algorithm.
1 / CSP V2.0	26-APR-2018	6	Clarification of treatment algorithm resulted in a revised definition for prohibited medication (section 6.10). Restructuring of section 6.11 'Warnings and Precautions'.
1 / CSP V2.0	26-APR-2018	9, 11	Update and clarification regarding the handling of laboratory samples and the assessment of results.
2 / CSP V3.0	07-JUN-2019	Signature page, Introduction, 4	Introduction of a new BiostatisticianPPD Update with clarification of wording, corrections and formatting.
2 / CSP V3.0	07-JUN-2019	Synopsis, Flowchart, 3, 4, 7, 9, 10	Intra-operative inclusion criterion was adapted. Based on patients' bodyweight and clinical condition, the clinical need of FFP transfusion during surgery can already occur after a clinically relevant bleeding of approximately 1 liter. Instead of measurement and calculation of blood loss prior to the 'decision to treat', in case of a clinically relevant bleeding an estimation of blood loss will take place.
2 / CSP V3.0	07-JUN-2019	4.2	Inclusion criterion 4 aims to ensure that only patients without hereditary bleeding disorders are to be included in this study. Therefore, a footnote for clarification of wording was included.
2 / CSP V3.0	07-JUN-2019	Synopsis, Flowchart, 3, 6, 7, 9	The dosage was adapted in order to avoid under-dosing of subjects. The first BT524 treatment was changed to a minimum dose of 2 g. The option for repeated dosing with IMP was included. The wording of the

Amendment No / CSP Version	Date	Sections concerned	Rationale
			secondary endpoints was adapted accordingly. The dose justification was updated.
2 / CSP V3.0	07-JUN-2019	Flowchart, 7	The time points '90 minutes after treatment start' and 'end of the surgery' can be close together. In this case, blood samples do not have to be taken at both times. Update with clarification of wording. The option for repeated dosing with IMP was included.
2 / CSP V3.0	07-JUN-2019	7	Clarification of wording regarding the re-screening of subjects.
2 / CSP V3.0	07-JUN-2019	9.3, Appendix 2	Update and clarification regarding the definition of Adverse Events of Special Interest (AESI) and the respective reporting procedures.
3 / CSP V4.0	04-Dec-2019	Cover Page, Signature page, 1, 9	Introduction of a new Biostatistician PPD . General update with clarification of wording, corrections and formatting.
3 / CSP V4.0	04-Dec-2019	Synopsis 2, 3, 5, 7.2, 8.1	Study synopsis, study objectives and study design have been modified to extend the target population of the study to allow inclusion of subjects undergoing pseudomyxoma peritonei surgery (only applicable in the United Kingdom) and to introduce the active comparator cryoprecipitate in this treatment group.
3 / CSP V4.0	04-Dec-2019	4.1 and 4.2, 6.6	Update in order to take particular account of subjects with pseudomyxoma peritonei.
3 / CSP V4.0	04-Dec-2019	Synopsis, 3, 4.2, 6.1, 6.6, 7	Clarification of wording of the intra-operative inclusion criterion.
3 / CSP V4.0	04-Dec-2019	Synopsis, 10	Update with clarification of wording and revision to include interim analyses. Following the Data Monitoring, the assumed standard deviation has been adjusted and the power has been reduced.
3 / CSP V4.0	04-Dec-2019	19	Update of scientific literature mainly regarding the inclusion of subjects with pseudomyxoma peritonei.

I. SIGNATURE PAGE

PPD

I.I 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 subject in this study.
  - To obtain informed consent for all subjects 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 subject 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 all Adverse Events

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, Case Report Forms, and other scientific data.

Principal Investigator
Name

_____
Date, signature

Investigator stamp:

Please insert stamp of investigational site

II. STUDY SYNOPSIS

Title	A randomized, active-controlled, multicenter, phase III study investigating efficacy and safety of intra-operative use of BT524 (human fibrinogen concentrate) in subjects undergoing major spinal or abdominal surgery (AdFIrst)
Clinical Phase	III
Coordinating Investigator	PPD
Study Objectives	The main purpose of this phase III study is to demonstrate the efficacy of BT524 as a complementary therapy to management of uncontrolled severe hemorrhage in subjects undergoing elective major spinal or abdominal surgery. The **primary objective** of this study is to demonstrate that BT524 is non-inferior that means not worse than fresh frozen plasma (FFP)/cryoprecipitate with a non-inferiority margin of 150 mL in reducing intra-operative blood loss by intravenous (IV) administration in subjects with acquired hypofibrinogenaemia undergoing elective major spinal or abdominal surgery. If therapeutic equivalence (non-inferiority) has been demonstrated, therapeutic superiority of BT524 compared with FFP/cryoprecipitate will also be assessed. **Secondary objectives** are to demonstrate the efficacy of BT524 by assessing the correction of the fibrinogen level intra-operatively, the transfusion requirements, post-operative blood loss in the first 24 hours, the number of subjects with rebleeds, the hospital length of stay and the in-hospital mortality. Secondary objectives also comprise the safety of BT524 by documenting the number of adverse events (AE) including changes in laboratory parameters, the virus status, and the frequency and severity of thrombosis and of thromboembolic events (TEEs).
Study Design	Prospective, randomized, active-controlled, multicenter, non-inferiority study
Study Population	Adult subjects (≥ 18 years) of both gender undergoing elective spinal or abdominal surgery with expected major blood loss
Inclusion Criteria	**<u>At screening:</u>** 1. Written informed consent 2. Subjects scheduled for elective major spinal or cytoreductive pseudomyxoma peritonei (PMP)[1] surgery with expected major blood loss 3. Male or female, aged ≥ 18 years 4. No increased bleeding risk as assessed by standard coagulation tests and medical history

[1] Only applicable for subjects in the United Kingdom (UK)

	5. Intra-operative trigger for treatment: **a. Subjects undergoing spinal surgery:** Intra-operative clinically relevant bleeding of approximately 1 L, requiring hemostatic treatment during surgery. **b. Subjects undergoing cytoreductive PMP surgery[2]:** Intra-operative prediction of clinically relevant bleeding of > 2 L, requiring hemostatic treatment during surgery.
Exclusion Criteria	1. Pregnancy or unreliable contraceptive measures or breast feeding (women only) 2. Hypersensitivity to proteins of human origin or known hypersensitivity reactions to components of the Investigational Medicinal Products (IMP) 3. Participation in another clinical study within 30 days before entering the study or during the study and/or previous participation in this study 4. Treatment with any fibrinogen concentrate and/or fibrinogen-containing product within 30 days prior to infusion of IMP 5. Employee or direct relative of an employee of the Contract Research Organization (CRO), the study site, or Biotest 6. Inability or lacking motivation to participate in the study 7. Medical condition, laboratory finding (e.g. clinically relevant biochemical or hematological findings outside the normal range), or physical exam finding that in the opinion of the investigator precludes participation 8. Presence or history of venous/arterial thrombosis or TEE in the preceding 6 months
Number of Subjects	100 evaluable subjects per treatment arm
Countries / Number of Study Sites	Multicenter, multinational, Europe / 15-20 sites **EU and Switzerland:** Spine surgery, FFP as comparator **United Kingdom:** PMP surgery, cryoprecipitate as comparator
Investigational Medicinal Products (IMP)	**BT524** (human fibrinogen concentrate) and **FFP** (fresh frozen plasma) and **cryoprecipitate** **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 IV infusion. **FFP** refers to the liquid portion of human blood that has been frozen and preserved after a blood donation and will be used for blood transfusion.

[2] Only applicable for subjects in the UK

	Cryoprecipitate is made from FFP which is frozen and repeatedly thawed in a laboratory to produce a source of concentrated clotting factors including fibrinogen, factor VIII, factor XIII, von Willebrand factor (vWF) and fibronectin and platelet microparticles.
Dosage and Mode of Administration	**Subjects undergoing spinal surgery:** **BT524,** administered intravenously: Dosage according to FIBTEM A10 values to restore baseline fibrinogen level: **BT524 dose (g) = [baseline FIBTEM A10 - actual FIBTEM A10] x actual body weight (BW) /140** **First dose at least 2 g**, subsequent intra-operative infusions as required. **FFP**, administered intravenously: Dosage according to local standards; the recommended dose of FFP is 15 mL per kg body weight (BW). Subsequent intra-operative infusions as required.
Duration of Treatment	**Single or repeated intra-operative administration of IMP.** *Follow-up per subject:* Each subject will be followed for at least 5 weeks, with clinical and laboratory data collected on visits scheduled on Days 2, 3, 5 and 8, and the closing visit, scheduled on Day 36* after the day of surgery (*+35, up to Day 71 if required).
Criteria for Evaluation ***- Efficacy***	***Primary Endpoint:*** • Intra-operative blood loss after decision to treat the subject with IMP until the end of surgery as measured by amount of blood from the blood suction unit and amount of blood from surgical cloths and compresses. ***Secondary Endpoints:*** • Proportion (%) of subjects with successful correction of fibrinogen level 15 minutes after start of first IMP administration • Time to first successful correction of fibrinogen level • Total amount of transfusion products (allogenic blood products) or autologous blood transfusion infused after start of first IMP administration until end of surgery • Amount of red blood cells (allogenic and autologous RBCs) infused after start of first IMP administration until end of surgery • Post-operative blood loss in the first 24 hours • Proportion (%) of subjects with rebleeds after the end of surgery until Day 8 • Hospital length of stay after surgery • In-hospital mortality

- Safety	***Secondary Endpoints:*** • AEs • Changes in vital signs • Changes in clinical laboratory assessments of hematology, clinical chemistry, and urinalysis • Changes in clinical laboratory assessments of markers of coagulation • Changes in clinical laboratory assessments of coagulation factors • Frequency and severity of thrombosis and of TEEs • Virus status
Biostatistical Concept	Assuming a blood loss of about 500 mL in the FFP-/cryoprecipitate-treatment arm after the decision to treat the subject with IMP until the end of surgery, a standard deviation of 375 mL, a non-inferiority margin of 150 mL, and an alpha-level of 2.5% (1-sided) 100 evaluable subjects per treatment arm are needed to demonstrate the non-inferiority of BT524 by using a t-test with 80% power. The sample size was calculated with nQuery Advisor Version 4.0 or higher. The primary endpoint is intra-operative blood loss after the decision to treat the subject with IMP until the end of surgery. The primary analysis of this endpoint will test for non-inferiority. The final analysis will be performed using analysis of covariance (ANCOVA) with the predictive blood loss (> 1,000 mL to ≤ 2,000 mL and > 2,000 mL) as a covariate. Non-inferiority will be demonstrated if the upper confidence limit of the 2-sided 95% confidence interval for the difference in the least square means is less than the non-inferiority margin (150 mL). If non-inferiority is demonstrated, then superiority will be assessed. **Interim analyses:** In this study, 3 interim analyses with an alpha-adjustment according to Haybittle/Peto (Haybittle, 1971; Peto et al., 1976; Schulz and Grimes, 2005) are planned. This leads to local alpha levels of 0.001 for each interim analysis, a significance level of 0.05 for the final analysis, and to an overall global alpha level of 0.05. All interim analyses will be based on the per-prototocl set. The first interim analysis is planned with approximately 50 spine subjects, the second one with at least 40 PMP subjects and all other evaluable spine subjects at that time-point. The third interim analysis is planned with approximately 80% of subjects of the total sample size. Aim of all interim analyses is to adapt the sample size according to the observed blood losses and the standard deviations:

	a.) Early termination due to non-inferiority of BT524 in comparison with the used standard therapies. b.) Continuation with the sample size as initially planned. c.) Adjustment of sample size to take into account changes from the previous assumptions on the additional blood loss. d.) Stopping the study early due to futility if the sample size re-estimation indicates a much higher number than planned before. All secondary efficacy endpoints will be summarized descriptively by treatment arm. The secondary endpoints of proportion of subjects with a successful correction of fibrinogen level and proportion of subjects with rebleeds will be compared between the treatment arms using a Cochran-Mantel-Haenszel (CMH) approach stratified by predictive blood loss. The secondary endpoint 'time to first successful correction of fibrinogen level' will be compared between the treatment arms using a Chi-Square test. The secondary endpoints of consumption of transfusion products, amount of RBCs and post-operative blood loss in the first 24 hours will be analysed using ANCOVA with the predictive blood loss as a covariate. Safety will be assessed based on AEs, laboratory data, vital signs data, frequency and severity of thrombosis and of TEE and virus status which will be summarized descriptively. An independent Data Safety Monitoring Board (DSMB) will review unblinded safety data at regular intervals during the study. After 40 subjects have completed, the overall mean and standard deviation of the primary endpoint will be derived using blinded data of all 40 subjects without separating according to treatment to assess if the sample size needs to be adjusted.
First Subject In	Q1 2018
Last Subject Last Visit *(planned)*	Tbd

Confidentiality Statement

III. FLOWCHART OF STUDY

Study Schedule **Day**	**D-42 to D-1**	**D-2 to D1**	**D1**	**D1**	**D1**	**D1**	**D2**	**D3**	**D5**	**D8**	**D36** (+35)
Assessments **Visit**	**Screening**	**Prior surgery** (Baseline)	**Surgery**				**Follow-up**	**Follow-up**	**Follow-up**	**Follow-up**	**Closing**
			prior 1st dose	**pre-dose**	**post-dose**	**end of surgery**					
Informed Consent	•										
Check/re-check of inclusion / exclusion criteria	•	•[1]									
Demographic data	•										
Classification of type of spine surgery	•										
Recording expected blood loss		•									
Body weight	•	•[2]									
Physical examination	•	•[2]					•	•	•	•	•
Pregnancy test, only in females of childbearing potential	•	•[2]									
Medical and surgical history	•	•[3]									
Viral safety: Collection of retention sample	•										•
Virus serology (hepatitis B, hepatitis C, HIV)	•										•
Vital signs	•	•	•	•	•	•	•	•	•	•	•
Hematology and clinical chemistry	•	•[2]	•			•	•	•	•	•	•
Urinalysis	•	•[2]					•	•		•	•
Markers of coagulation (coagulation activation tests)	•	•[2]	•		•[4]	•[5]	•	•	•	•	•
Plasma concentration of fibrinogen activity (Clauss assay)	•	•[2]	•		•[4]	•[5]	•				
FIBTEM A10 (ROTEM)	•	•[2]	•	•	•[4]	•[5]	•				
Maximum clot firmness (MCF) (ROTEM)	•	•[2]	•	•	•[4]	•[5]	•				

[1] Diagnostic tests will be repeated at the investigator's discretion.
[2] Diagnostic tests have to be done prior to surgery. In case of short time-period between screening and baseline (≤ 2 days) these tests have only to be repeated based on medical judgment of the investigator. If not repeated, screening results will serve as baseline.
[3] Previous medication: change from screening.
[4] Tests have to be done only 15 and 90 minutes after start of 1st IMP administration.
[5] Tests for *markers of coagulation and plasma activity of fibrinogen (Clauss assay, FIBTEM A10, MCF)* have to be done '90 min after start of 1st IMP administration' and at the 'end of surgery'. In case of a short time-period between these two time-points (<30 min) these tests have only to be repeated based on medical judgment of the investigator.

Study Schedule **Day**	**D-42 to D-1**	**D-2 to D1**	**D1**	**D1**	**D1**	**D1**	**D2**	**D3**	**D5**	**D8**	**D36** (+35)
Assessments **Visit**	**Screening**	**Prior surgery** (Baseline)	**Surgery**				**Follow-up**	**Follow-up**	**Follow-up**	**Follow-up**	**Closing**
			prior 1st dose	**pre-dose**	**post-dose**	**end of surgery**					
Coagulation factors		•	•		•[6]						
Intra-operative inclusion criteria			•								
Intravenous infusion(s) of IMP (BT524 or FFP)			•[7]								
Recording start/end of surgery			•			•					
Continuous measurement of blood loss from start of surgery			•			•	•				
Calculation and recording of blood loss						•[8]	•[9]				
Recording time of decision to treat the subject with IMP			•								
Order of IMP			•	•							
Randomization			•								
Rebleeding episodes						•	•	•	•	•	
Concomitant medication or treatment			•			•	•	•	•	•	•
Transfusion products			•			•	•	•	•	•	•
Adverse events	•	•	•			•	•	•	•	•	•

[6] Test has to be done only 90 minutes after start of 1st IMP administration.
[7] Total volume and total infusion time (start and end of each infusion) to be recorded.
[8] Intra-operative blood loss from time-point of decision to treat the patient with IMP until end of surgery.
[9] Recording of blood loss until 24 hours after end of surgery.

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V. LIST OF ABBREVIATIONS

ADR	Adverse Drug Reaction
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALAT	Alanine aminotransferase
ANCOVA	Analysis of Covariance
AP	Alkaline phosphatase
aPTT	Activated partial thromboplastin time
ASAT	Aspartate aminotransferase
AT III	Antithrombin III
BDRM	Blind Data Review Meeting
BUN	Blood Urea Nitrogen
BW	Body Weight
CDS	Corporate Drug Safety
CHMP	Committee for Medicinal Products for Human Use
CMH	Cochran-Mantel-Haenszel
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CRO	Contract Research Organization
DEVP	Drug Exposure Via Parent
DIC	Disseminated Intravascular Coagulation
DOAC	Direct Oral Anti-Coagulants
DSMB	Data Safety Monitoring Board
eCRF	electronic Case Report Form
EDC	Electronic Data Capture
EMA	European Medicines Agency
IEC	Ethics Committee
IRB	Institutional Review Board
FAS	Full Analysis Set
FII	Factor II
FV	Factor V
FVII	Factor VII
FVIII	Factor VIII
FIX	Factor IX
FX	Factor X
FXI	Factor XI
FXIII	Factor XIII
F_{1+2}	Prothrombin Fragments 1+2
FAS	Full Analysis Set
FFP	Fresh Frozen Plasma
GCP	Good Clinical Practice
ɣ-GT	Gamma glutamyltransferase
IB	Investigator's Brochure
HAV	Hepatitis A Virus
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HEV	Hepatitis E Virus

HIV	Human Immunodeficiency Virus
ICF	Informed Consent Form
IMP	Investigational Medicinal Product
ICH	International Conference on Harmonization
i.e.	id est
INR	International normalized ratio
IRAE(s)	Immediately Reportable Adverse Event(s)
IV	Intravenous
IWRS/IVRS	Interactive Web/Voice Response System
MCF	Maximum Clot Firmness
MedDRA®	Medical Dictionary for Regulatory Activities
NTEAE	Non-Treatment Emergent Adverse Event
NIMP	Non-Investigational Medicinal Product
PC	Protein C
PEI	Paul-Ehrlich-Institut, Germany
PHI	Protected Health Information
PPS	Per-Protocol Set
PS	Protein S
PMP	Pseudomyxoma peritonei
PT(INR)	Prothrombin Time (International Normalized Ratio)
QBL	Quantification of Blood Loss
RBC	Red Blood Cells
ROTEM	Rotational Thromboelastometry
SAE	Serious Adverse Event
SAF	Safety Analysis Set
SAP	Statistical Analysis Plan
SAS	Statistical Analysis Software
SmPC	Summary of Product Characteristics
SOC	System Organ Class
TAT	Thrombin-antithrombin III complex
TEAE	Treatment-Emergent Adverse Event
TEE	Thromboembolic Event
TMF	Trial Master File
TT	Thrombin Time
TXA	Tranexamic Acid
vWF	von Willebrand factor
WBC	White Blood Cells

1 INTRODUCTION

BT524 is a lyophilized, heat-treated fibrinogen concentrate manufactured from human plasma. BT524 is currently developed for the treatment and prophylaxis of bleeding in patients with congenital afibrinogenaemia or severe congenital hypofibrinogenaemia with bleeding tendency. Moreover, BT524 will be developed as complementary therapy to management of uncontrolled severe hemorrhage in acquired hypofibrinogenaemia.

To date, no clinical studies have previously been conducted with BT524 in subjects with acquired hypofibrinogenaemia. The pharmacokinetic properties of BT524 were investigated in the treatment and prophylaxis of bleeding in patients with congenital fibrinogen deficiency (afibrinogenaemia or severe hypofibrinogenaemia) in the ongoing prospective, open-label, phase I/III study PPD Details on the clinical pharmacology of BT524 and further information on non-clinical studies with BT524 are provided in the Investigator's Brochure.

In addition to the ongoing clinical development in congenital fibrinogen deficiency, the present prospective, multi-center, randomized, active-controlled, pivotal phase III study aims to demonstrate the efficacy and safety of BT524 in subjects with acquired hypofibrinogenaemia caused by major surgery associated with major blood loss.

Fibrinogen (coagulation factor I) is a soluble plasma glycoprotein synthesized by hepatic parenchymal cells. The normal blood fibrinogen concentration is between 2.0 and 4.5 g/L although this range can vary (Levy and Goodnough, 2015). 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 case of a fibrinogen deficiency the blood coagulation is disordered, which leads to (severe) hemorrhagic events.

Acquired fibrinogen deficiency is the most common type of fibrinogen deficiency. It is characterized by an impaired hemostatic function caused by fibrinogen concentrations below the normal ranges, classified as hypofibrinogenaemia. Hypofibrinogenaemia results from either reduced fibrinogen synthesis due to hepatic disorders, increased intravascular consumption due to a breakdown of fibrinogen, disseminated intravascular coagulation (DIC) or increased fibrinogen loss caused by certain medical conditions such as surgical procedures or uncontrolled life-threatening bleeding. Acquired fibrinogen deficiency can cause severe intra-operative bleeding. Depending on the severity and the extent of the event (i.e. trauma, surgery) and the patient's clinical condition fibrinogen plasma concentrations are highly variable in acquired fibrinogen deficiency.

Acquired fibrinogen deficiency is associated with increased morbidity and mortality. Thus, effective management of this hemostatic disorder is necessary to prevent potentially life-threatening bleeding, to reduce increased blood loss, transfusion requirements and the risk of surgery (Fenger-Eriksen et al., 2009).

Fibrinogen is an important contributor to clot strength and is the first coagulation factor to become critically reduced during intra-operative hemorrhage (Haas et al., 2012). Therefore, a rapid and accurate determination of fibrinogen level is important during hemorrhage to establish a timely hemostatic intervention. The rapid fibrinogen supplementation to restore plasma levels is an important component for normalizing clot formation in bleeding patients and maintaining fibrinogen levels is an important therapeutic target in bleeding, particular in intra-operative settings (Levy and Goodnough, 2015).

There is growing evidence that fibrinogen levels > 1.5 to 2 g/L are necessary to control major bleeding in the intra-operative settings (Haas et al., 2012; Levy and Goodnough, 2015). Accordingly, European trauma guidelines from 2013 (Spahn et al., 2013) and the guidelines from the European Society of Anaesthesiology (Kozek-Langenecker et al., 2013) recommend target levels of at least 1.5 to 2.0 g/L in intra-operative settings. Because of the large variability in fibrinogen concentrations among bleeding patients, individualized dosing of fibrinogen concentrate based upon both the level of bleeding and the plasma fibrinogen concentration are recommended (Levy et al., 2012). Fibrinogen concentrate infusion guided by point-of-care tests is recommended by the European Society of Anaesthesiology (Kozek-Langenecker et al., 2013) and the FIBTEM test has been used extensively in clinical studies to determine fibrinogen levels and calculate dosing (Levy and Goodnough, 2015).

Nevertheless, the optimal treatment level, the use of pre-emptive treatment and the preferred source of fibrinogen for acquired fibrinogen deficiency remain disputed. Fibrinogen concentrate is increasingly used and recommended for bleeding with acquired hemostatic deficiencies in several countries, but evidence is inconsistent regarding surgery settings, dosing and efficacy. Fresh frozen plasma (FFP) also contains fibrinogen and is available in all hospital settings and is comparatively cheap but requires the administration of large quantities of FFP to achieve a reasonable fibrinogen dose. Therefore, further clinical studies investigating fibrinogen replacement in acquired fibrinogen deficiency are needed.

Currently, conventional replacement therapy in fibrinogen deficiency consists of transfusion of allogenic blood products such as **FFP** and **cryoprecipitate.**

FFP is a blood product that has been available since 1941. Initially used as a volume expander, it is currently indicated for the management and prevention of bleeding in coagulopathic patients (Nascimento et al., 2010).

FFP is the liquid portion of blood that contains all the clotting factors, as well as other blood proteins and that is stored by freezing (WHO 2007). FFP is usually authorized nationally. Examples of FFP authorized in Germany are available from the website of the German authority Paul-Ehrlich-Institut (PEI). A solvent/detergent treated frozen plasma (PPD by PPD) is nationally approved in several EU countries (PPD).

Compared to fibrinogen concentrate FFP is stored frozen and must be thawed before use which is a limitation in time critical and potentially life-threatening situations such as severe bleeding. FFP contains 2.0 to 4.5 g/L of fibrinogen which is much lower than in fibrinogen concentrates (i.e. up to 10-fold lower than in BT524 with 20 g/L). Since FFP contains relatively low amounts of fibrinogen, it requires the administration of large volumes to provide meaningful increases in the fibrinogen plasma level. The large volumes carry the risk of hypervolemia, cardiac stress, circulatory overload, transfusion-related acute lung injury, hypothermia and metabolic complications once bleeding resolves (Bornikova et al., 2011; Elliott and Aledort, 2013; Mumford et al., 2014; Ofosu et al., 2008). Furthermore, the use of allogenic blood confers an additional risk for blood borne pathogens. Also noteworthy is the risk for transfusion related reactions, immune suppression, and a decrease in coagulation factors. There is also evidence that transfusion of allogenic blood is increasingly harmful as more blood is transfused (Verma et al., 2015).

As the concentration of fibrinogen in fibrinogen concentrates is markedly higher than in plasma the required dose to reach the fibrinogen target concentration can be administered in a minor volume. Furthermore, the amount of fibrinogen in FFP varies making it difficult to predict the increase in plasma fibrinogen concentration. The precisely defined fibrinogen content in fibrinogen concentrates allows accurate calculation of the amount of reconstituted concentrate needed for a targeted fibrinogen supplementation.

Cryoprecipitate is made from FFP and contains various proteins including fibrinogen. It contains higher concentrations of fibrinogen than FFP and some (but not all) coagulation factors, so less volume is needed. The minimum amount of fibrinogen required by standards of the American Association of Blood Banks is 150 mg per bag of cryoprecipitate; current preparations yield a median of 388 mg per bag, but the amount of fibrinogen is variable and cannot be determined accurately. A single unit of cryoprecipitate also contains variable amounts of FVIII, FXIII, von Willebrand factor (vWF), fibronectin and platelet microparticles (Callum et al., 2009). Therefore, the use of cryoprecipitate for fibrinogen replacement alone exposes the patient to potentially unneeded coagulation proteins which could increase the risk of thrombosis (Elliott and Aledort, 2013; Franchini and Lippi, 2012). Cryoprecipitate was withdrawn from most European countries some years ago because of safety concerns (Karkouti et al., 2018; Schochl et al., 2013) but remains available in Scandinavia, the UK and the USA, essentially for the purpose of fibrinogen replacement.

In summary fibrinogen concentrate seems to have certain advantages over other replacement therapies like FFP and cryoprecipitate, such as precisely determined high amounts of purified fibrinogen dissolved in a small volume, low risk of pathogen transmission and instant administration without need for thawing or testing AB0 blood group compatibility (Warmuth et al., 2012).

A number of clinical studies have been published in subjects with acquired hypofibrinogenaemia, such as following trauma, cardiothoracic surgery and obstetric hemorrhage, documenting that fibrinogen concentrate is able to improve clotting function and reduce blood loss. The results of these studies have shown that fibrinogen concentrate raises the levels of fibrinogen and improves clot firmness. Additionally, fibrinogen substitution has been reported to reduce bleeding and post-operative transfusion requirements. Published data from completed clinical studies in subjects undergoing major surgeries not only suggest that fibrinogen plays a critical role in achieving and maintaining hemostasis; in particular, they appear to show benefit of individualized dosing of fibrinogen concentrate using a target ROTEM/FIBTEM value integrating rapid diagnostic testing with appropriate therapeutic dosing of fibrinogen concentrate in line with patients' needs (Haas et al., 2015; Rahe-Meyer et al., 2013a; Rahe-Meyer et al., 2009a; Rahe-Meyer et al., 2013b; Rahe-Meyer et al., 2009b; Ranucci et al., 2015). In a prospective, randomised, single-center, controlled phase 2 study, published in 2019 (PPD), 45 adult subjects undergoing cytoreductive surgery for pseudomyxoma peritonei (PMP) were treated pre-emptively with fibrinogen concentrate or cryoprecipitate. Subjects were randomised to one of the two treatment groups (4 g fibrinogen concentrate or 2 pools cryoprecipitate), when assessment after the start of surgery predicted intra-operative blood loss ≥ 2 L without targeted fibrinogen replacement. Further intra-operative doses were based on thromboelastometry (FIBTEM A20 < 12 mm). Haemostatic efficacy was successful in 100% of subjects in both groups, with similar blood loss. No thromboembolic events (TEEs) occurred in subjects who received fibrinogen concentrate.

The published data indicate that fibrinogen concentrate is at least comparable with cryoprecipitate in terms of benefits for haemostatic therapy in the treatment of clinically relevant bleeding associated with acquired fibrinogen deficiency in subjects undergoing cytoreductive surgery for PMP (Roy et al., 2019).

As there is no guideline on the clinical investigation of fibrinogen in patients with uncontrolled severe hemorrhage in acquired hypofibrinogenaemia available, the EMA guideline on core SmPC for human fibrinogen products (EMA, 2015a) has been taken into account when planning this phase III study in acquired fibrinogen deficiency. Furthermore, currently ongoing clinical studies with fibrinogen concentrate as well as recently finalized clinical studies in this clinical setting (Roy et al., 2019) have been considered.

BT524 will be developed as complementary therapy to management of uncontrolled severe hemorrhage in acquired hypofibrinogenaemia caused by major surgeries associated with major blood loss. As it is expected that BT524 will show a safety advantage over the standard treatment with FFP/cryoprecipitate, an efficacy comparison to the standard is required to allow a risk-benefit assessment to be made for BT524.

Therefore, the present prospective, multi-center, randomized, active-controlled, pivotal phase III non-inferiority study aims to investigate efficacy and safety of BT524 in subjects with acquired hypofibrinogenaemia.

2 STUDY OBJECTIVES

The main purpose of this phase III study is to demonstrate the efficacy of BT524 as a complementary therapy to management of uncontrolled severe hemorrhage in acquired hypofibrinogenaemia in subjects undergoing elective major spinal or abdominal surgery.

The primary objective of this study is to demonstrate that BT524 is non-inferior that means not worse than FFP/cryoprecipitate with a non-inferiority margin of 150 mL in reducing intra-operative blood loss by IV administration in subjects with acquired hypofibrinogenaemia undergoing elective major spinal or abdominal surgery.

If therapeutic equivalence (non-inferiority) has been demonstrated, therapeutic superiority of BT524 compared with FFP/cryoprecipitate will also be assessed.

Secondary objectives are to demonstrate the efficacy of BT524 by assessing the correction of the fibrinogen level intra-operatively, the transfusion requirements, post-operative blood loss in the first 24 hours, the number of subjects with rebleeds, hospital length of stay and in-hospital mortality. Secondary objectives also comprise the safety of BT524 by documenting the number of AEs including changes in laboratory parameters, the virus status, and the frequency and severity of thrombosis and of TEEs.

3 STUDY DESIGN

This is a phase III, prospective, randomized, active-controlled, multicenter, non-inferiority clinical study in subjects undergoing major spinal or abdominal surgery to demonstrate the efficacy and the safety of intra-operative use of BT524 as a complementary therapy to management of uncontrolled severe hemorrhage in acquired hypofibrinogenaemia.

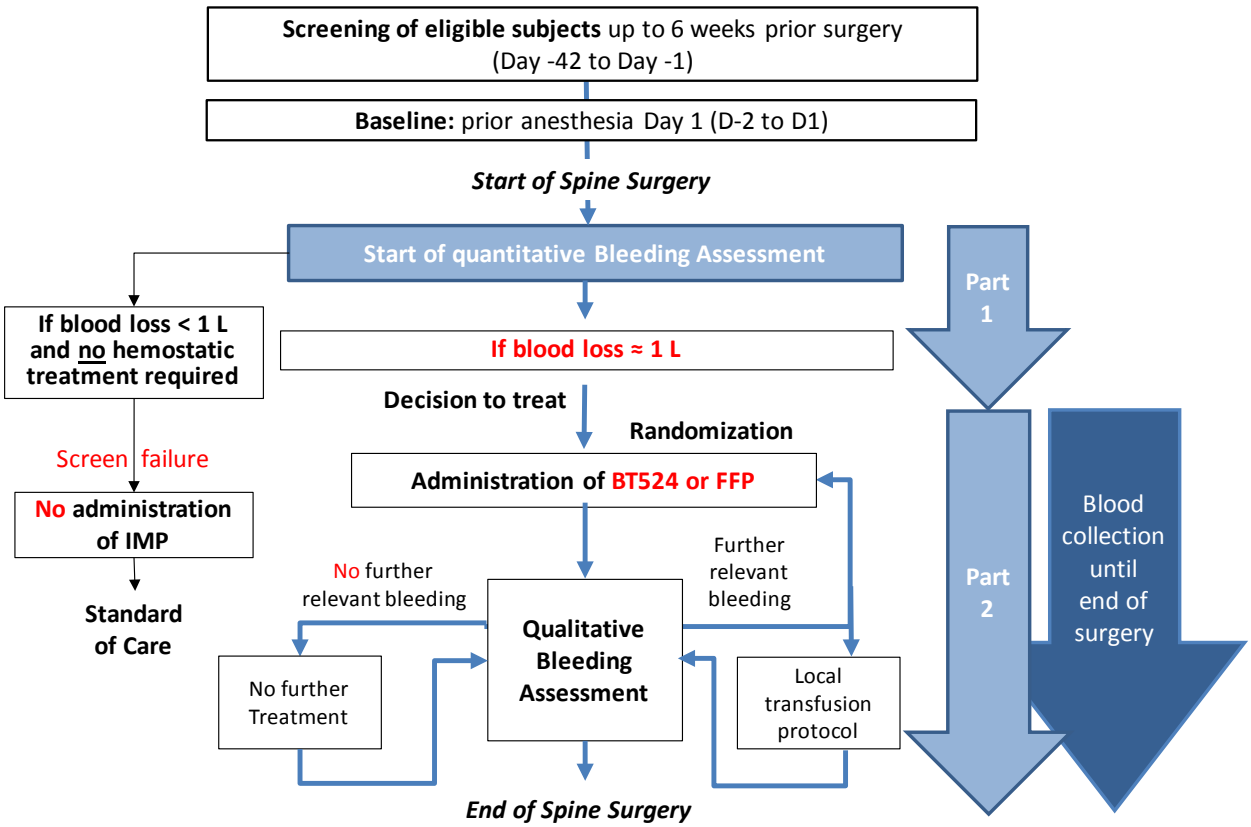
This non-inferiority study is focused on the **primary objective**, to demonstrate that BT524 is non-inferior that means not worse than FFP/cryoprecipitate with a non-inferiority margin of 150 mL in reducing intra-operative blood loss by IV administration in subjects with acquired hypofibrinogenaemia undergoing elective major spinal or abdominal surgery. If therapeutic equivalence has been demonstrated, therapeutic superiority of BT524 compared with FFP/cryoprecipitate will also be assessed.

Secondary objectives are to demonstrate the efficacy of BT524 by assessing the correction of fibrinogen level during surgery, the transfusion requirements, post-operative blood loss in the first 24 hours, the number of subjects with rebleeds, the hospital length of stay and the in-hospital mortality. Secondary objectives also comprise the safety of BT524 by documenting the number of AEs including changes in laboratory parameters, the virus status, and the frequency and severity of thrombosis and of TEEs.

The study comprises a screening visit within 42 days prior to surgery to assess subjects eligibility, a baseline visit on the day of the surgery prior anaesthesia (Day 1, but if required this could be Day -2 or Day -1 due to local hospital procedures), the surgery phase (including randomization, Day 1) and the follow-up phase of at least 5 weeks with 4 follow-up visits on Days 2, 3, 5 and 8 and the closing visit, including the final safety examination, scheduled on Day 36* after the day of surgery (*+35, up to Day 71 if required). The duration of individual study participation for eligible screened subjects is at least 5 weeks.

The study design for subjects undergoing spine surgery is shown in the following figure (Figure 1):

Figure 1: Overview of Study Design



Further details on the assessment schedule (including the follow up period) that will be used for the assessment of the efficacy and safety parameters in this study are presented in the flowchart in section III and in the visit schedule section 7.1.

At least 200 subjects will be enrolled to ensure data are available for 100 evaluable subjects per treatment arm (BT524 or FFP/cryoprecipitate). The multicenter, multinational study will be conducted in approximately 15-20 sites in Europe (subjects undergoing major spinal surgery) and in one site in the United Kingdom (subjects undergoing cytoreductive PMP surgery).

Detailed Description of the Spinal Surgery Phase

The continuous determination/measurement of blood loss during the entire surgery will be separated into two parts:

- **First part:** blood loss will be determined from start of surgery until decision to treat by **estimating** the bleeding mass in the blood suction unit, taking the blood loss in surgical cloths and compresses into account. This is the prerequisite for the intra-operative inclusion criterion (clinically relevant blood loss of approximately 1 L, requiring hemostatic treatment) and the decision to treat the subject with IMP.
- **Second part:** blood loss will be **measured** after decision to treat until end of surgery and represents the blood loss considered for the primary objective. During this part of the surgery the blood loss will be quantified by measuring the continuous bleeding mass removed from the surgical field by a blood suction unit (and/or a cell saver) and by calculation of the amount of blood absorbed by surgical cloths and compresses. In a final step, the total blood loss will be calculated.

Prior to the start of surgery dry surgical cloths and compresses will be weighed (weight recorded), to be available in case a manual compression is required.

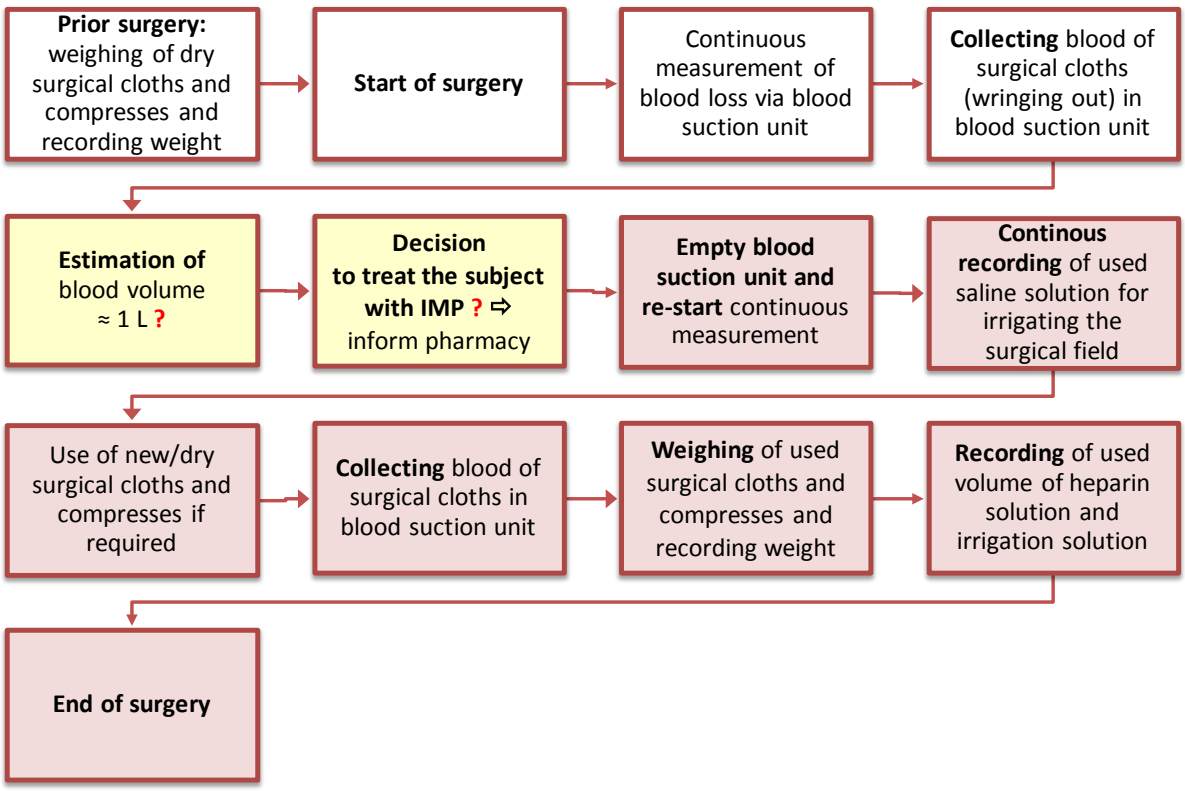
The **first part** of blood measurement starts at the start of surgery with the collection of blood in the blood suction unit: The blood is salvaged by a suction catheter from the operating field. This blood is suctioned into a reservoir which contains a heparinised saline solution (or citrate anticoagulant solution) used for anticoagulation during blood collection. The quantity of anticoagulant introduced into the blood collection system will be adapted continuously to the volume of blood loss.

In case a manual compression is necessary, dry surgical cloths and compresses will be applied to the surgical field, and - at the latest - prior to the decision to treat the subject with IMP removed. By wringing out surgical cloths, the blood can be caught in a kidney dish and finally also be collected in the suction container.

The anaesthesiologist will estimate the blood volume collected in the suction container continuously, taking the blood loss in surgical cloths and compresses into account. Allowance must be made for the presence of heparinised saline solution and irrigation solution. During the surgery, the anaesthesiologist must calculate the amount of solution suctioned into the container through irrigation of the wound. This will be done by knowing the capacity of the irrigation syringe in use and keeping track of the number of times it is used. The anaesthesiologist subtracts these amounts **to estimate the volume of blood in the container.**

The quantification of blood loss (QBL) intra-operatively is shown in Figure 2:

Figure 2: Quantification of Blood Loss Intra-operatively



After an estimated blood loss of approximately 1 L, and the assessment that hemostatic treatment will be required during surgery (high risk for the need of fibrinogen supplementation, either with FFP or BT524), the decision to treat the subject with IMP can be made.

At this point the **time has to be documented**.

Immediately after an estimated blood loss of approximately 1 L, requiring haemostatic treatment during surgery, the pharmacy will be informed about the decision to treat the subject with IMP. The subject will be randomized to one of the treatment arms.

At the same time, the **suction container will be emptied** and all remaining surgical cloths and compresses will be removed from the surgical area.

Blood lost within the surgical field is collected into the blood suction container and the collection can be undertaken with or without further processing via cell saver and reinfusion. Cell savers separate the RBCs by centrifugation, and reinfuse the RBCs. The packed RBCs are collected in a separate bag. The collected RBCs can be reinfused according to institutional practice.

Cell salvage is not recommended by the manufacturers in patients undergoing surgery for malignancy because of the possibility of reinfusion of tumor cells.

The **second part of blood measurement** is initiated with collection of blood in the empty blood suction unit. In addition, in case a manual compression is necessary after decision to treat the subject with IMP, new surgical cloths and compresses will be applied to the surgical area.

Dosing of BT524 will be guided by FIBTEM A10 results and the dose will be calculated according to the predefined formula. However, the first BT524 dose is at least 2 g. The recommended therapeutic dose of FFP is 15 mL per kg BW. IMP dose will be prepared and delivered to the operating room by the pharmacy according to local standards and administered by the unblinded anaesthesiologist.

The content of each syringe with BT524 (1 g fibrinogen concentrate dissolved in 50 mL water for injection) can be administered in less than 20 seconds. FFP can be infused as rapidly as possible by the anaesthesiologist.

In the further course of the surgery, qualitative assessment of bleeding will be used by the spine surgeon to estimate if further bleeding intervention is required. Spine surgeon and surgical staff are blinded to therapy and will inform the anaesthesiologist regarding the bleeding assessment. In addition, FIBTEM A10 should be determined in order to calculate individual BT524 doses. If no further relevant bleeding occurred, surgery will be proceeded to completion.

If the bleeding remained unchanged and an ongoing relevant blood loss will be confirmed or the hemostatic control is not considered sufficient and requires further intervention or a new major blood loss occurred in the course of the surgery, subjects will be treated with repeated IMP administration according to their randomized treatment group or using a transfusion protocol according to local standards.

At the end of the surgery, all surgical cloths and compresses will be removed from the surgical area, wrung out until almost dry (blood will be collected) and weighed (weight will be recorded). The end of surgery is defined as time of last suture.

The fluid volume collected in the blood suction container will be measured and recorded, the proportion of blood, heparinised saline solution and irrigation solution will be calculated and also recorded.

Standardized Transfusion Algorithm

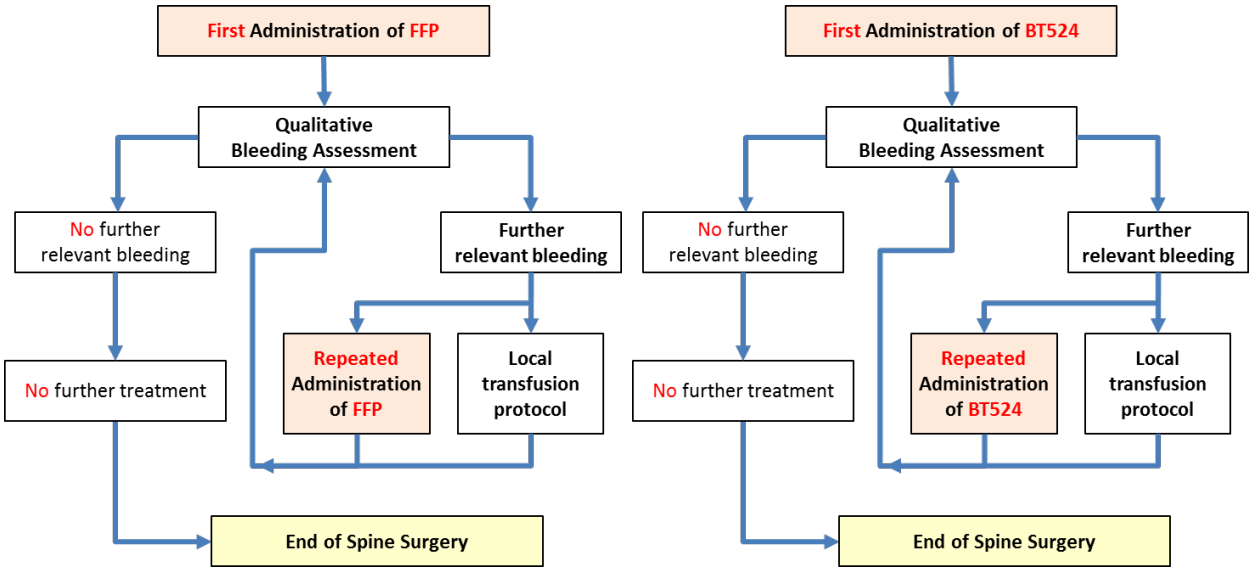
Tranexamic Acid (TXA) can be administered prophylactically in all subjects according to local standards, e.g. TXA 1 g at the start of surgery as a single IV infusion, followed by a further dose of 1 g TXA 6 hours after first dose, if required (in case the surgery is still ongoing).

Repeated IMP Administration

According to the study design and the described treatment algorithm BT524 or FFP will be administered as the primary haemostatic therapy if subjects have clinically relevant bleeding intra-operatively after completion of surgical haemostasis.

If bleeding continued after completion of IMP administration, a transfusion protocol according to local standards can be followed. Repeated intra-operative administration of IMP is possible depending on the subjects' clinical condition and their individual FIBTEM A10 results (Figure 3).

Figure 3: Repeated IMP Administration



The decision to transfuse allogeneic or autologous blood products in the intra-operative period depends on the concentration of hemoglobin, the amount and speed of the blood loss and the clinical condition of the subject at the discretion of the surgeon and/or the anaesthesiologist.

The blood components that can be used for transfusion support are autologous RBC concentrates, derived from intra-operative salvage, allogeneic RBCs, platelet concentrates and allogeneic FFP.

The RBCs collected intra-operatively can be reinfused according to institutional practice.

Furthermore, plasma-derived drugs (e.g. albumin) can be used according to local standards. The total volume (number of units and volume per unit) of all blood components (e.g. RBCs, platelets, FFP) or plasma derivatives (such as albumin and coagulation factors) given intra-operatively will be recorded.

4 STUDY POPULATION

4.1 Study Population, Diagnosis and Number of Subject

A total of at least 200 adult subjects (≥ 18 years) of both gender undergoing elective spinal or abdominal surgery with expected major blood loss are planned to be treated within this study. Eligibility is defined by the inclusion and exclusion criteria as described below. The type of spine surgery is not restricted by the eligibility criteria to surgery for an expected major blood of approximately 1 L. The following table gives examples of the types of spine surgery often associated with severe hemorrhage (Table 1):

Table 1: Examples of Major Spine Surgeries with Expected Large Volume of Blood Loss

Surgeries on spinal meninges and spinal cord
• access to craniocervical junction and cervical spine, dorsal > 2 vertebral segments
• access to thoracic spine, dorsal > 2 vertebral segments
• upper thoracic spine ventral via sternotomy
• access to lumbar spine, dorsal > 2 vertebral segments
Spondylodesis (Spinal Fusion)
• spinal fusion, dorsal > 2 vertebral segments
• spinal fusion, dorsal and ventral approach > 3 vertebral segments
• spinal fusion, ventral approach > 3 vertebral segments
Vertebral body replacement and complex spine reconstruction
Other complex spine reconstructions
• corrective spinal fusion with instrumentation, dorsal
• corrective spinal fusion with instrumentation, ventral
• corrective spinal fusion with instrumentation, dorsal and ventral
Release and scoliosis deformity correction
Complex 360°-reconstruction with fusion, ventrodorsal procedure
Complex 360°-reconstruction with fusion, ventrodorsal procedure after tumor resection
Bony decompression of the spinal canal, ≥ 4 vertebral segments
Re-operations

4.1.1 Gender Distribution

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

Since men and women undergoing elective surgery might suffer from acquired hypofibrinogenaemia, subjects 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 1).

4.2 **Inclusion Criteria**

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

Inclusion Criteria	Rationale	Screening	Intra-operatively
1. Written informed consent obtained from subjects indicating that they understand the purpose of and procedures required for the study and are willing to participate in it	Ethical aspects	X	
2. Subjects scheduled for elective major spinal or cytoreductive PMP surgery with expected major blood loss	Disease requirement	X	
3. Male or female, aged ≥ 18	Study population requirement	X	
4. No increased bleeding risk as assessed by standard coagulation tests and medical history *	Pre-treatment requirement	X	
5. Intra-operative trigger for treatment a. Subjects undergoing spinal surgery: Intra-operative clinically relevant bleeding of approximately 1 L, requiring hemostatic treatment during surgery ** b. Subjects undergoing cytoreductive PMP surgery: Intra-operative prediction of clinically relevant bleeding of > 2 L, requiring hemostatic treatment during surgery ***	Pre-treatment requirement		X

* Inclusion criterion no. 4 aims to ensure that only subjects without hereditary bleeding disorders are to be included in this study.

Subjects with continuous 'aspirin intake', subjects under Direct Oral Anti-Coagulants (DOACs), or with a hepatic disease are at higher bleeding risk. Nevertheless, these subjects can be included at the discretion of the investigator.

** A clinically relevant bleeding, resulting in a high risk for the need of fibrinogen supplementation with BT524 or FFP during surgery. The amount of clinically relevant blood loss depends on the subject's clinical condition, e.g. underlying disease, significant comorbidities, low body weight, relevant change of a laboratory value.

*** Only applicable for subjects in the UK.

4.3 Exclusion Criteria

Subjects having any of the following criteria, either at screening and/or at baseline will not be included in the study:

Exclusion Criteria	Rationale	Screening	Baseline (prior start of surgery)
1. Pregnancy or unreliable contraceptive measures or breast feeding (women only)	Lack of suitability due to not yet established safety in a clinical study	X	
2. Hypersensitivity to proteins of human origin or known hypersensitivity reactions to components of the IMP	Lack of suitability for study due to safety reasons	X	
3. Participation in another clinical study within 30 days before entering the study or during the study and/or previous participation in this study	Lack of suitability for study	X	
4. Treatment with any fibrinogen concentrate and/or fibrinogen-containing product within 30 days prior to infusion of IMP	Lack of suitability for study	X	
5. Employee or direct relative of an employee of the CRO, the study site, or Biotest	Ethical aspects	X	
6. Inability or lacking motivation to participate in the study	Subject compliance	X	
7. Medical condition, laboratory finding (e.g. clinically relevant biochemical or hematological findings outside the normal range), or physical exam finding that in the opinion of the investigator precludes participation	Lack of suitability for study due to safety reasons	X	
8. Presence or history of venous/arterial thrombosis or TEE in the preceding 6 months	Lack of suitability for study due to safety reasons	X	

4.4 Subjects Withdrawal Criteria and Replacements

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

a. Withdrawal of written informed consent
b. Study discontinuation due to subject's own request (e.g. personal reasons)
c. Required treatment with any medication known or suspected to interfere with the IMP
d. Life threatening thrombosis or TEE or life threatening hypersensitivity or any AE, laboratory abnormality, or other medical condition or situation occurs suggesting that continued participation in the study would not be in the best interest of the subject.
e. Protocol deviation requiring discontinuation of study treatment
f. Evidence of exclusion criteria or inclusion criteria not met
g. Lack of study compliance
h. Recommendation of the Data Safety Monitoring Board (DSMB)

A subject is entitled to discontinue participation in the clinical study at their own request at any time without stating a reason.

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

The reason for withdrawal of the subject must be documented by the investigator together with all data collected until the day of premature study termination including laboratory results and assessment of AE. All examinations foreseen for the subject's last study visit (closing visit) should be performed. Afterwards, the subject will be treated according to local standards at the discretion of the investigator.

In case a subject withdraws due to an AE or SAE please follow the instructions given in section 15 Appendix 2: Reporting Procedures of this protocol.

Withdrawn subjects will not be replaced.

For screening failures occurring during the screening period the following data need to be documented in eCRF only:

- Informed Consent
- Demographic data
- In-/Exclusion criteria
- End of Study (day and reason)
- AE information

For intra-operative screening failures (not randomized subjects) the following data need to be documented in eCRF only:

- Informed Consent
- Demographic data
- In-/Exclusion criteria
- Classification of type of planned spine surgery
- Estimated blood loss
- FIBTEM A10 at Baseline
- Duration of surgery
- End of Study (day and reason)
- AE information

4.5 Subjects Information

The subject will be informed about the clinical study according to the requirements of GCP and the legal requirements of the country in which the subject is recruited.

The clinical study, its objectives, possible benefits and risks, and its consequences will be verbally explained to the subject. Moreover, the subject is provided with written information about the clinical study. Sufficient time will be allowed for the information to be read and for questions to be asked. Attention should be paid to signs of undue distress in subjects who are unable to clearly articulate their distress. The subject must be told that refusal to participate in the clinical 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.

Subjects 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 subject must be granted access to the insurance terms and conditions.

Any new and relevant information that evolves during the course of the clinical study concerning the IMP, alternative treatments, or the benefit/risk ratio will be communicated to the subject.

4.6 Declaration of Informed Consent

The subject must have given written consent to participate in the clinical study by signing and personally dating the Informed Consent Form (ICF). 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 subject before any study-related procedures are performed. The subject's written informed consent will be filed at the investigator's site.

A duplicate of the signed and dated written ICF must be handed over to the subject.

5 INVESTIGATIONAL MEDICINAL PRODUCTS

5.1 Investigational Medicinal Product BT524

BT524 is a lyophilized, heat-treated, virus and prion safe human fibrinogen concentrate manufactured from human plasma. Fibrinogen conversion to fibrin strands during blood clot formation is one of the major steps in the coagulation cascade to stop bleeding. In subjects with fibrinogen deficiencies, therapeutic substitution with human fibrinogen concentrate will help correct the hemostatic defect and arrest or prevent bleeding.

The manufacturing process of BT524 contains CCI steps that were shown to be effective for removal/inactivation of enveloped viruses such as HIV, HBV and HCV, and for the non-enveloped viruses such as Reo, HAV and parvovirus B19. Moreover, CCI [redacted] re effectively removed during the production process.

Thus, BT524 is a virus and prion safe plasma-derived product fulfilling the requirements of the national German and European (CHMP) guidelines on a virus and prion safe pharmaceutical product.

BT524 is presented as a single-use vial with a nominal content of 1 g fibrinogen (lyophilized powder for solution for injection/infusion) to be reconstituted under aseptic conditions with 50 mL of water for injections, resulting in a final concentration of 20 mg/mL for infusion.

5.1.1 Description of Investigational Medicinal Product BT524

Substance code:	BT524
Active ingredients:	Fibrinogen concentrate from human plasma
Composition:	Lyophilized powder for solution for injection/infusion
Dosage form:	1 g
Concentration:	20 mg/mL after reconstitution with 50 mL water for injections
Container:	100 mL glass vial with rubber stopper
Manufacturer:	Biotest AG, D-63303 Dreieich, Germany

Batch number and expiry date are given in the applicable certificates of analysis.

5.1.2 Formulation, Packaging and Labelling

BT524 is a lyophilized, heat-treated fibrinogen concentrate manufactured from human plasma according to the description of Ph. Eur. monograph 0024 on Human Fibrinogen.

BT524 drug product is presented as a single-use 100 mL Type I glass vial with a nominal content of 1 g fibrinogen (lyophilized powder for solution for injection/infusion).

The labelling of BT524 will be performed according to local requirements. A sample label will be filed in the Trial Master File (TMF).

Batch number and vial number must be documented in the eCRF and the drug accountability log.

5.1.3 Storage Conditions and Stability

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.

BT524 is to be stored at a temperature CCI [redacted]. Continuous temperature recording should be documented on a temperature log.

5.1.4 Preparation for Use

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.

BT524 will be delivered to the operating room by the pharmacy and/or according to local practice.

5.2 **Investigational Medicinal Product Fresh Frozen Plasma (FFP)**

FFP will be used as active comparator to BT524 in subjects undergoing major spinal surgery.

FFP is the standard of care in many European countries for replacement of coagulation factors during major bleeding in clinical settings such as surgery and trauma.

FFP is the liquid portion of blood that contains all the clotting factors, fibrinogen (400 to 900 mg/unit), plasma proteins (particularly albumin), electrolytes, physiological anticoagulants (protein C, protein S, antithrombin, tissue factor pathway inhibitor) and added anticoagulants, and that is stored by freezing (Nascimento et al., 2010). Standard FFP contains 2-5 mg fibrinogen per mL (American Society of Anesthesiologists Task Force on Perioperative Blood and Adjuvant, 2006; Stainsby et al., 2006). FFP is usually authorized nationally. FFP will be provided and used by the site according to local standards.

5.2.1 Description of Investigational Medicinal Product FFP

Substance code:	FFP
Active ingredients:	Human plasma proteins (including all coagulation factors)
Dosage form:	AB0-blood group specific solution for infusion, which appears (slightly) yellow
Container:	Blood bags containing approximately 200-250 mL frozen solution

5.2.2 Formulation, Packaging and Labelling

The labelling of FFP will be performed according to local requirements.

Bag number must be documented in the eCRF and the drug accountability log.

5.2.3 Storage Conditions and Stability

In general, FFP will be stored protected from light, at a temperature at ≤ -18°C. Continuous temperature recording should be documented on a temperature log.

5.2.4 Preparation for Use

FFP is to be thawed according to local standards. FFP should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Do not use if turbid. Avoid shaking.

5.3 **Investigational Medicinal Product Cryoprecipitate**

Cryoprecipitate will be used as active comparator to BT524 in subjects undergoing cytoreductive PMP surgery at one site in the UK.

6 STUDY TREATMENT

6.1 Dosage Regimen

After a quantitative bleeding assessment only subjects with an intra-operative clinically relevant bleeding of approximately 1 L, requiring hemostatic treatment (high risk for the need of fibrinogen supplementation with BT524 or FFP) during surgery, will be treated with BT524 or FFP according to the predefined treatment algorithm.

6.2 Dosage and Administration

In general, the dosage of IMP (BT524 or FFP) depends on the extent of bleeding and the subject's clinical condition. Therefore, the functional fibrinogen level should be determined intra-operatively on an individual subject basis by FIBTEM thromboelastometry, and the target level of fibrinogen FIBTEM A10 is defined as the baseline FIBTEM A10 measured prior anaesthesia.

Blinding

Study 995 will be partially blinded; surgeon, surgical staff and subjects will be blinded to treatment allocation throughout the entire surgery. The anaesthesiologist who will administer the IMP could not be blinded to treatment allocation because of the inherent characteristics of the IMPs BT524 and FFP. Whereas BT524 is administered by syringe with a small volume and fast infusion to rapidly supplement missing fibrinogen to restore haemostasis, FFP is administered as infusion bag with larger volume and longer infusion time. Due to the different methods of application, the different volume, resulting in different infusion times of the two IMPs a blinding technique at the level of the anaesthesiologist is considered not feasible (either impossible or heavily impractical) to allow the study to be conducted successfully.

The basis for the partial blinding in the operating room is the spatial separation between the anaesthetic field and the surgical, sterile field (operating field). As a basic principle, the anaesthesiologist remains outside of the operating field. By using a sterile drape with non-transparent material between these two fields, the surgeon will not be able to see which IMP is being administered by the anaesthesiologist. The sterile drape will especially cover up the infusion stands and therefore the administration of FFP. The anaesthesiologist has a professional and organizational responsibility regarding the maintenance of blinding of the surgeon and the surgical staff during the entire surgery. In general, the anaesthesiologist is responsible for administering all medications including IMP, and for monitoring and maintenance of vital functions (including e.g. heart rate, oxygen saturation) and laboratory values of the subject.

BT524

The dose of BT524 to be infused will be calculated based on the subject's BW and the measured FIBTEM A10 with the aim of restoring the individual baseline FIBTEM A10 values via the following formula:

BT524 dose (g) = (baseline FIBTEM A10 - actual FIBTEM A10) x BW/140

The calculated dose will be rounded to the nearest whole number of grams of fibrinogen. The first BT524 dose to be administered will be at least 2 g and the maximum dose of fibrinogen concentrate during surgery should not exceed 8 g. In case of repeated dosing,

regular monitoring of the plasma level of fibrinogen (FIBTEM A10) during therapy is indicated.

BT524 will be administered as IV infusion with a maximum infusion rate of CCI /min (1 g fibrinogen concentrate CCI). 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). Other administration routes are only allowed after approval from the sponsor.

Fresh Frozen Plasma

In general FFP contains between 2 and 5 mg/mL fibrinogen. The usual FFP dose in major bleeding is 10 to 15 mL/kg . This should increase the subject's plasma coagulation factor levels by approximately 15-25%.

In general, the fibrinogen replacement using FFP should be guided by clinical situation and coagulation results. The volume of FFP to be transfused depends on the subject's BW and the recommended adult therapeutic dose of FFP is 15 mL per kg BW:

Subsequent intra-operative infusions as required.

Calculations for One Adult Therapeutic Dose FFP

Patient Weight (kg)	FFP dose – Volume/Units†	
	15mL/kg	Units FFP
50kg	750mL	3
55kg	825mL	
60kg	900mL	
65kg	975mL	4
70kg	1,050mL	
75kg	1,125mL	
80kg	1,200mL	
85kg	1,275mL	5
90kg	1,350mL	
95kg	1,425mL	
100kg	1,500mL	

†Volume of FFP in a unit is variable, mean FFP unit volume = 273mLs[3].

Source: (NHS Blood and Transplant, November 2013. Access Date: 29-Jun-2016.)

FFP will be administered after thawing using an infusion set with a filter. FFP will be administered as IV infusion as rapidly as possible and at the discretion of the treating anaesthesiologist.

6.3 Compliance with Dosage Regimens

As the IMP (BT524 or FFP) will be administered IV to each subject under the supervision of the unblinded anaesthesiologist, the compliance is expected to be 100%. In addition, the assessment of plasma fibrinogen concentrations may also serve as an adherence measure.

If a subject's treatment deviates from the dosage regimen (e.g., a dosing interruption occurs due to the occurrence of an AE), this will be recorded in the eCRF.

6.4 Dose Justification

In general, the dosage of IMP (BT524 or FFP) depends on the clinical situation and the extent of bleeding during surgery.

The recommended therapeutic dose of FFP is a guide to the appropriate adult dose, it is not a directive, and should not be used in place of clinical assessment (NHS Blood and Transplant, November 2013. Access Date: 29-Jun-2016.).

Fibrinogen is the first coagulation factor to become critically reduced during major surgical blood loss and the observation that patients with higher fibrinogen levels experience fewer bleeding complications than those with low levels highlights the importance of fibrinogen in the maintenance of hemostasis (Charbit et al., 2007; Ucar et al., 2007). Consequently, fibrinogen replacement therapy targeting a high-normal level of plasma fibrinogen and fibrin-based clot formation may be an important first step in restoring hemostasis during major bleeding (Rahe-Meyer et al., 2013a).

The normal blood fibrinogen concentration is between 2.0 and 4.5 g/L although this range can vary (Levy and Goodnough, 2015). Restoring the individual physiological fibrinogen level seems reasonable to ensure sufficient fibrinogen supplementation without risk of overdosing.

Therefore, the repeated IMP dosing in this study will be guided by determination of the functional fibrinogen level via ROTEM/FIBTEM thromboelastometry intra-operatively with the aim to restore patient's specific baseline fibrinogen level obtained prior to start of surgery.

Instead of using a fixed fibrinogen target level for all patients, the patient specific baseline level prior to start of surgery was chosen to take the individual physiological fibrinogen level of each patient into account. The patient's individual baseline fibrinogen level is defined as therapeutic target level to assure that the patients are treated with fibrinogen supplementation according to their specific clinical situation and their individual needs.

Rotational thromboelastometry (ROTEM) is an established viscoelastic method for hemostasis testing in whole blood, and ROTEM/FIBTEM that measures the fibrin or fibrinogen contribution to clot strength can be used to determine the most appropriate therapeutic dose of fibrinogen concentrate (Levy et al., 2014).

The ROTEM/FIBTEM test will be used in the intra-operative setting to quickly identify deficits in fibrin quality, and to guide hemostatic therapy. In contrast to conventional laboratory tests (measurement of fibrinogen concentration via Clauss assay), ROTEM/FIBTEM can measure early variables describing the clot firmness, such as clot amplitude obtained after 10 minutes (A10), and provide a forecast on the expected Maximum Clot Firmness (MCF) value at an earlier stage already. This early variable allows for a more rapid decision about therapeutic interventions. Owing to its rapid assessment of fibrinogen, ROTEM is frequently used to guide transfusion therapy (Schochl et al., 2011), and the data from Schochl and colleagues revealed the effective

use of ROTEM-guided coagulation management in trauma patients by reducing the amount of allogeneic blood product transfusion (Schochl et al., 2010).

Accordingly, the IMP treatment in this clinical study will be based on ROTEM/FIBTEM to obtain results more quickly and the dosing is targeted on the correction of the plasma fibrinogen level to the patient's individual fibrinogen FIBTEM A10 baseline level prior surgery.

According to the investigators' feedback, there is a certain amount of time between 'decision to treat' and start of IMP treatment. The FIBTEM value determined at decision to treat applies to the dose calculation of BT524. If treatment starts only about 30 to 45 minutes later after measuring the FIBTEM, there is a great risk of under-dosing the patients. In the time-window between decision to treat (measuring FIBTEM) and start of IMP treatment, patients' blood loss continues and fibrinogen levels continue to decline. The BT524 dose required at start of IMP treatment to restore fibrinogen plasma level is likely to be higher than the dose calculated at the time of treatment decision. Therefore, the first BT524 dose administered should be a dose of at least 2 g. This is in line with the dose recommendation given in the core SmPC for human fibrinogen concentrate (EMA, 2015b).

The FIBTEM guided dosing is only possible for the human fibrinogen concentrate BT524 with a defined concentration of fibrinogen. The content of fibrinogen in FFP varies between 2 and 5 mg/L. Therefore, the fibrinogen replacement using FFP will be performed according to treatment guidelines and local standards. The volume of FFP to be transfused depends on the patient's BW and the recommended adult therapeutic dose of FFP is 15 mL per kg BW (NHS Blood and Transplant, November 2013. Access Date: 29-Jun-2016.).

6.5 Treatment of Overdose

In order to avoid overdosage in subjects with acquired hypofibrinogenaemia undergoing major surgery, point-of-care FIBTEM guided dosing according to fibrinogen plasma levels will be used for the fibrinogen concentrate BT524 during surgery. The fibrinogen content in FFP is much lower and the amount of FFP will be applied based on BW according to local standards. Monitoring of the plasma level of fibrinogen intra-operatively will be performed as defined in section III.

In case of overdosage, the risk of development of thromboembolic complications is enhanced (EMA, 2015a).

6.6 Randomization Code

There will be a stratified randomization per surgery type. Subjects undergoing spine surgery are to be randomized on a 1:1 basis to receive either BT524 or FFP, and subjects undergoing cytoreductive PMP surgery are to be randomized separately on a 1:1 basis to receive either BT524 or cryoprecipitate.

For subjects undergoing spine surgery there will be a stratified randomization according to the expected blood loss: > 1,000 mL to ≤ 2,000 mL and > 2,000 mL. The expected blood loss will be recorded prior surgery.

Randomization of subjects to treatment will occur intra-operatively (predose) when eligibility for the clinical study has been confirmed. After an intra-operative blood loss of approximately 1 L, requiring hemostatic treatment (high risk for the need of fibrinogen supplementation with BT524 or FFP) during surgery, the randomization request will be

sent to the pharmacy (if applicable). The pharmacy retrieves the randomization code via Interactive Web Response System (IWRS) and provides the prepared IMP to the unblinded anaesthesiologist. In case the anaesthesiologist retrieves the randomization code via IWRS, the pharmacy will be informed accordingly and can provide the IMP.

Subject Identification

For the coherent assignment of the study documents all subjects having signed the informed consent and having entered the screening period will receive a subject number. The subject number comprises a five digit number of which the first two digits define the investigational site and the last three digits the subject enrolled at the corresponding site. Subject numbers are assigned consecutively per site. Subject numbers are assigned unique and will not be replaced i.e., in case of a screening failure.

An interactive web/voice response system (IWRS/IVRS) will be implemented and used for randomization and re-supply. Detailed instructions for the use of IWRS systems are provided in a separate document that will be filed in the Investigator Site File.

The random allocation of treatments to subjects will be done using a computerized randomization program. Subjects will receive a randomization number, which will be recorded along with the date of randomization in the eCRF.

6.7 Procedures for Emergency Unblinding

In the event of an emergency, each study site will be able to unblind subject treatment allocation via IWRS (either the principal investigator or a designated medic sub-investigator at the study site) without undue delay.

However, unblinding shall only be carried out if a medical emergency requires the identification of the IMP for that particular participant. If possible and time allows, investigators should make every effort to discuss the subject's case with the sponsor or representative prior to breaking the blind. If the code is broken for a subject (via the IWRS), Biotest must be informed immediately. The reason for opening the code break must be documented on the appropriate eCRF page along with the date and the initials of the person who broke the code.

Any subject for whom the blind is broken will be discontinued from the clinical study, however will be followed-up.

6.8 Drug Accountability

The IMP BT524 will be supplied to the investigator 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 subjects were provided the doses specified in the protocol and reconcile all IMPs received for the clinical study. The investigator has to ensure that consignments of IMP are received correctly by a dedicated person (e.g. pharmacy) and that the IMP is safely and appropriately handled and stored.

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 investigator must allow the monitor to perform drug reconciliation before any IMP is returned or destroyed. The documentation must include dates, quantities, subject numbers, batch numbers and expiry dates.

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.

6.9 Previous and Concomitant Medication or Treatment

All previous medication and treatment in the previous 4 weeks prior to the elctive surgery and the administration of IMP are to be recorded in the eCRF.

Concomitant medication therapeutically required is allowed 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).

6.10 Prohibited Medication or Treatment

The administration of allogeneic or autologous blood products interacting relevantly with the coagulation system (e.g. platelet concentrates, cryoprecipitate) and of hemostatic agents (including coagulation factor concentrates) is not allowed prior to start of or during the first IMP administration within this study. In such instances, the subject can not be randomized or will be withdrawn from the study.

RBCs can be infused according to institutional practice.

6.11 Warnings and Precautions

Brief Summary

A Guideline for Core SmPC for Human Fibrinogen Products (EU Core SmPC) is in place which also describes the well established benefit-risk profile of the authorized fibrinogen concentrates [Guideline on Core SmPC for Human Fibrinogen Products (EMA, 2015a)].

It provides the following AEs as undesirable effects considered established for all authorized and marketed human fibrinogen concentrate formulations:

In the MedDRA System Organ Class (SOC) "Immune system disorders": Allergic or anaphylactic-type reactions; in the MedDRA SOC "Vascular disorders": Thromboembolic episodes (including myocardial infarction and pulmonary embolism); and in the MedDRA SOC "General disorders and administration site conditions": Increase in body temperature.

Description of Potential Risks

There is a risk of thrombosis when subjects, with either congenital or acquired deficiency, are treated with human fibrinogen particularly with high dose or repeated dosing. Subjects given human fibrinogen should be observed closely for signs or symptoms of thrombosis. In subjects with a history of coronary heart disease or myocardial infarction, in subjects with liver disease, in peri- or post-operative subjects, in neonates, or in subjects at risk of TEEs or DIC, 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.

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.

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.

There is currently no data on fibrinogen inhibitors available with human fibrinogen.

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

The measures taken are considered effective for enveloped viruses such as human immunodeficiency virus (HIV), hepatitis B virus (HBV) and hepatitis C virus (HCV) and for the non-enveloped hepatitis A and parvovirus B19 viruses. It is strongly recommended that every time that fibrinogen is administered to a patient, the name and batch number of the product are recorded in order to maintain a link between the patient and the batch of the product.

Special precautions for BT524 administration

All plasma-derived human products may lead to allergic or anaphylactic reactions. Thus, the administration of BT524 will be performed under medical supervision where proper medical care for allergic or anaphylactic reactions can be provided. 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.

Prothrombin time PT(INR), activated partial thromboplastin time (aPTT), prothrombin fragments F_{1+2}, thrombin-antithrombin III complex (TAT), D-dimer, PS, PC, antithrombin III (AT III) activity and thrombin time (TT) and further coagulation parameters are monitored regularly to detect a hypercoagulable state.

Changes in vital signs (including pulse [heart rate], blood pressure, respiratory rate, body temperature) are monitored during the surgery and according to the flow chart (see section III).

Incompatibilities

Fibrinogen must not be mixed with other medicinal products and should be administered by a separate injection/infusion line.

7 COURSE OF THE CLINICAL STUDY

7.1 Visit Schedule

Screening Visit Day -42 through Day -1:

All subjects will attend a screening visit (if required more than one visit) between Day -42 and Day -1 prior to elective major spine surgery, where the following procedures will be performed:

- **Written informed consent** will be obtained.
- In general, eligibility to take part in the study will be assessed against the **inclusion and exclusion criteria**.
- **Demographic data** (including sex, year of birth, race) will be recorded.
- Classification of **type of the planned spine surgery** will be recorded.
- **Physical examination** (including body weight and body height) will be performed.
- **Body weight** will be recorded.
- A serum **pregnancy test** (human chorionic gonadotropin) will be performed for all females of child-bearing potential (a woman of child bearing potential is one that has NOT had a hysterectomy and/or a bilateral oophorectomy, or has NOT been naturally postmenopausal for at least 24 consecutive months).
- **Medical and surgical history** with regard to the subjects' drug history, previous medication and treatment, disease history, and other medical and surgical history will be recorded. Previous medication taken up to 4 weeks before enrollment will be recorded. The type of previous medication, dose schedule, duration, and the indication the previous medication was given for will be documented.
- **Vital signs** (including pulse [heart rate], blood pressure, respiratory rate, body temperature) will be recorded.
- Samples for **clinical laboratory** parameters (hematology, clinical chemistry, urinalysis) will be taken:
    - **Hematology** (RBC, WBC, platelet count, hemoglobin, hematocrit)
    - **Clinical chemistry** (ALAT, ASAT, γ-GT, AP, total bilirubin, creatinine, creatinine clearance, BUN/Urea, potassium, sodium, calcium, chloride)
    - **Urinalysis** (pH, blood, WBC, protein, glucose, ketone bodies, nitrite, bilirubin, urobilinogen)

  Some of these tests for clinical laboratory parameters may have been performed by the investigator as standard of care prior to the subject signing the Informed Consent Form. If test(s) were done within 42 days before the first scheduled treatment with IMP (BT524 or FFP), the investigator may use the results obtained from standard of care for the purpose of this study.
- Sample for **coagulation activation tests** (PT(INR), aPTT, TAT, F_{1+2}, D-dimer, PS, PC, AT III, TT) will be taken.
- Sample for **plasma activity of fibrinogen** (Clauss assay) will be taken.
- **FIBTEM A10 and Maximum clot firmness (MCF)** (ROTEM) will be performed.
- **Retention samples for viral safety** laboratory parameters will be taken.

- **Samples for virus serology laboratory parameters** (hepatitis B, hepatitis C, HIV) will be taken.
- **AEs** will be documented.

If a subject does not fulfill the eligibility criteria, re-assessment is allowed within the 42 days screening period.

Baseline Visit Day 1 (or Day -2 or Day -1, prior to surgery):

All subjects will attend a baseline visit on Day 1, the day of spine surgery. The baseline visit can be scheduled one or two days prior to spine surgery (Day -2 or Day -1) if required due to local hospital procedures.

The following assessments will be performed **prior to start of surgery, before** the potential IMP administration (BT524 or FFP):

- **Re-check of inclusion and exclusion criteria**: Eligibility to take part in the study will be confirmed against the inclusion and exclusion criteria, as appropriate (i.e., diagnostic tests will be repeated at the investigator's discretion).
- Any **changes in medical and surgical history** since the screening visit will be recorded. The type of previous medication, dose schedule, duration, and the indication the previous medication was given for, will be documented.
- **Expected blood loss** will be recorded.
- **Physical examination** will be performed.
- **Pregnancy test** (urine or serum) will be performed for all females of child-bearing potential (a woman of child bearing potential is one that has NOT had a hysterectomy and/or a bilateral oophorectomy, or has NOT been naturally postmenopausal for at least 24 consecutive months).
- **Body weight** will be recorded to calculate subject dose.
- **Vital signs** (including pulse [heart rate], blood pressure, respiratory rate, body temperature) will be recorded.
- Samples for **clinical laboratory** parameters (hematology, clinical chemistry, urinalysis) will be taken:
  - **Hematology** (RBC, WBC, platelet count, hemoglobin, hematocrit)
  - **Clinical chemistry** (ALAT, ASAT, γ-GT, AP, total bilirubin, creatinine, creatinine clearance, BUN/Urea, potassium, sodium, calcium, chloride)
  - **Urinalysis** (pH, blood, WBC, protein, glucose, ketone bodies, nitrite, bilirubin, urobilinogen)
- Sample for **coagulation activation tests** (PT(INR), aPTT, TAT, F_{1+2}, D-dimer, PS, PC, AT III, TT) will be taken.
- Sample for **coagulation factors** (FII, FV, FVII, FVIII, FIX, FX, FXI, FXIII) will be taken.
- Sample for **plasma activity of fibrinogen** (Clauss assay) will be taken and
- **FIBTEM A10 and MCF** (ROTEM) will be performed.
- **AEs** will be documented.

Please note: *The following tests and assessments have to be done prior to surgery. In case of a short time-period between screening and baseline (≤ 2 days) these tests have only to be repeated based on medical judgment of the investigator. If not repeated, screening results will serve as baseline.*

- Physical examination
- Pregnancy test
- Body weight
- Hematology
- Clinical chemistry
- Urinalysis
- Coagulation activation tests
- Plasma activity of fibrinogen (Clauss assay)
- FIBTEM A10 and MCF (ROTEM)

Surgery Day 1 (pre-dose):

- **Time of start of surgery** will be recorded.
- Continuous **collection and measurement of blood loss** from start of surgery.
- Amount of blood in blood suction unit and surgical cloths and compresses will be estimated.
- **Eligibility** to take part in the study will be assessed against the intra-operative inclusion criteria:

  an intra-operative clinically relevant blood loss of approximately 1 L, requiring hemostatic treatment (high risk for the need of fibrinogen supplementation with BT524 or FFP) during surgery.

In subjects who do not meet the intra-operative inclusion criteria no IMP administration will take place and no further assessments intra-operatively will be performed. These subjects will be considered as screening failures and will be treated with standard of care.

Only for subjects considered to be eligible for IMP administration with BT524 or FFP the following assessments will be performed:

- **Time of decision** to treat the subject with IMP will be recorded.
- **Amount of blood** from blood suction unit and from surgical cloths and compresses after decision to treat the subject with IMP until end of surgery will be measured.
- Sample for plasma **activity of fibrinogen** (Clauss assay) will be taken.
- **FIBTEM A10 and MCF** (ROTEM) will be performed.
- **Calculation** of FIBTEM A10 guided dose for BT524 (first dose should be at least 2 g) or weight-based dose of FFP.
- **Randomization** will be initiated **with order of IMP.**
- Sample for **coagulation activation tests** (PT(INR), aPTT, TAT, F_{1+2}, D-dimer, PS, PC, AT III, TT) will be taken prior start of first IMP administration.

- Sample for **coagulation factors** (FII, FV, FVII, FVIII, FIX, FX, FXI, FXIII) will be taken prior start of first IMP administration.
- Samples for **clinical laboratory parameters** (hematology, clinical chemistry) will be taken prior start of first IMP administration:
  - **Hematology** (RBC, WBC, platelet count, hemoglobin, hematocrit)
  - **Clinical chemistry** (ASAT, ALAT, creatinine, creatinine clearance, BUN/Urea, γ-GT, AP, total bilirubin, potassium, sodium, calcium, chloride)
- **Vital signs** (pulse [heart rate], blood pressure, respiratory rate, body temperature) will be recorded prior start of IMP administration.
- **Transfusion products** (allogenic blood products or autologous blood transfusion/cell salvage) given intra-operatively will be documented.
- **Concomitant medication or treatment** will be recorded. The type of concomitant medication/treatment, dose/schedule, duration, and the indication the concomitant medication was given for will be documented.
- **AEs** will be documented.
- **IMP** will be infused IV.

  The total volume and the total infusion time of each IMP administration (start and end of infusion) will be recorded.

Surgery Day 1 (post-dose):

- Continuous **collection and measurement of blood loss**
- **Vital signs** (pulse [heart rate], blood pressure, respiratory rate, body temperature) will be recorded **15 minutes** and **90 minutes** after start of IMP administration.
- Sample for **coagulation activation tests** (PT(INR), aPTT, TAT, F_{1+2}, D-dimer, PS, PC, AT III, TT) will be taken **15 minutes** and **90 minutes** after start of first IMP administration.
- Sample for **coagulation factors** (FII, FV, FVII, FVIII, FIX, FX, FXI, FXIII) will be taken **90 minutes** after start of first IMP administration.
- Sample for plasma **activity of fibrinogen** (Clauss assay) will be taken **15 minutes** and **90 minutes** after start of first IMP administration.
- **FIBTEM A10 and MCF** (ROTEM) will be performed **15 minutes** and **90 minutes** after start of first IMP administration.
- **Transfusion products** (allogenic blood products or autologous blood transfusion/cell salvage) given intra-operatively will be documented.
- **Concomitant medication or treatment** will be recorded. The type of concomitant medication/treatment, dose/schedule, duration, and the indication the concomitant medication/treatment was given for will be documented.
- **AEs** will be documented.

Please note: *The following tests have to be done 90 minutes after start of first IMP treatment. In case this time-point is within a short timeframe (< 30 min) after the 'end of surgery', these tests have only to be repeated based on medical judgment of the investigator.*

- Markers of coagulation (Coagulation activation tests)
- Plasma activity of fibrinogen (Clauss assay)
- FIBTEM A10 and MCF (ROTEM)

Surgery Day 1 (prior to repeated IMP administration):

- **Vital signs** (pulse [heart rate], blood pressure, respiratory rate, body temperature) will be recorded prior start of each IMP administration.
- **FIBTEM A10 and MCF** (ROTEM) will be performed.
- **FIBTEM A10 guided dose for BT524** or weight-based dose of FFP will be calculated.
- **IMP** will be ordered**.**
- **IMP** will be administered. The total volume and the total infusion time of each IMP administration (start and end of infusion) will be recorded.
- **Amount of blood** from blood suction unit and from surgical cloths and compresses will be collected and measured.
- **Transfusion products** (allogenic blood products or autologous blood transfusion/cell salvage) given intra-operatively will be documented.
- **Concomitant medication or treatment** will be recorded.
- **AEs** will be documented.

Surgery Day 1 (end of surgery):

- **Vital signs** (including pulse [heart rate], blood pressure, respiratory rate, body temperature) will be recorded at the end of the surgery.
- Samples for **clinical laboratory parameters** (hematology, clinical chemistry) will be taken at the end of the surgery:
  - **Hematology** (RBC, WBC, platelet count, hemoglobin, hematocrit)
  - **Clinical chemistry** (ASAT, ALAT, creatinine, creatinine clearance, BUN/Urea, γ-GT, AP, total bilirubin, potassium, sodium, calcium, chloride)
- Sample for **coagulation activation tests** (PT(INR), aPTT, TAT, F_{1+2}, D-dimer, PS, PC, AT III, TT) will be taken at the end of the surgery.
- Sample for plasma **activity of fibrinogen** (Clauss assay) will be taken at the end of the surgery.
- **FIBTEM A10 and MCF** (ROTEM) will be performed at the end of the surgery.
- Start continuous **measurement of blood loss** until 24 hours post-operative.
- **Amount of blood** from blood suction unit and from surgical cloths and compresses will be calculated and recorded (blood loss after the decision to treat the subject with IMP until end of surgery).
- **Transfusion products** (allogenic blood products or autologous blood transfusion/cell salvage) given intra-operatively will be documented.

- **Concomitant medication or treatment** will be recorded. The type of concomitant medication/treatment, dose/schedule, duration, and the indication the concomitant medication//treatment was given for will be documented.
- **AEs** will be documented.
- **Time of end of surgery** (time of last suture) will be recorded.
- **Rebleeding episodes** will be recorded.

Please note: *The following tests have to be done at the 'end of surgery'. In case the end of surgery is within a short timeframe (< 30 min) after the blood draw '90 minutes after start of first IMP treatment', these tests have only to be repeated based on medical judgment of the investigator.*

- Markers of coagulation (Coagulation activation tests)
- Plasma activity of fibrinogen (Clauss assay)
- FIBTEM A10 and MCF (ROTEM)

Follow-up Visit Day 2:

All subjects treated with IMP will attend the follow-up visit one day after surgery (Day 2). The following procedures will be performed:

- Continuous measurement of post-operative blood loss and recording until 24 hours after end of surgery.
- **Physical examination** will be performed.
- **Vital signs** (including pulse [heart rate], blood pressure, respiratory rate, body temperature) will be recorded.
- Sample for **coagulation activation tests** (PT(INR), aPTT, TAT, F_{1+2}, D-dimer, PS, PC, AT III, TT) will be taken.
- Samples for **clinical laboratory parameters** (hematology, clinical chemistry, urinalysis) will be taken:
  - **Hematology** (RBC, WBC, platelet count, hemoglobin, hematocrit)
  - **Clinical chemistry** (ASAT, ALAT, creatinine, creatinine clearance, BUN/Urea, γ-GT, AP, total bilirubin, potassium, sodium, calcium, chloride)
  - **Urinalysis** (pH, blood, WBC, protein, glucose, ketone bodies, nitrite, bilirubin, urobilinogen)
- Sample for plasma **activity of fibrinogen** (Clauss assay) will be taken and
- **FIBTEM A10 and MCF** (ROTEM) will be performed.
- **Transfusion products** (allogenic blood products or autologous blood transfusion/cell salvage) will be documented.
- **Concomitant medication or treatment** will be documented. The type of concomitant medication/treatment, dose/schedule, duration, and the indication the concomitant medication/treatment was given for will be documented.
- **AEs** will be documented.
- **Rebleeding episodes** will be recorded.

Follow-up Visits Day 3, Day 5 and Day 8:

All subjects treated with IMP will attend the follow-up visits 2, 4 and 7 days after surgery (Day 3, 5 and 8):

The following procedures will be performed:

- **Physical examination** will be performed.
- **Vital signs** (including pulse [heart rate], blood pressure, respiratory rate, body temperature) will be recorded.
- Sample for **coagulation activation tests** (PT(INR), aPTT, TAT, F_{1+2}, D-dimer, PS, PC, AT III, TT) will be taken.
- Samples for **clinical laboratory parameters** (hematology, clinical chemistry, urinalysis) will be taken:
  - **Hematology** (RBC, WBC, platelet count, hemoglobin, hematocrit)
  - **Clinical chemistry** (ASAT, ALAT, creatinine, creatinine clearance, BUN/Urea, γ-GT, AP, total bilirubin, potassium, sodium, calcium, chloride)
  - **Urinalysis** (pH, blood, WBC, protein, glucose, ketone bodies, nitrite, bilirubin, urobilinogen)
- **Transfusion products** (allogenic blood products or autologous blood transfusion/cell salvage) will be documented.
- **Concomitant medication or treatment** will be documented. The type of concomitant medication/treatment, dose/schedule, duration, and the indication the concomitant medication/treatment was given for will be documented.
- **AEs** will be documented.
- **Rebleeding episodes** will be recorded.

Discharge from Hospital:

- If the discharge from hospital will take place on **Day 6** or **Day 7**, the follow-up visit on **Day 8** will be performed prior to the scheduled visit on the day of discharge.
- The day of the discharge from hospital will be recorded at the **closing visit D36**.

Closing Visit Day 36 (+35, up to Day 71 if required):

All subjects treated with IMP will attend a closing visit including the final safety examination at least 5 weeks after the surgery, scheduled on Day 36 (+35, up to Day 71 if required). The following procedures will be performed:

- A **physical examination** will be performed.
- **Vital signs** (including pulse [heart rate], blood pressure, respiratory rate, body temperature) will be recorded.
- Sample for **coagulation activation tests** (PT(INR), aPTT, TAT, F_{1+2}, D-dimer, PS, PC, AT III, TT) will be taken.
- Samples for **clinical laboratory parameters** (hematology, clinical chemistry, urinalysis) will be taken:
  - **Hematology** (RBC, WBC, platelet count, hemoglobin, hematocrit)
  - **Clinical chemistry** (ASAT, ALAT, creatinine, creatinine clearance, BUN/Urea, γ-GT, AP, total bilirubin, potassium, sodium, calcium, chloride)

  - **Urinalysis** (pH, blood, WBC, protein, glucose, ketone bodies, nitrite, bilirubin, urobilinogen)
- **Retention samples for viral safety laboratory parameters** will be taken.
- **Samples for virus serology laboratory parameters** (hepatitis B, hepatitis C, HIV) will be taken.
- **Transfusion products** (allogenic blood products or autologous blood transfusion/cell salvage) will be documented.
- **Concomitant medication or treatment**: type of concomitant medication/treatment, dose/schedule, duration, and the indication the concomitant medication/treatment was given for will be documented continuously up to Day 36.
- **AEs** will be recorded continuously up to Day 36.

Further details on the visit schedule that will be used for the assessment of the efficacy and safety parameters in this study are presented in section III, Flowchart of Study.

7.2 Duration of the Clinical Study

First Subject in (planned)	Q1 2018
Last Subject Last Visit *(planned)*	tbd

Individual Subject

Regular duration of individual study participation for eligible screened subjects is at least 5 weeks plus time between screening (signed Informed Consent) and surgery.

Each subject fulfilling the intra-operative inclusion criteria will be administered BT524 or FFP/cryoprecipitate during surgery. The usual stay in hospital after elective surgery varies depending on the type of surgery and subjects overall conditions. Each subject will have follow-up visits 1, 2, 4 and 7 days after surgery (Day 2, 3, 5 and 8) and the day of discharge from hospital will be recorded. Subsequent, each subject has to return into the hospital for the closing visit including the final safety examination at least 5 weeks after surgery, scheduled on Day 36. The closing visit can be postponed up to Day 71 (Day 36 +35) if required due to subject's availability (e.g. stay in rehabilitation center).

Subjects not meeting inclusion criteria or meeting exclusion criteria are screen failures and will end study participation at the day of screen failure. Subjects that do not meet the intra-operatively inclusion criterion are also considered as screen failure and will end study participation on the day of the surgery.

A subject is considered to have completed the study when he/she is presumed to have followed the protocol (i.e., completed visits approximately 5 weeks after surgery). If for any reason, a subject discontinues involvement in the study early, every effort should be made to ensure the subject attends a closing visit (section 4.4).

For each subject date and reason for the end of the study participation will be recorded.

7.2.1 End of Study

The end of clinical study will be defined as the Last Visit of the Last Subject.

7.3 Criteria for Premature Termination

7.3.1 Premature Termination of the Entire Clinical Study

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

a) Unacceptable delay of study completion
b) Low recruitment rate
c) A large number of subjects with premature termination
d) Changed benefit-risk ratio according to the efficacy and/or safety results from this or parallel studies
e) Lack of efficacy
f) Recently emerged information suggest that the study population can be offered a more advantageous study design

In case of premature termination of the entire clinical study, the sponsor has to notify the appropriate Ethics Committees and Regulatory Authorities as soon as possible but at the latest within 15 days.

7.3.2 Premature Termination of an Individual Study Site

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

a) Determination of unexpected, significant, or unacceptable risk to subjects.
b) Low recruitment rate,
c) Lack of co-operation,
d) Severe deviations from study protocol,
e) Manipulation of study data,
f) Violation of other ethical or legal principles.

7.4 Treatment and Care after the End of the Study

For subjects who have finished the clinical study and for all subjects who drop out prematurely it is the responsibility of the investigator to choose adequate therapeutic measurements.

After termination of the clinical study, any unexpected safety issue that changes the benefit-risk evaluation and is likely to have an impact on the subjects who have participated in it, should be reported as soon as possible to the sponsor. Sponsor expeditiously reports the event to the competent authority(ies) concerned (See also section 9.3.4).

8 BENEFIT-RISK EVALUATION

8.1 Benefit of BT524

Fibrinogen plays a critical role in achieving and maintaining hemostasis in patients undergoing major surgeries and the observation that patients with higher fibrinogen levels experience fewer bleeding complications than those with low levels highlights the importance of fibrinogen in the maintenance of hemostasis. Consequently, fibrinogen replacement therapy targeting a high-normal level of plasma fibrinogen and fibrin-based clot formation may be an important first step in restoring hemostasis during major bleeding.

Major spinal and abdominal surgeries represent elective surgeries often associated with significant intra- and post-operative blood loss resulting in decreased fibrinogen levels. An accurate and rapid determination of (functional) fibrinogen level is important during hemorrhage to establish a timely hemostatic intervention. Individualized dosing of fibrinogen concentrate using a target ROTEM/FIBTEM value integrates rapid diagnostic testing with appropriate therapeutic dosing of fibrinogen concentrate according to patients' needs.

The principal benefit for the participating subjects randomized to the BT524 treatment arm will be to receive the required individualized fibrinogen replacement therapy in a goal-directed treatment algorithm as a timely hemostatic intervention if significant bleeding is accompanied by acquired hypofibrinogenaemia. Moreover, fibrinogen concentrate seems to have certain advantages over the standard replacement therapy with FFP/cryoprecipitate, such as precisely determined, high amount of purified fibrinogen dissolved in a small volume, low risk of pathogen transmission and instant administration without need for thawing or testing AB0 blood group compatibility.

8.2 Foreseeable Risk and Discomfort Related to BT524

At that point of time the pre-clinical and clinical study data are still considered too scarce to finally define risks as "identified" in the context of BT524. Therefore at present all signals as derived from class-labelling, currently remain to be regarded as potential risks. Please also refer to section 6.11 Warnings and Precautions.

8.3 Other Sources of Possible Risk and Discomfort

Please refer to section 6.11 Warnings and Precautions.

8.4 Summary of Possible Risk and Discomfort

Human fibrinogen concentrate is a well-known substance, established for decades in the treatment of congenital fibrinogen deficiency as well as of various indications of acquired fibrinogen deficiency. Fibrinogen concentrates have shown to be safe and well-tolerated (Fenger-Eriksen et al., 2009; Henselmans et al., 1999).

A Guideline for Core SmPC for Human Fibrinogen Products (EU Core SmPC) is in place which also describes the well established benefit-risk profile of the authorized fibrinogen concentrates (EMA, 2015a).

It provides the following AEs as undesirable effects considered established for all authorized and marketed human fibrinogen concentrate formulations: In the MedDRA SOC "Immune system disorders": Allergic or anaphylactic-type reactions; in the MedDRA SOC "Vascular disorders": Thromboembolic episodes (including myocardial infarction

and pulmonary embolism); and in the MedDRA SOC "General disorders and administration site conditions": Increase in body temperature.

Currently, there is no data with human fibrinogen products in regard to inhibitor formation.

With regard to transmissible agents refer to section 6.11 Warnings and Precautions.

The safety profile of BT524 is anticipated to be in line with the marketed fibrinogen concentrates and the content of the EU Core SmPC [Guideline on Core SmPC for Human Fibrinogen Products (EMA/CHMP/BPWP/691754/2013 Rev 1)].

The safety and tolerability and the benefit-risk profile of BT524 (fibrinogen concentrate from human plasma) is considered favorable.

9 ASSESSMENT OF OBJECTIVES / CRITERIA FOR EVALUATION

9.1 Efficacy

9.1.1 Specification of Efficacy Parameters

9.1.1.1 Primary Efficacy Parameter

The primary efficacy parameter is determined from the intra-operative blood loss after the decision to treat the subject with IMP until the end of the surgery as measured by the amount of blood from the blood suction unit and the amount of blood from surgical cloths and compresses.

9.1.1.2 Secondary Efficacy Parameter

Secondary efficacy will be determined using the following parameters:

- Proportion (%) of subjects with successful correction of fibrinogen level (FIBTEM A10) 15 minutes after start of first IMP administration
- Time to first successful correction of fibrinogen level (15 minutes or 90 minutes after start of first IMP administration, end of surgery, not within surgery)
- Total amount (volume in mL and number of units) of transfusion products (allogenic blood products) or autologous blood transfusion infused after start of first IMP administration until end of surgery
- Amount (volume in mL and number of units) of RBCs (allogenic and autologous) infused after start of first IMP administration until end of surgery
- Post-operative blood loss in the first 24 hours
- Proportion (%) of subjects with rebleeds after the end of surgery until Day 8
- Hospital length of stay after surgery
- In-hospital mortality

9.1.2 Methods for Assessing and Recording Efficacy Parameters

9.1.2.1 Methods for Assessing Primary Efficacy Parameter

Amount of Blood Loss

The blood loss will be quantified by measuring the continuous bleeding mass with a **blood suction unit** (and/or a **cell saver**) and by calculation of the amount of blood from **surgical cloths and compresses** (see section 3).

The **blood suction unit** will be used to remove the blood from the area being operated. The blood is salvaged by a suction catheter from the operating field and suctioned into a reservoir which contains a **heparinised saline solution** (or citrate anticoagulant solution) used for anticoagulation during blood collection. The quantity of anticoagulant introduced into the blood collection system will be adapted continuously to the volume of blood loss.

Allowance must be made also for the presence of **irrigation solution**. The amount of solution suctioned into the container through irrigation of the wound must be recorded. This will be done by knowing the capacity of the irrigation syringe in use and keeping track of the number of times it is used.

The total volume of fluid collected in the suction container will be recorded. Then the amount of heparinised saline solution and of irrigation solution must be subtracted **from the entire fluid volume in the suction container to** determine the actual blood lost.

Prior to the start of surgery **dry surgical cloths and compresses** will be weighed (weight recorded), to be available in case a manual compression is required. In case a **manual compression** is necessary during surgery, dry surgical cloths and compresses will be applied to the surgical area, afterwards removed and wrung out until almost dry. By wringing out surgical cloths, the blood can be caught in a kidney dish and finally collected in the suction container. Subsequently, all cloths and compresses will be weighed (before they dry out) and the weight will be recorded.

For the primary endpoint the amount of blood loss will be measured from the time of decision to treat the subject with IMP until the end of the surgery:

Immediately after an estimated blood loss of approximately 1 L, and the assessment that hemostatic treatment will be required during surgery (high risk for the need of fibrinogen supplementation, either with FFP or BT524 during surgery), the pharmacy will be informed about the decision to treat the subject with IMP. At the same time, the **suction container will be emptied and the blood measurement for the primary endpoint is initiated** with collection of blood in the empty blood suction unit.

In addition, in case a manual compression is necessary after decision to treat the subject with IMP, new surgical cloths and compresses will be applied to the surgical area.

At the end of the surgery, all surgical cloths and compresses will be removed from the surgical area, wrung out until almost dry (blood will be collected) and weighed. The weight will be recorded. The end of surgery is defined as time of last suture.

The fluid volume collected in the blood suction container will be measured and documented, the proportion of blood, heparinised saline solution and irrigation solution will be calculated and also recorded.

In a final step the **total blood loss will be calculated**. The calculation of blood loss based on the volume of blood removed from the surgical field by the blood suction unit and that absorbed by surgical cloths and compresses.

9.1.2.2 Methods for Assessing Secondary Efficacy Parameter

Correction of Fibrinogen Level via FIBTEM A10 (mm)

The correction of the fibrinogen level will be measured via thromboelastometry (ROTEM/FIBTEM A10). ROTEM is an established viscoelastic method for hemostasis testing in whole blood and ROTEM/FIBTEM that measures the fibrin or fibrinogen contribution to clot strength, can be used to determine the most appropriate therapeutic dose of fibrinogen concentrate (Levy et al., 2014).

Whole blood viscoelastic tests such as the fibrin-based thromboelastometry (ROTEM) test FIBTEM will be used in the intra-operative setting to quickly identify deficits in fibrin quality, and to guide hemostatic therapy. In contrast to conventional laboratory tests (measurement of fibrinogen concentration via Clauss assay), ROTEM/FIBTEM can measure early variables describing the clot firmness, such as clot amplitude obtained after 5 minutes (A5) or 10 minutes (A10), and provide a forecast on the expected MCF value at an earlier stage already. These early variables allow for a more rapid decision about therapeutic interventions.

The fibrinogen activity will be measured by FIBTEM A10, MCF and Clauss assay at screening, prior surgery (baseline), predose, 15 and 90 minutes after the start of first IMP administration, at the end of the surgery and one day after surgery.

For the evaluation of the secondary efficacy endpoint successful correction of the fibrinogen level is defined as restoring fibrinogen FIBTEM A10 baseline levels measured by ROTEM 15 minutes after start of first IMP administration.

Accordingly, the time to first successful correction of fibrinogen level is defined as the time point (15 minutes or 90 minutes after start of first IMP administration, end of surgery, not within surgery) the fibrinogen FIBTEM A10 baseline levels measured by rotational thromboelastometry are restored the first time.

However, correction of fibrinogen will also be analysed based on results obtained from MCF and Clauss assay to perform sensitivity analyses.

Clauss Assay

The most widely used technique for determination of fibrinogen concentration is the Clauss (FIBClauss) assay (Clauss, 1957). In this method, dilutions of a plasma standard of known fibrinogen concentration are clotted by addition of a high concentration of thrombin, and a standard curve is prepared. Because the clotting time is inversely proportional to the fibrinogen concentration, the clotting time of diluted patient plasma is used to read the fibrinogen concentration from the standard curve. This method is reliable, accurate, and precise, and easily adapted to automated coagulation analyzers.

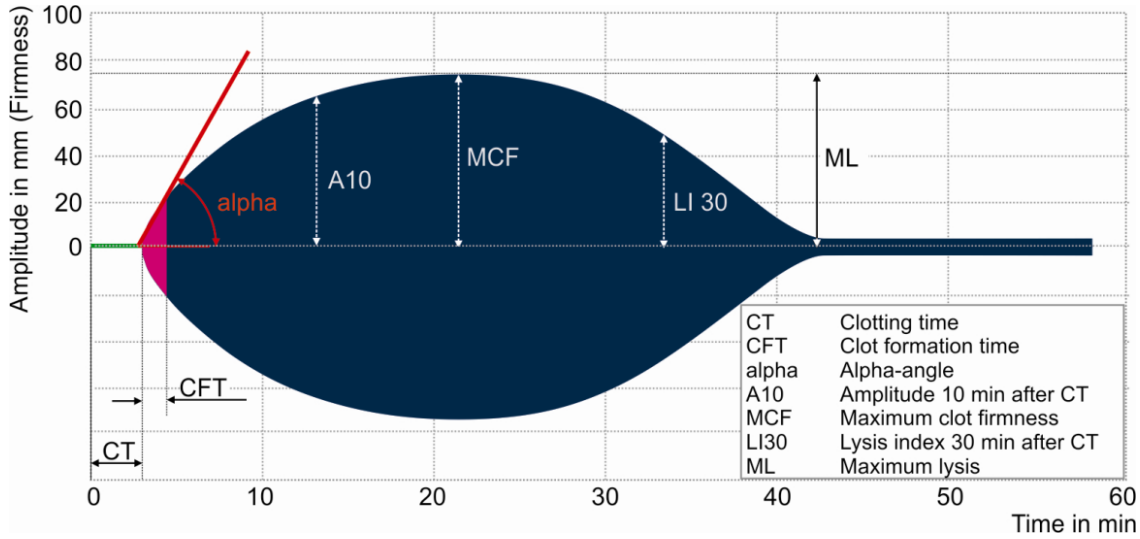
Maximum Clot Firmness (MCF, mm)

MCF addresses the clot integrity and will be measured by ROTEM® (ROTEM delta or ROTEM sigma).

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 system reagent (PPD , Mar 2011) for the ROTEM delta/sigma which allows the assessment of the fibrinogen level and the quality of the fibrin polymerization in citrated blood by inhibiting the platelets. For ROTEM sigma the FIBTEM C system reagent will be used accordingly.

Fibtem 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 4** shows an example of the ROTEM readout of citrated normal blood.

Figure 4: 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 (Schöchl 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 (Fib-tem S 2011).

Consumption of Transfusion Products

The **amount of transfusion products** (allogenic blood products or autologous blood transfusion) given after start of first IMP administration (BT524 or FFP) until end of surgery to counteract hemodynamic instability will be documented (volume in mL and number of units if applicable) and evaluated.

The **amount of RBCs** (allogenic and autologous) required intra-operatively after start of first IMP administration (BT524 or FFP) until end of surgery will be documented (volume in mL and number of units if applicable) and evaluated.

Intra-operative Blood Salvage (Cell Salvage)

Intra-operative blood salvage is the collection and reinfusion of blood lost during and immediately after surgery. The blood from the surgical field is recovered, mixed with an anticoagulant and pumped through a cell salvage machine where it is centrifuged and washed. The resulting RBCs are then pumped into a transfer bag. The RBCs may be reinfused to the patient immediately or at a later time.

Autologous RBCs obtained by blood salvage are usually transfused immediately; in special circumstances they can be stored, for a maximum of 6 hours, at 4±2 °C, but must be identified unequivocally.

Autologous RBCs which are re-transfused to the subject after start of first administration of IMP until end of surgery have to be included in the amount of RBCs to be defined for the secondary efficacy parameter.

Postoperative Drainage Volume

The plasma drainage tube and disposable drainage bag will be emptied 24 hours after the end of the surgery. The end of surgery is defined as time of last suture. The drainage volume will be measured and recorded.

Rebleeds

Any bleed judged by the surgeon and/or the anaesthesiologist as requiring haemostatic treatment (including reoperation) after the end of the surgery until follow-up Day 8 will be recorded. The end of surgery is defined as time of last suture.

Hospital Length of Stay after Surgery

The day of the surgery and the day of the discharge from hospital will be recorded.

The hospital length of stay after surgery is used to compare the number of days patients stayed in the hospital after surgery. The hospital length of stay after surgery is calculated by the following formula:

Length of stay after surgery = date of discharge - date of surgery

In-hospital Mortality

In-hospital mortality is defined as death occurring during the hospital stay. A death during hospitalization will be recorded as an SAE.

9.1.3 Specification of Efficacy Endpoints

9.1.3.1 Specification of Primary Efficacy Endpoint

Intra-operative blood loss as measured by amount of blood from the blood suction unit and amount of blood from surgical cloths and compresses after the decision to treat the subject with IMP until end of surgery. The end of surgery is defined as time of last suture.

9.1.3.2 Specification of Secondary Efficacy Endpoints

- Proportion (%) of subjects with successful correction of fibrinogen level 15 minutes after start of first IMP administration.

Successful correction of fibrinogen level in a subject is defined as restoring fibrinogen FIBTEM A10 baseline level to at least 95% measured by ROTEM 15 minutes after start of first IMP administration. A correction of at least 95% is considered successful, as measurement methods has a coefficient of variation of about 5% (Solomon et al., 2015).

- Time to first successful correction of fibrinogen level (15 minutes or 90 minutes after start of first IMP administration, end of surgery, not within surgery).
- Total amount of transfusion products (allogenic blood products) or autologous blood transfusion infused after start of first IMP administration until end of surgery. The end of surgery is defined as time of last suture.
- Amount of RBCs (allogenic and autologous) infused after start of first IMP administration until end of surgery. The end of surgery is defined as time of last suture.
- Post-operative blood loss in the first 24 hours.
- Proportion (%) of subjects with rebleeds.
  Rebleeds are defined as any bleed requiring haemostatic treatment (including reoperation) after the end of surgery until Day 8.
- Hospital length of stay after surgery, defined as the date of discharge minus the date of surgery.
- In-hospital mortality.

9.2 **Safety**

9.2.1 Specification of Safety Parameters

Safety and tolerability in this clinical study will be addressed by the following safety parameters:

- AEs
- Changes in vital signs (including pulse [heart rate], blood pressure, respiratory rate, body temperature)
- Change in clinical laboratory assessments of hematology, clinical chemistry and urinalysis.
- Change in clinical laboratory assessments of markers of coagulation:
  PT(INR), aPTT, TAT, F_{1+2},D-dimer, PS, PC, AT III, TT
- Change in clinical laboratory assessments of coagulation factors:
  FII, FV, FVII, FVIII, FIX, FX, FXI, FXIII
- Frequency and severity of thrombosis and of TEEs
- Virus status.

For the timing of individual safety parameters refer to section 7.1 Visit Schedule and section III FLOWCHART OF STUDY. Any abnormal observation or finding detected during the screening procedures after subject's informed consent that is considered clinically relevant must be documented as concomitant disease (ongoing medical history) or as past medical history. All medications other than the study medications should also be documented.

9.2.1.1 Adverse Events

After informed consent has been signed, AE data are obtained by the investigator through observation of the subject (including examinations and investigations) before, during and after surgery, from any information volunteered by the subject, and through active questioning. At each visit, subjects will be asked about AE that occurred since the last visit, by questioning them with regard to their well-being by 'non-leading' questions. All AEs should be recorded and reported to safety department (see section 9.3.2). This includes AEs occurring after informed consent has been signed (before, during or after surgery), as well as changes in concomitant diseases (i.e., ongoing medical history).

Occurrence, frequency, nature and severity of AEs will be recorded. This includes observations or abnormalities in physical examination, vital signs, laboratory or other investigations reported as AEs. Any treatments for AEs will also be recorded.

For further details regarding AEs including definitions and reporting procedures refer to Appendix 1: Safety Definitions.

9.2.1.2 Physical Examination

For each subject, a complete physical examination will be performed at the time points specified in III Flowchart of Study (before and after surgery). Physical examination includes inspection of general appearance, skin, neck (including thyroid) eyes, ears, nose, throat, heart, lungs, abdomen, lymph nodes, vascular system, extremities, musculoskeletal system and nervous system. Clinical findings and existing diseases at screening are to be documented as medical and surgical history. A new appearance of an abnormal finding or worsening of a concomitant disease that occurs after signature of informed consent must be documented as AE.

- BW is measured in kilograms (kg) only at screening visit and at baseline.
- Body height is measured in cm once at screening visit for the purpose of calculation of BMI.

9.2.1.3 Vital Signs

Before and after surgery (Screening, baseline, follow-up Day 2 to Day 36) vital signs are measured with the following methods/units:

- Blood pressure is measured in mmHg according to the Riva Rocci method while the subject has been resting in supine position for at least 15 minutes. The same arm should be used for blood pressure measurements throughout the study. The size of the cuff has to be chosen appropriately in relation to the subject's arm circumference.
- Heart rate and pulse is measured in beats per minute (either electronically and/or by palpation for 1 minute) while the subject is supine and has been resting for at least 15 minutes. When heart rate is of concern, cardiac monitors are used to determine not only rate, but also rhythm.
- Respiratory rate per minute.
- Body temperature is measured in °C.

<u>During surgery (Day 1):</u> Surgery/anaesthesia standard methods should be used for monitoring of vital parameters including standard measurement methods for blood pressure, pulse, heart rate and rhythm, respiratory rate and temperature. These

monitoring results are to be reviewed by the investigator, under consultation with a specialist if necessary.

Results must be summarized in writing and classified as ‘normal’ or ‘abnormal’. Abnormal monitoring results must in addition be classified as ‘abnormal, clinically not relevant’ or ‘abnormal, clinically relevant’. Abnormal, clinically relevant findings have to be reported as AE (unless already pre-existing at baseline with the same severity).

In addition, vital signs will be assessed and recorded in the eCRF at the following time-points: prior IMP treatment, 15 and 90 min after start of first IMP administration and end of surgery.

Measurements outside the normal range (according to the age and gender of the subject) or even changed values within the normal range showing a trend have to be assessed for clinical relevance by the investigator, and reported as AE if considered to represent a clinically significant change as compared to pre-treatment values.

9.2.1.4 Laboratory Parameters

All laboratory results have to be evaluated either in the eCRF or in the web-base tool of the central lab by the investigator/subinvestigator (anaesthesiologist) according to the following pattern:

a) Within reference range (normal range)
b) Outside reference range but not clinically relevant (e.g. marginal deviation only, due to underlying medical history diseases in the study population)
c) Outside reference range and clinically relevant

Laboratory values occurring (by date of blood sampling) after signature of informed consent, which are outside the reference range and assessed as clinically relevant (as determined by investigator), have to be documented as AE.

An abnormal laboratory value that is a sign of an AE (e.g. increased leukocytes due to bacterial infection) that has already been reported during the present clinical study, has to be documented as a symptom together with the diagnosis (bacterial infection) and does not constitute a separate AE.

For the routine laboratory parameters, the total volume of blood that will be drawn from a subject who completes the study is defined in the Laboratory Manual.

The laboratory parameters to be assessed are summarized in Table 2:

Table 2: Clinical Laboratory Parameters

Clinical Chemistry	**Assessment to be done locally or centrally**
• Alanine aminotransferase (ALAT)	• locally
• Aspartate aminotransferase (ASAT)	• locally
• Gamma-glutamyltransferase (ɣ-GT)	• locally
• Alkaline phosphatase (AP)	• locally
• Bilirubin (direct and indirect if total bilirubin is elevated)	• locally
• Creatinine / creatinine clearance	• locally
• Blood Urea Nitrogen (BUN) or Urea (UREA)	• locally
• Sodium	• locally
• Chloride	• locally
• Potassium	• locally
• Calcium	• locally
Hematology	
• Hematocrit	• locally
• Hemoglobin	• locally
• Red blood cells (RBCs)	• locally
• White blood cells (WBC)	• locally
• Differential white blood cells	• locally
• Platelets	• locally
Coagulation	
Markers of Coagulation	
• Prothrombin time (PT) / international normalized ratio (INR)	• locally
• Activated partial thromboplastin time (aPTT)	• locally
• Thrombin-antithrombin III complex (TAT)	• centrally
• Prothrombin fragments (F_{1+2})	• centrally
• D-Dimer	• centrally
• Protein S (PS)	• centrally
• Protein C (PC)	• centrally
• Antithrombin III (AT III) activity	• centrally
• Thrombin Time (TT)	• centrally
Coagulation Factors	
• Factor II (FII)	• centrally
• Factor V (FV)	• centrally
• Factor VII (FVII)	• centrally
• Factor VIII (FVIII)	• centrally
• Factor IX (FIX)	• centrally
• Factor X (FX)	• centrally
• Factor XI	• centrally
• Factor XIII (FXIII)	• centrally
Urinalysis	
• pH	• locally
• Qualitative for blood	• locally
• White blood cells (WBC)	• locally
• Protein	• locally
• Glucose	• locally
• Ketone bodies	• locally
• Bilirubin	• locally
• Urobilinogen	• locally
• Nitrites	• locally

The following markers of coagulation will be assessed at the time points specified in section III, Flowchart of clinical study:

- 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) value supplied by its manufacturer (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} a hypercoagulable state can be detected (Wagner C, 2008).

- Prothrombin Fragments 1 and 2 (F1+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 a hypocoagulable state (Wagner C, 2008).

- D-dimer

  D-dimer is a fibrin degradation product, 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).

- Antithrombin III (AT III) Activity (functional ATIII level)

  Antithrombin is a glycoprotein and is a natural anticoagulant that inhibits the activated coagulation factors thrombin (factor IIa), factor Xa, and, to a lesser extent, factor XIa and factor IXa. Heparin significantly increases the inhibition rate. The antithrombin level does not influence the results of screening coagulation tests such as partial thromboplastin time (PTT), PT, and TT (Teruya and Kostousov, Updated: Jan 30, 2014. Access Date: 15-Jun-2016.).

- Thrombin Time (TT)

  TT is a screening coagulation test designed to assess fibrin formation from fibrinogen in plasma. TT is performed as the next step in the evaluation of abnormally prolonged aPTT or PT (Rodgers and Lehman, 2007).

- Protein C (PC)

  PC is an inactive protein. When activated, it plays a significant part in blood clot, inflammation, and cell death regulation, as well as in maintenance of blood vessel cell wall permeability. The inactive form of PC circulates in blood plasma and is a vitamin K–dependent glycoprotein. When inactive PC binds to thrombin, it becomes activated (Beckmann et al., 1985; Foster et al., 1985; Mather et al., 1996).

  PC has a crucial role as an anticoagulant, and individuals with a PC deficiency or with some type of P activation dysfunction are at much greater risk of thrombosis (Beckmann et al., 1985).

- Protein S (PS)

  PS is a vitamin K-dependent plasma glycoprotein. The two forms of PS are a free form that is active and a complex form (65%) that is inactive (Lundwall et al., 1986).

  PS plays a significant role in the anticoagulation cascade, where it functions as a cofactor to the serine protease activated PC in the inactivation of factors Va and VIIIa. Through direct binding to factors Va, Xa, and VIII, PS exerts activated PC–independent anticoagulant activity (Francis, 1988). If the amount of PC or PS is inadequate or if either one is not functioning properly, thrombin generation essentially remains undeterred, which may promote inappropriate or excessive clotting, with resultant blockage of blood flow in the veins and, rarely, the arteries (thrombosis) (Esmon, 2003; Mosnier et al., 2007). (Bonhomme and Fontana, 2015; Castoldi and Rosing, 2011)

The following coagulation factors will be assessed at the time points specified in section III, Flowchart of clinical study:

- Factor II (FII)

  Clotting factor II, or prothrombin, is a vitamin K–dependent proenzyme that functions in the blood coagulation cascade (Harel et al., 2016).

- Factor V (FV)

  Factor V is an essential component in the blood coagulation cascade. The factor V protein is a catalyst, accelerating the process by which prothrombin is converted to thrombin, the initial step in clot formation.

- Factor VII (FVII)

  Factor VII is a vitamin K-dependent serine protease glycoprotein. The physiological activator of factor VII is thought to be factor Xa. The factor VIIa/tissue factor complex activates both factors IX and X (Roberts et al., 2001).

- Factor VIII (FVIII)

  Factor VIII (antihemophilic factor) is a key factor of the intrinsic clotting cascade. Normal hemostasis requires at least a quarter (25%) of factor VIII activity (Bishnu Prasad Devkota, Updated: Jan 17, 2014. Access Date: Jun 15, 2016.).

- Factor IX (FIX)

  Factor IX, or Christmas factor, is one of the serine proteases of the coagulation system. Factor IX can be activated either by factor XIa or by the factor VIIa/tissue factor complex. In complex with its cofactor, factor VIIIa, factor IXa activates factor X (Roberts et al., 2001).

- Factor X (FX)

  Clotting factor X, or Stuart-Prower factor, is a vitamin K–dependent serine protease that serves as the first enzyme in the common pathway of thrombus formation (Schwartz, Updated: Mar 01, 2017. Access Date: 15-Mar-2017.).

- Factor XI (FXI)

  Factor XI or plasma thromboplastin antecedent is the zymogen form of factor XIa, one of the enzymes of the coagulation cascade. It is a serine protease. Deficiencies of factor XI may lead to a bleeding tendency reflecting the significant role of factor XI in hemostasis (Roberts et al., 2001).

- Factor XIII (FXIII)

  Factor XIII (FXIII), which was initially termed fibrin stabilizing factor, is involved in clot preservation (Shanbhag et al., 2016). Thrombin, generated by reactions initiated by activated tissue factor VII/factor IX pathways, leads to clot formation. Fibrin monomers polymerize spontaneously; this is followed by development of a complex branching clot as a result of the actions of activated FXIII (FXIIIa) (Andersen et al., 2009; Casadio et al., 1999; Fox et al., 1999). Several controls in the complex activation process focus the actions of FXIIIa on fibrin rather than on fibrinogen. Cross-linking of polymerized soluble fibrin by FXIIIa is the final step in hemostasis (Lorand, 2000; 2001). (Sadler, 1998; Shahidi, 2017; Taylor, 2015)

In addition, the following specific safety laboratory parameters will be assessed at the time points specified in section III, Flowchart of clinical study:

- Pregnancy Test

  In females of childbearing potential, a pregnancy human chorionic gonadotropin test in serum will be performed at screening as specified in section III, Flowchart of clinical study. In addition, a second pregnancy test in urine (or serum) will be performed at baseline as specified in section III, Flowchart of clinical study. Pregnancy tests will be performed in the local lab.

- Virus Serology

  The immunological status of viral infections will be assessed at screening and closing visits for HIV, HBV and HCV, section III, Flowchart of clinical study. The following tests will be performed in the local lab:

  - **HIV** (anti HIV1 and anti HIV2)
  - **hepatitis B** (total hepatitis B core antibody [anti HBc], hepatitis B surface antibody [anti HBs], hepatitis B surface antigen [HBsAg])
  - **hepatitis C** (anti HCV)

9.2.1.5 Retention Samples

In order to respond rapidly to any reports on additional viral infections, a pre-treatment serum sample (5 mL) from each subject included in the study must be taken pre-dose and stored at -70 °C for possible future testing (screening visit).
At closing visit (D36) an additional serum sample (5 mL) must be taken and stored up to 6 months after study end.
Viral safety retention samples will be analysed in the central lab (if applicable).

9.2.2 Methods for Assessing and Recording Safety Parameter(s)

The following safety parameters are recorded in the eCRF: AEs, vital signs (including pulse [heart rate], blood pressure, respiratory rate, body temperature), clinical laboratory values of hematology, clinical chemistry and urinalysis. Clinical laboratory assessments of markers of coagulation and coagulation factors: PT(INR), aPTT, TAT, F1+2, D-dimer, PS, PC, AT III, TT, FII, FV, FVII, FVIII, FIX, FX, FXI, FXIII. Virus status.

For documentation of abnormal, clinically relevant findings refer to the respective sections above: section 9.2.1.4.

The results of all analyses performed by the central laboratory PPD , will be transferred to the investigational site, CRO's Data Management, and Biotest CCR&D Medical Advisor in a timely manner. All laboratory analyses performed by the local laboratory using standard assay methods will be transcribed to the eCRF by the investigator also in a timely manner.

For alert processes in the situation of abnormal results refer to Laboratory Manual.

9.2.3 Safety Endpoints

The following variables are defined as secondary safety endpoints:

- AEs
- Changes in vital signs
- Changes in clinical laboratory assessments of hematology, clinical chemistry, and urinalysis
- Changes in clinical laboratory assessments of markers of coagulation
- Changes in clinical laboratory assessments of coagulation factors
- Frequency and severity of thrombosis and of TEEs
- Virus status

9.3 **Adverse Events**

9.3.1 Definitions

(also refer to Appendix 1: Safety Definitions)

- **Adverse Event (AE)**
  Any untoward medical occurrence in a patient or clinical study subject administered an IMP and which does not necessarily have a causal relationship with this treatment. An AE may be any aggravation or new unfavorable and unintended sign, symptom, or disease temporally associated with the use of an IMP, whether or not considered related to the IMP (ICH Guideline for Good Clinical Practice E6(R2)).

- **Adverse drug reaction of an investigational medicinal product (ADR):**
  All untoward and unintended responses to an IMP related to any dose administered. All AEs judged by either the reporting investigator or the sponsor as

having a reasonable causal relationship to a medicinal product qualify as adverse reactions. The expression reasonable causal relationship means to convey in general that there is evidence or argument to suggest a causal relationship. All non-serious AE (related and not related) should also be entered in eCRF as soon as possible but not later than one month after occurrence.

- **Serious Adverse Event (SAE)**
  An SAE is any untoward medical occurrence or effect that at any dose*:
    - results in death
    - is life-threatening
    - requires hospitalization or prolongation of existing hospitalization
    - results in persistent or significant disability / incapacity
    - is a congenital anomaly / birth defect
    - is another important medical event

  * "At any dose" does not necessarily imply that the subject is receiving the study drug at the time of the event.

  Reporting requirements are detailed in Appendix 2.

- **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 requirements are detailed in Appendix 2.

  The following AEs have been defined as AESI for this study:
    - Thrombosis or TEE
    - Relevant bleeding complication:
      Relevant changes of a vital sign or laboratory value (e.g. severe tachycardia, severe hypotension, hypovolemic shock, severe anemia) occurring after IMP administration, during and/or after surgery that require immediate corrective action/treatment and are caused by bleeding.
      Note: Corrective treatment includes e.g. the administration of unplanned blood products or other drugs.
    - Suspicion of transmission of infective agents (viral safety).

- **Immediately Reportable Adverse Event (IRAE)**
  An AE that must be reported to the sponsor **within 24 hours** of the study site being aware of the AE. Reporting requirements are detailed in Appendix 2.

  For this clinical study, IRAEs include
    - all SAEs
    - all AESIs (serious and **non-serious**)
    - all AEs that result in a subject's withdrawal from the study (including suspected allergic reaction)
    - Medication error (incl. overdose)
      Pregnancy

- **Adverse Events Leading to Subject's Withdrawal from the Clinical Study**
  An AE, serious or non-serious, resulting in subject's withdrawal from the clinical study, i.e. permanent treatment discontinuation (see section 4.4). Reporting requirements by the investigator are detailed in section Appendix 2.

- **Medication Error**
  A medication error is an unintended failure in the drug treatment process that leads to, or has the potential to harm the patient (EMA Good Practice Guide definition).
  - A 'failure in the drug treatment process' does not refer to lack of efficacy of the drug, rather to human or process mediated failures.
  - The error is unintended. The concepts of intentional overdose, off-label use, misuse and abuse as defined in GVP (good pharmacovigilance practices) Module VI.A.2.1.2 are outside scope and should be clearly distinguished from medication errors.
  - 'Drug treatment process' includes prescribing, storing, dispensing, preparation for administration and administration of a medicine in clinical practice.

  The dose and administration of the study medication is described in section 6 Study Treatment. Any deviation from the study medication (wrong medication, wrong dose, wrong route of administration, wrong patient) is a medication error. Any higher administered dose of the study medication, than described in section 6 Study Treatment, is an overdose.

9.3.2 Recording Adverse Events

All AEs, serious and non-serious, that occur during the period of observation defined for the clinical study (section III, Flowchart of Study) have to be fully documented in the eCRF according to the provisions given in this section of the study protocol and eCRF completion guidelines, as well as in the subject's source data. This applies also to AEs in subjects who signed the informed consent but never received the study drug. AEs considered not related to study medication observed after Day 36 (defined closing visit) will not be recorded in the eCRF.

In addition, for a subset of AEs (SAE, AESI, AE leading to withdrawal) immediate reporting from investigator to sponsor is required (Immediately Reportable Adverse Events, IRAE). This is further detailed in Appendix 2. The following information is necessary:

- **Diagnosis vs. Signs/Symptoms**
  The investigator should provide a diagnosis rather than individual signs and symptoms, wherever possible and appropriate. However, if there is not enough information to provide a diagnosis, individual signs and symptoms are to be recorded. If a diagnosis is accompanied by unusual symptoms, the diagnosis itself and the unusual symptoms have to be reported separately. For serious and other IRAEs the investigator shall provide any other supporting information that may be required for the assessment of the events.

  A complication of an AE constitutes another AE. For example in diarrhea leading to dehydration, diarrhea and dehydration would be captured as separate AEs.

  The eCRF provides for a number of items to be completed for each AE. This includes the onset date, end date, intensity/severity, seriousness, action taken with

study medication, treatment for the AE, outcome, and causal relationship of the AE with the study medication, other drugs, or study procedures (Appendix 2: Reporting Procedures).

Severe vs. Serious: The severity is used to describe the intensity of an event. This is not the same as seriousness, which is based on subject/event outcome or action criteria usually associated with events that pose a threat to subject's life or functioning. Seriousness, not severity, serves as the guide for defining regulatory reporting obligations.

- **Causal Relationship of AE**

  The causal relationship with the study medication has to be reported for each AE. It refers to the presence or absence of a reasonable possibility of a causal relationship between the study medication and the AE.

  The investigator is asked to use medical judgment and take into account the nature of the AE, subject's medical and surgical history, temporal relation, response to withdrawal or interruption of study drug (dechallenge), response to re-introduction of study drug (rechallenge), any alternative explanations such as underlying or concomitant diseases, concomitant drugs, study procedures.

  The investigator should also provide the causality assessment with the NIMP (e.g. background medication, concomitant medication - See Appendix 1 for definition).

  The following categories are used:

  - Related: There is a reasonable possibility of a causal relationship between the study medication and the AE.
  - Not related: There is no reasonable possibility of a causal relationship between the study medication and the AE.

  For serious and other immediately reportable AEs the investigator is asked to specify if there are alternative and/or additional explanations for the occurrence of the event, e.g. concomitant drugs, study procedures, or concomitant/underlying disease and should provide this information already with the initial case report.

9.3.3 Period of Observation

The period of observation for collection of AEs extends from the time the subject signs the ICF until the last study visit (D36), which is scheduled 5 weeks after the day of the surgery (day of IMP administration).

Abnormal, clinically relevant findings or observations made prior to signature of informed consent are to be recorded as medical history/concomitant disease but not as AEs.

AEs (including any change in severity or trait of the concomitant disease/ medical history) occurring in the pre-treatment period between signature of informed consent until first administration of study medication are non-treatment emergent AEs (NTEAEs).

AEs (including any change in severity or trait of the concomitant disease/ medical history) occurring from the administration of study medication until the subject's last study visit are treatment-emergent AEs (TEAEs).

If an SAE occurs in a subject after the period of observation, i.e. after the last study visit, which is considered by the investigator to be related to the study medication, this should be recorded as SAE and follow the immediate reporting process for SAEs as described

in Appendix 2. If the eCRF has been closed for the subject, the investigator should contact the sponsor to determine how to report the SAE (see also section 7.4).

9.3.4 Assessment of Adverse Events

- **Responsibilities of Investigator**

  AEs are assessed by the investigator in a standardized manner including, but not limited to the seriousness, severity, outcome, and causality. This has to be performed in line with the definitions and provisions given in Appendix 1.

  Laboratory values outside the reference range have to be assessed for clinical relevance taking into account the pre-treatment values. For reporting of abnormal laboratory values as AEs refer to section 9.2.1.4.

  If an AE meets the definition of any of the mandatory AE related stopping rules (section 9.3.1), the investigator must withdraw the subject and report the AE as IRAE according to section Appendix 2. If no mandatory AE related stopping rules defined for the study, delete this sentence.

  For all AEs the causality assessment has to be provided in the eCRF, even if based on preliminary data. Once more information is available, the investigator may change a preliminary causality assessment.

  During and after participation of a subject in a clinical study the investigator/institution has to ensure that adequate medical care is provided to the subject for any ongoing AEs including clinically significant abnormal laboratory values. The investigator has to inform the subject when medical care is needed for any intercurrent disease of which the investigator becomes aware.

- **Responsibilities of Sponsor**

  AEs are reviewed and assessed by the sponsor during ongoing safety monitoring activities throughout the study, as well as medical evaluation and regulatory assessment for reportability of SAEs and IRAEs. For the purpose of regulatory reporting, the causality assessment given by the investigator will not been 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.

  Regulatory assessment of an AE by the sponsor comprises further the assessment of expectedness. For BT524, Fibrinogen Concentrate from Human Plasma it is based on section 7 of the IB . For FFP it is based on the Summary of Product Characteristics of a reference FFP product PPD , solution for infusion, PPD).

- **Follow-up of Adverse Events**

  AEs 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 AEs, 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 subject ID, 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 Appendix 2.

AE data in the eCRF 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.

9.3.5 Immediate Reporting by Investigator to Sponsor

(also refer to Appendix 2: Reporting Procedures)

9.3.6 Use of IMP outside the Specifications of the Clinical Study Protocol

Situations may occur where the IMP is used outside the specifications of the protocol, which may or may not be associated with an AE. These special situations comprise

- Medication errors (including overdose)
- Abuse/ misuse of the IMP.

Such situations, whether or not associated with an AE, are documented in the eCRF on dedicated pages. Any AE that occurred in association with such a special situation has to be cross-referenced on the dedicated eCRF page. An IRAE/SAE occurring in conjunction with a medication error or abuse/ misuse of the IMP has to follow the

immediate reporting process for IRAE/SAE as described in Appendix 2 in addition to its documentation in the eCRF (also refer to sections 9.3.8 and 10.2).

9.3.7 Investigational Medicinal Product Complaints

IMP complaints must be recorded in the eCRF and in addition reported to the sponsor on the "Investigational Medicinal Product Complaint Report Form" **within 24 hours** of the investigator becoming aware of the IMP complaint. If the IMP complaint is associated with an AE, the AE must be entered in the eCRF also.

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

9.3.8 Special Situations Requiring Immediate Reporting

Special situations may occur that may or may not be associated with AEs. For these situations special reporting provisions apply.

Special situations comprise:

- Pregnancy in a female study subject or the partner of a male study subject
- Investigational Medicinal Product Complaint.
- Use of IMP outside the specifications of the Clinical Study Protocol (CSP) (e.g. Medication errors, overdose, misuse and abuse (also refer to sections 9.3.6 and 10.2).
- Protocol deviations (refer to section 10.2)

If such a situation occurs, the investigator should contact the sponsor immediately. A special paper report form has to be completed always in these situations and sent to the sponsor immediately, but not later **than 24 hours** after the investigator becoming aware of the situation.

9.3.8.1 Pregnancy

Pregnant women are excluded from the study, and female study subjects of child-bearing potential undergo pregnancy testing at screening and regularly during the study (section III, Flowchart of study). If pregnancy is suspected in a study subject during treatment with the IMP, the IMP must be immediately withheld until the result of a confirmatory test is available. If confirmed, the subject must be withdrawn from the study.

Although not an AE per se, pregnancy in a female study subject or the partner of a male study subject must be recorded if it occurs during the period of observation of the study (see definition in section 9.3.3). The investigator must contact the sponsor immediately in such a situation.

The pregnancy must be documented on a "Drug Exposure Via Parent" (DEVP) Report Form and reported to the sponsor **within 24 hours** of the investigator becoming aware of the pregnancy. If an AE occurs in relation to the pregnancy, it has to be noted on the DEVP form and recorded in the eCRF. If an IRAE/SAE occurs in relation to the pregnancy, it has to be noted on the DEVP form and recorded in the eCRF and follow the immediate reporting process for IRAE including SAE as described in Appendix 2.

The investigator must make all reasonable efforts to follow up the pregnancy until its end and will report all outcomes associated with the pregnancy to the sponsor. In the situation of pregnancy of the female partner of a male study subject, consent for the release of

medical data should be obtained from the female partner to allow collection of information on the outcome of the pregnancy.

9.4 Data Safety Monitoring Board

A DSMB will independently monitor the study.

The DSMB will independently review and assess the unblinded safety data throughout the entire study at regular intervals. The DSMB consists of three voting members: an expert in pharmacovigilance, an expert in the field of hematology/hemostaseology and an expert in anaesthesiology. Two members of the DSMB constitute a quorum.

In addition, a statistician without a vote will be responsible for adequate data supply. Prior to the data safety monitoring phase, a meeting will be held to familiarize the DSMB with all relevant procedures. The DSMB members are unblinded during both evaluation periods and will be provided with the following information: reports of SAEs and AEs, data on markers of coagulation and coagulation factors, clinical laboratory assessments of hematology, clinical chemistry and urinalysis, and vital signs.

DSMB meetings will take place at regular intervals. The DSMB will be provided with data covering the screening visit, the day of surgery plus 4 additional follow-up visits (Day 2, 3, 5 and 8) and will evaluate the subjects' risks at a formal DSMB meeting with regards to the relevant parameters and outcome criteria. In addition, subject's data from the closing visit will also be evaluated if data already available at the time of the DSMB meeting. After each meeting treatment of the following subjects can continue unless the DSMB has not actively disapproved it.

Minutes of the DSMB will describe the proceedings from all sessions of the DSMB meeting, and will summarize all recommendations, which will also be reported to Biotest and the principal investigator.

The DSMB members can propose to stop the study at any time after a scheduled or unscheduled meeting in case of major safety concerns related to study treatment.

Further details will be provided in the DSMB Charter.

10 STATISTICS

The statistical planning and evaluation of the clinical study will be carried out by a qualified biostatistician in accordance with the ICH-guidelines and adequate biostatistical SOPs in SAS version 9.4 or later. A detailed Statistical Analysis Plan (SAP), providing details about the statistical methods for the analyses, will be finalized before unblinding. This ensures that the integrity of the analyses is maintained.

Any deviations from the planned analyses will be described and justified in the Clinical Study Report (CSR).

10.1 **Analysis Sets**

The following analysis sets will be defined:

All Subjects Enrolled Set:
The All Subjects Enrolled Set includes all subjects who have given informed consent to this study.

Safety Set (SAF):
The SAF comprises all subjects who have received at least one dose of IMP. Subjects will be analyzed according to the treatment received.

Full Analysis Set (FAS):
The FAS comprises all subjects who received at least one dose of IMP prior to the 'end of surgery' and have at least one post dose efficacy assessment.

Subjects will be analyzed as randomized.

Per-protocol Set (PPS):
The PPS includes all subjects who are compliant with the study protocol without any major protocol deviations thought to have the potential to impact the results of the efficacy analysis, e.g. no treatment with IMP, treatment with IMP after the 'end of surgery', no post dose efficacy assessment. Classification of protocol deviations as major or minor will be agreed upon at the Blind Data Review Meeting (BDRM) prior to database lock.

Subjects will be analyzed according to the treatment received.

10.2 **Protocol Deviations**

Deviations from the protocol will be documented on an on-going basis during conduct of the clinical study based on monitoring reports (e.g. failure of eligibility criteria), data management checks and statistical programming (e.g. prohibited medications based on drug codes). Protocol deviations will be discussed and agreed in the BDRM to find protocol deviations with major impact on subject safety or the validity of the study data. Subjects with major protocol deviations will be excluded from the PPS under the assumption that the deviation may have an impact on the efficacy analysis.

The investigator should not implement any deviation from, or changes of the protocol without agreement by the sponsor and prior review and documented approval/ favorable opinion from the IRB/IEC of an amendment, except where necessary to eliminate an immediate hazard(s) to study subjects. The investigator, or person designated by the investigator, should document and explain any deviation from the approved protocol.

10.3 General Considerations

BT524 will be compared with standard treatment (FFP/cryoprecipitate) whereas FFP and cryoprecipitate will be considered as one treatment group.

The global significance level will be 2.5% (one-sided), confidence intervals will be 95% (two-sided). All statistical tests will be two-sided, unless otherwise stated.

Quantitative (continuous) data - absolute values and differences from baseline, where appropriate - will be summarized with number of observations (n), arithmetic mean, standard deviation, median, minimum, and maximum.

Qualitative (categorical) data will be summarized using number of observations (n), frequency and percentages of subjects. Unless stated otherwise the calculation of percentages will be based on the total number of subjects in the population of interest. Thus counts of missing observations will be included in the denominator and presented as a separate category.

Definition of Baseline

If not stated otherwise, the last non-missing valid observation prior to surgery will serve as the baseline measurement.

Missing Data Conventions

In this short study, not many missing values are expected. Therefore, data will not be imputed for safety analyses or continuous efficacy endpoints.

For binary endpoints, an observed case analysis (excluding missing data) will be considered to be the primary analysis method and a non-responder analysis (treating missing values as non-responders or the worst case) may be performed as a sensitivity analysis if deemed necessary. Details will be given in the SAP.

Pooling of Centers

In case of low number of subjects per center, summaries of data by center would be unlikely to be informative. Therefore, data from all centers per country/region (if applicable) and in total will be pooled prior to analysis.

Subgroups

A subgroup analysis according to the predictive blood loss is planned at least for the primary efficacy variable blood loss.

Disposition

The number of subjects screened and who failed screening prior to surgery or during surgery will be summarized. The number of subjects randomized; number and percentage of subjects treated with IMP; and number and percentage of subjects who prematurely withdrew from the study with the reason for withdrawal will be summarized by treatment arm. The number and percentage of subjects in each of the analysis sets will also be summarized by treatment arm.

Demographic and Baseline Data

Demographic and baseline data will be summarized descriptively.

10.4 Efficacy Analyses

Analyses of the efficacy parameters will be based on the PPS and FAS as appropriate and defined in the SAP.

10.5 **Primary Efficacy Analysis**

The primary endpoint / efficacy variable is the intra-operative blood loss after decision to treat the subject with IMP until the end of surgery as measured and calculated by amount of blood from the blood suction unit and amount of blood from surgical cloths and compresses.

The primary analysis of this endpoint will test for non-inferiority in the PPS.

The null hypothesis for the primary analysis is that the degree of inferiority of BT524 compared to standard treatment (FFP/cryoprecipitate) is greater than or equal to the non-inferiority margin. The alternative hypothesis is that the degree of inferiority of BT524 compared to FFP/cryoprecipitate is less than the non-inferiority margin.

H_0: $\mu_1 - \mu_2 \geq \delta$
H_1: $\mu_1 - \mu_2 < \delta$

where

μ_1 = mean intra-operative blood loss after the decision to treat the subject with IMP in the BT524 treatment arm
μ_2 = mean intra-operative blood loss after the decision to treat the subject with IMP in the FFP-/cryoprecipitate-treatment arm
δ = non-inferiority margin = 150 mL

The final analysis will be performed using ANCOVA with the intra-operative blood loss after the decision to treat the subject with IMP until the end of surgery as the dependent variable and the predictive blood loss (>1,000 mL to ≤ 2,000 mL and > 2,000 mL) as a covariate. The least square means and difference in least square means will be presented with the corresponding 95% confidence intervals and 2-sided p-value. Non-inferiority will be demonstrated if the upper confidence limit of the 2-sided 95% confidence interval for the difference in the least square means is less than the non-inferiority margin (150 mL).

This analysis will also be performed in the FAS as a sensitivity analysis.

If non-inferiority is demonstrated, then superiority will be assessed in the FAS with superiority demonstrated if the 2-sided p-value is less than 0.05 (i.e. the upper confidence interval is less than 0 mL) using the analysis performed to assess Non-Inferiority.

No imputation for missing values will be applied.

10.6 **Secondary Efficacy Analyses**

All secondary efficacy analyses will be conducted with the FAS. The secondary endpoints / efficacy variables are:

- Proportion (%) of subjects with successful correction of fibrinogen level 15 minutes after start of first IMP administration. Successful correction of fibrinogen level in a subject is defined as restoring fibrinogen FIBTEM A10 baseline levels measured by ROTEM 15 minutes after start of first IMP administration. A correction of at least 95% is considered successful.
- Time to first successful correction of fibrinogen level (15 minutes or 90 minutes after start of first IMP administration, end of surgery, not within surgery).

- Total amount of transfusion products (allogenic blood products) or autologous blood transfusion infused after start of first IMP administration until end of surgery.
- Amount of RBCs (allogenic and autologous) infused after start of first IMP administration until end of surgery.
- Post-operative blood loss in the first 24 hours.
- Proportion (%) of subjects with rebleeds after the end of the surgery until Day 8.
- Hospital length of stay after surgery.
- In-hospital mortality.

10.6.1 Correction of Fibrinogen Level

The proportion of subjects with a successful correction of fibrinogen level will be compared between the treatment arms using a CMH approach stratified by predictive blood loss (> 1,000 mL to ≤ 2,000 mL and > 2,000 mL). The number and percentage of subjects with a successful correction of fibrinogen level will be presented with corresponding 95% confidence intervals. The estimated treatment effect (i.e., the difference in correction rate between the treatment arms), corresponding 95% confidence interval, and 2-sided p-value for the difference will be presented.

The time to first successful correction of fibrinogen level will be compared between the treatment arms using a Chi-Square test. The number and percentage of subjects reaching a successful correction at each time point (15 minutes or 90 minutes after start of first IMP administration, end of surgery, not within surgery) will be presented together with the p-value for differences between treatment arms.

Absolute values and change from baseline in fibrinogen levels will be presented descriptively over time by treatment arm.

10.6.2 Consumption of Transfusion Products

The total amount of transfusion products (allogenic blood products or autologous blood transfusion or cell salvage) infused until end of surgery will be descriptively summarized by type of transfusion product and treatment arm.

10.6.3 Amount of Red Blood Cells

The amount of RBCs required intra-operatively will be descriptively summarized by treatment arm.

An ANCOVA analysis will be performed with the amount of RBCs required as the dependent variable and the predictive blood loss (> 1,000 mL to ≤ 2,000 mL and > 2,000 mL) as a covariate. The least square means and difference in least square means will be presented with the corresponding 95% confidence intervals and 2-sided p-value.

10.6.4 Post-operative Blood Loss

The post-operative blood loss in the first 24 hours will be descriptively summarized by treatment arm.

An ANCOVA analysis will be performed with the post-operative blood loss in the first 24 hours as the dependent variable and the predictive blood loss (> 1,000 mL to ≤ 2,000 mL and > 2,000 mL) as a covariate. The least square means and difference in least square

means will be presented with the corresponding 95% confidence intervals and 2-sided p-value.

10.6.5 Proportion of Subjects with Rebleeds

The proportion of subjects with rebleeds after the end of surgery (until Day 8) will be compared between the treatment arms using a CMH approach stratified by predictive blood loss (> 1,000 mL to ≤ 2,000 mL and > 2,000 mL). The number and percentage of patients with a rebleed will be presented with corresponding 95% confidence intervals. The estimated treatment effect (i.e., the difference in rebleed rate between the treatment arms), corresponding 95% confidence interval, and 2-sided p-value for the difference will be presented.

10.6.6 Hospital Length of Stay after Surgery

The hospital length of stay after surgery will be descriptively summarized by treatment arm.

10.6.7 In-hospital Mortality

The number and percentage of subjects died during hospital stay will be presented by treatment arm.

10.7 **Safety Analysis**

AEs will be coded using the most current version of Medical Dictionary for Regulatory Activities (MedDRA®). The version used will be defined in the SAP. Incidence rates (i.e. number and percentage of affected subjects) will be calculated for the coding levels *SOC* and *preferred term* and will be presented by treatment arm. Further analyses of AEs will focus on seriousness, intensity, causal relationship to IMP, and outcome. IRAE including SAEs etc. will be displayed in detail.

Safety laboratory assessments (hematology, clinical chemistry, urinalysis and coagulation parameters) 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” by treatment arm as well as summarized with descriptive statistics by time point and treatment arm.

Vital signs data will be summarized descriptively before and after surgery by treatment arm.

The frequency of thrombosis and of TEEs, virus status, exposure data and concomitant medication will be summarized by treatment arm.

All safety analyses will be based on the SAF.

10.8 **Interim Analyses**

In this study, 3 interim analyses of the observed blood losses are planned to have the option of adjusting the sample size needed (primary: PPS, secondary: FAS).

For this purpose, an alpha-adjustment according to Haybittle/Peto (Haybittle, 1971; Peto et al., 1976; Schulz and Grimes, 2005) is planned. This leads to local alpha levels of 0.001 for each interim analysis and a significance level of 0.05 for the final analysis to reach a global significance level of 5%.

All interim analyses will be based on the PPS.

The first interim analysis is planned with approximately 50 spine subjects, the second one with at least 40 PMP subjects and all other evaluable spine subjects at that time-point. The third interim analysis is planned after approximately 80% of subjects of the total sample size.

Aim of all interim analyses is to adapt the sample size according to the observed blood losses and the standard deviations:

a.) Early termination due to non-inferiority of BT524 in comparison with the used standard therapies.
b.) Continuation with the sample size as initially planned.
c.) Adjustment of sample size to take into account changes from the previous assumptions on the additional blood loss.
d.) Stopping the study early due to futility if the sample size re-estimation indicates a much higher number than planned before.

10.9 **Determination of Sample Size**

The non-inferiority margin is defined as 150 mL blood loss, as such difference in blood loss after the decision to treat the subjects with IMP is considered as clinically not relevant.

The intra-operative blood loss of approximately 1 L, requiring hemostatic treatment during surgery, is defined as the time of decision to treat the subjects with IMP. Based on the assumption of an additional blood loss of about 500 mL in the FFP-/cryoprecipitate-treatment arm after the decision to treat, a further intra-operative blood loss of approximately 150 mL would not lead to a further transfusion of ≥ 1 unit of packed RBCs, ≥ 1 unit of FFP/cryoprecipitate, or ≥ 1 unit of whole blood.

Whole blood contains RBCs and plasma components of circulating blood. A single whole blood donation contains approximately 500 mL of blood with a minimum hematocrit of 38%. When the plasma is removed, RBCs remain and have a hematocrit of > 80% and a volume of 225-350 mL. Additive solutions mixed with the red cells result in a hematocrit of 55-65% and a volume of 300-400 mL. One unit of whole blood or one unit of RBCs can be expected to result in a hemoglobin increase of 1 g/dL or a hematocrit increase of 3% in a typical adult. Therefore, one unit of RBCs can replace a blood loss of 500 mL (Avery and Avery, Spring 2010; Liumbruno et al., 2009). Accordingly, a volume of 150 mL (after an assumed blood loss of 500 mL) is still below a clinically relevant blood loss and would not trigger an additional administration of transfusion products.

It is assumed that BT524 is non-inferior that means not worse than FFP/cryoprecipitate with a non-inferiority margin of 150 mL in reducing intra-operative blood loss. Assuming a blood loss of about 500 mL in the FFP-/cryoprecipitate-treatment arm after the decision to treat the subject with IMP until end of surgery, a standard deviation of 375 mL, a non-inferiority margin of 150 mL, an alpha-level of 2.5% (1-sided) 100 evaluable subjects per treatment arm are needed to demonstrate the Non-Inferiority of BT524 by using a t-test (equivalence) with 80% power.

The sample size will be recalculated at the interim analyses as defined in section 10.8. Sample size estimations will be performed by using nQuery Advisor Version 4.0 or higher.

With 100 subjects per treatment arm superiority of BT524 can also be tested with a power of >80% (t-test, alpha=0.05 2-sided, effect size Δ=0.5).

10.9.1 Data Monitoring

After 40 subjects have completed the study, the overall mean and standard deviation for the primary efficacy variable intra-surgery blood loss after decision to treat the subject with IMP will be derived using blinded aggregate data of all 40 subjects without separating according to treatment.

If the assumed mean and standard deviation blood loss are not reflected in these subjects, then a sample size adjustment will be considered to ensure that a sufficient number of subjects has been randomized to maintain a power of 90%.

If an adaption of the sample size is intended, this will be documented in a protocol amendment.

This data monitoring is not an interim analysis because the analysis is performed with all subjects without separating the subjects according to treatment. Therefore, no alpha-adjustment is necessary.

11 DATA MANAGEMENT

11.1 **Data Collection**

Electronic Case report form (eCRF)

The eCRF is the primary data collection instrument for the clinical study. All data to be recorded according to this CSP must be documented. 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 in each study site.

eCRF completion guidelines will be provided as electronic version with the eCRF as a link on the dashboard.

Clinical study data will be directly entered via eCRF into the study database on a central server by authorized investigator and/or study personnel.

It is ensured that the *electronic data capture (*EDC) system (including the eCRF) is built up with following requirements: validated system, functionality of different user roles and access administration, password protection, given traceability, record keeping, and availability of audit trail functionality as well appropriate standard operation procedures are maintained.

The investigator and/or assigned study personnel at each site will enter data from source documents corresponding to a subject's visit into the protocol-specific eCRF. Subjects will be identified by a unique study specific number and/or code in any database. The subject's name and any other identifying detail will not be included in any study data-electronic file.

Laboratory samples (e.g. safety lab, clinical immunology, pharmacokinetic, other study specific laboratory data) will be collected and analyzed in local labs at each site or shipped to central lab for analysis (section 9.2.1.4). The results of local lab samples will be sent back to the investigator to be entered into the eCRF. The central lab data will be available for evaluation by the investigator via the web-based tool provided by the vendor.

Data will be sent to the CRO on a regular basis to join with the clinical data entered via eCRF.

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

MedDRA® dictionary will be used for coding of AE, concomitant diseases and medical history. Concomitant medication will be coded using the Word Health Drug Dictionary (WHO-DD). Details are provided in the data management plan and the study specific safety manual.

11.2 Correction of Data

After data have been entered into the clinical study database, a system of computerized data validation checks will be implemented and applied to the database on a regular basis.

Definition and details are provided in the data validation specifications.

Queries are entered, tracked, and resolved through the eCRF system directly. If a correction is required for an eCRF, the time and date stamps tracking function creates an electronic audit trail for the person entering/updating the eCRF data.

11.3 Data Handling

The data will be entered into a validated database. The Data Management personnel will be responsible for data processing, in accordance with procedural documentation. Database lock will occur once all data entered are clean and quality assurance procedures have been completed.

All procedures for the handling and analysis of data will be conducted according to available ICH-GCP guidelines for the handling and analysis of data for clinical studies.

12 QUALITY CONTROL AND QUALITY ASSURANCE

12.1 Study Initiation Activities

The investigator(s) is/are 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.

12.2 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 investigational product(s) 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.

12.3 **Documentation and Filing**

List of Subjects (subject identification log)

The investigator is asked to keep a confidential list of names of all subjects participating in the study, giving reference to the subjects' records.

With the help of this list it must be possible to identify the subjects and their medical records. In addition, the investigator is asked to keep a list of all subjects screened on a screening log to document identification of subjects 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, subjects' 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, subject files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical study). Any data recorded directly in the eCRFs (i.e. no prior written or electronic record of data) will also be considered to be source data.

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, but at **least for 25 years** after completion of the study.

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

12.4 **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 subjects' source data.

The extent and nature of monitoring will be described in detail within the monitoring plan.

12.5 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, PM-CRO (Project Manager CRO) or CCR (Clinical Manager (cM) Biotest) 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 has to notify the sponsor immediately of any such inspection. The investigator and institution will permit and support 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. The principal investigator shall personally participate in all audits and inspections.

12.6 Archiving

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

13 GENERAL REGULATIONS, AGREEMENTS AND ORGANISATIONAL PROCEDURES

13.1 Study Administrative Structure

Details for the study administrative structure are kept as a separate list filed in the Trial Master File.

13.2 Ethical and Regulatory Considerations

This CSP and any amendments will be submitted to a properly constituted Independent Ethics Committee (IEC) / Institutional Review Board (IRB) and/or Regulatory Authorities (RA), 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 CSP must be made in the form of an amendment that has the prior written approval of Biotest. Substantial CSP amendments need to be notified to/approved by IEC/IRB and/or Competent Authorities (CA) / Regulatory Authorities (RA) prior to implementation as required by applicable regulations.

The clinical study will be performed according to the applicable regulatory requirements taking into account the principles of GCP and the latest version of the Declaration of Helsinki.

13.3 Committees / Monitoring Boards

Safety data from the clinical study will be evaluated by a DSMB at regular intervals during the study, to ensure that the continuation of the study is appropriate and to make recommendations to the sponsor. The DSMB will consist of permanent members who are not associated with the sponsor or with the operative conduct of the study. A description of the scope of work and operating procedures for the DSMB is provided in the DSMB Charter. The composition of the DSMB will also be outlined in the DSMB Charter.

13.4 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.

13.5 Insurance/Liability

In accordance with the relevant national regulations, the sponsor has taken out a subject liability insurance for all subjects who have given their consent to the clinical study. The subjects are insured against injury caused by study medication or participation. The subjects 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.

13.6 Investigator's Brochure (IB)

The investigator will be informed about current knowledge concerning the study medication BT524 through an Investigator´s Brochure (IB). All investigators will be informed immediately about relevant new information available.

13.7 Amendments to the Protocol

Changes to the CSP must be made in the form of a CSP Amendment that has the prior written approval of Biotest. Substantial changes to the protocol need to be notified to/approved by IEC/IRB and/or Regulatory Authorities prior to implementation, as required by applicable regulations.

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

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

13.8 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.

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996. Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

13.9 **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 CSR **within < 1 year** 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, are to 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.

14 LIST OF REFERENCES

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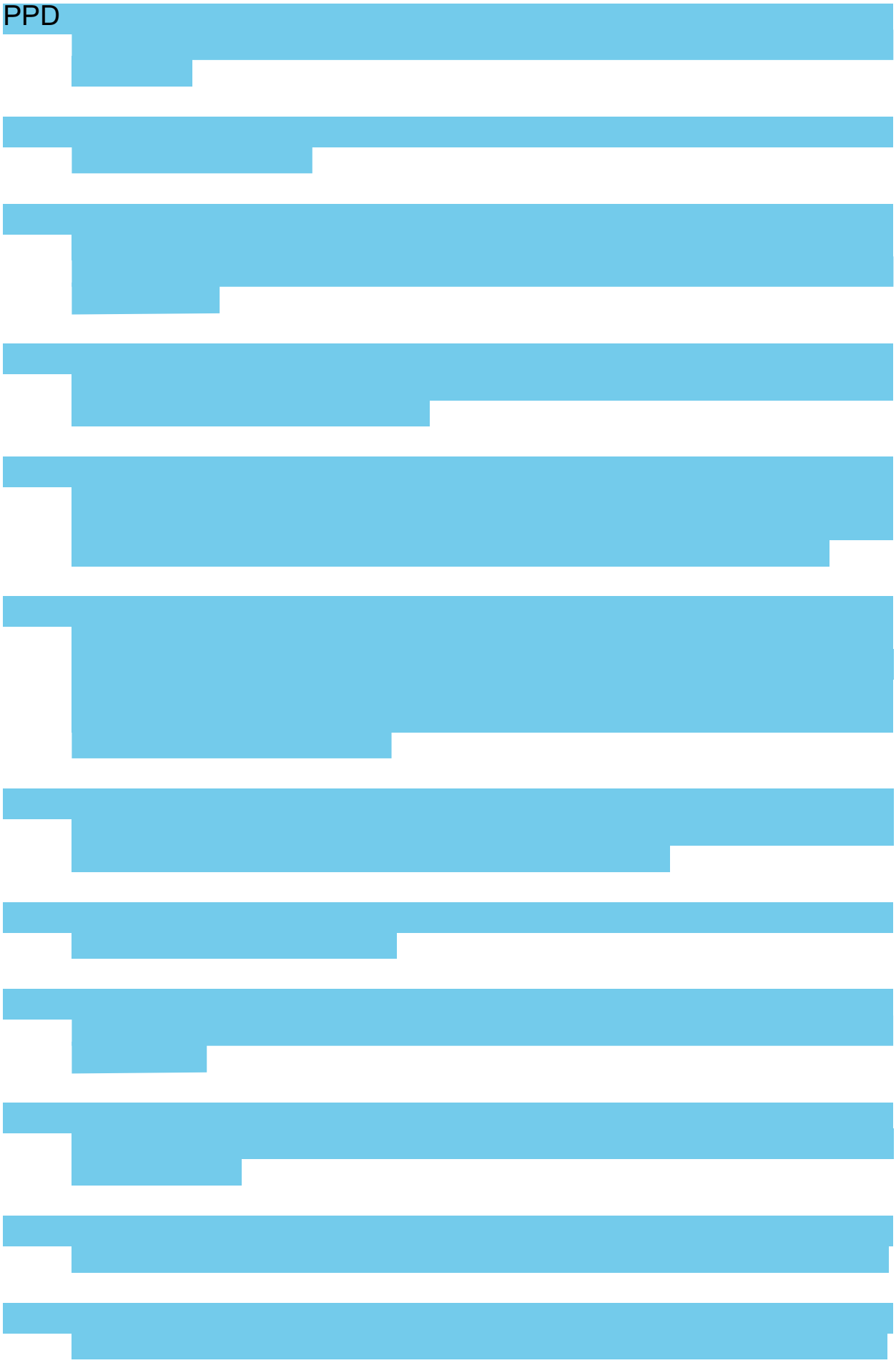

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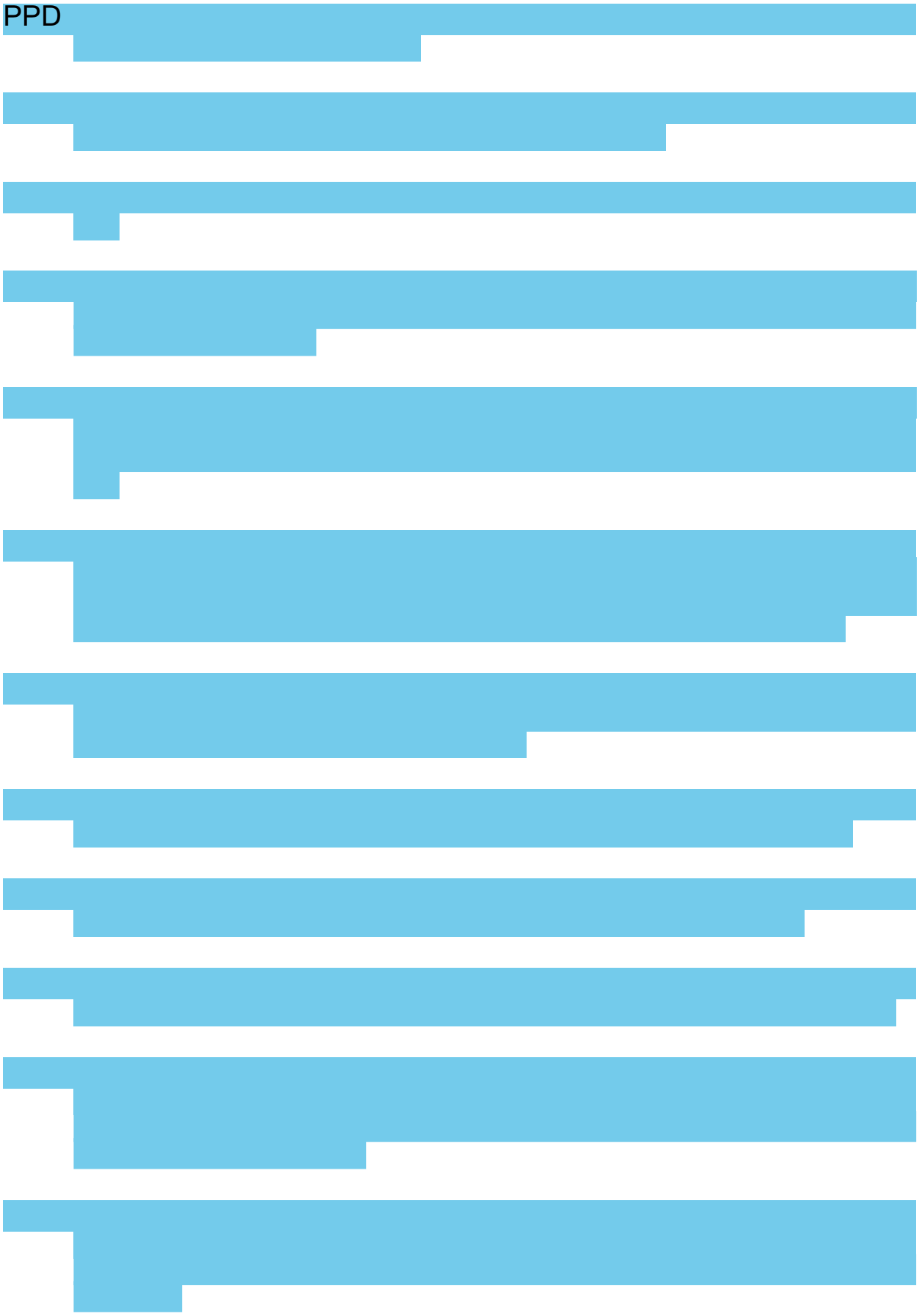

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15 APPENDICES

Appendix 1: Safety Definitions

Appendix 2: Reporting Procedures

Appendix 1: Safety Definitions

- **Adverse Event (AE)**

  Any untoward medical occurrence in a patient or clinical study subject administered an IMP and which does not necessarily have a causal relationship with this treatment. An AE may be any aggravation or new unfavorable and unintended sign, symptom, or disease temporally associated with the use of an IMP, whether or not considered related to the IMP.

  This includes abnormal laboratory and other investigation results which are considered clinically relevant by the investigator (unless already pre-existing at baseline). However, if an abnormal laboratory value is a sign of an already reported AE (e.g. infection), the respective abnormal laboratory value does not constitute a separate AE.

  A surgical or invasive procedure is not an AE in itself. Instead, the condition for which the surgical or invasive procedure is performed may be an AE. Planned or elective surgery or procedures (i.e. planned prior to signature of informed consent) for a pre-existing condition and the pre-existing condition leading to surgery or procedure are not AEs. However, if the pre-existing condition worsened after signature of informed consent, the worsening of the condition constitutes an AE.

  Worsening of the disease under study (underlying disease): This will be captured by efficacy parameters and should not usually be recorded as AE, unless one or more of the following criteria are met:

  - The worsening of the disease under study constitutes a serious AE
  - A deterioration exceeding the usual fluctuations of the disease under study has occurred in the opinion of the investigator
  - The worsening leads to discontinuation of the study medication
  - Additional treatment is required for the worsening, e.g. concomitant medication is added or changed.

  No causal relationship with the investigational drug, or comparator drug, or study procedures is implied by the use of the term “Adverse Event”.

- **Adverse reaction of an investigational medicinal product:**

  All untoward and unintended responses to an IMP related to any dose administered. All AEs judged by either the reporting investigator or the sponsor as having a reasonable causal relationship to a medicinal product qualify as adverse reactions. The expression reasonable causal relationship means to convey in general that there are facts, evidence or arguments to suggest a causal association with the drug.

- **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 in itself. All deaths, regardless of cause or relationship must be reported for study subjects.*
  - is life-threatening

- *"Life-threatening" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.*

- requires hospitalization or prolongation of existing hospitalization
  - *In-subject hospitalization means that the subject 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.*
  - *A complication that occurs during hospitalization and prolongs the existing hospitalization is an SAE. Complications that occur during hospitalization but do not prolong the existing hospitalization and do not meet any other seriousness criteria are non-serious AEs.*
  - *Elective or pre-planned (prior to signature of informed consent) hospitalization for investigations, medical or surgical treatment does not meet this seriousness criterion. However, if the underlying condition for which hospital treatment or surgery had been planned worsened during the study, the worsening of the condition is to be reported as SAE.*
- results in persistent or significant disability / incapacity
- is a congenital anomaly / birth defect
- is another important medical event
  - *Adverse events that may not be immediately life-threatening or result in death or hospitalization but my jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed above, should be reported as serious. Medical and scientific judgment must be exercised in deciding whether an event is serious.*

* "At any dose" does not necessarily imply that the subject is receiving the study drug at the time of the event.

- **Diagnosis vs. Signs/Symptoms**

  The investigator should provide a diagnosis rather than individual signs and symptoms, wherever possible and appropriate. However, if there is not enough information to provide a diagnosis, individual signs and symptoms are to be recorded. If a diagnosis is accompanied by unusual symptoms, the diagnosis itself and the unusual symptoms have to be reported separately. For serious and other IRAEs the investigator shall provide any other supporting information that may be required for the assessment of the events, specifically in the free text narrative description of the case. This is of particular importance in situations where a diagnosis cannot (yet) be made. Any subject identifying data on supporting documents (e.g. name, address, phone number) have to be obliterated prior to sending them to the sponsor.

A complication of an AE constitutes another AE. For example in diarrhea leading to dehydration, diarrhea and dehydration would be captured as separate AEs.

The eCRF provides for a number of items to be completed for each AE. This includes the onset date, end date, intensity/severity, seriousness, action taken with study medication, treatment for the AE, outcome, and causal relationship of the AE with the study medication, other drugs, or study procedures.

- **Onset date, end date**

If an AE started during the study but did not end before the final follow-up visit, the investigator must make a reasonable effort to establish the outcome and the end date. If this is not possible, e.g. because the AE is still ongoing, or the subject is lost to follow-up, there will be no end date for the AE.

For all AEs that resolve, resolve with sequelae, or have a fatal outcome, an end date must be provided.

If an AE stops and restarts later, all occurrences have to be recorded separately.

If an AE starts as non-serious AE and becomes serious at a later point in time, the following applies in regard to onset and end dates:

- **Intensity/Severity**

Refers to the extent to which an AE affects the subject's daily activities. Severity will be categorized according to the following criteria:

Table: Adverse Event Severity

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

Severe vs. Serious: The severity is used to describe the intensity of an event. This is not the same as seriousness, which is based on subject/event outcome or action criteria usually associated with events that pose a threat to subject's life or functioning. Seriousness, not severity, serves as the guide for defining regulatory reporting obligations.

Example: While an event may be of "severe" intensity, it may be of relatively minor medical significance, such as severe headache. On the other hand, a myocardial infarction would be usually regarded as serious, even if its intensity is "mild".

If formal severity classifications are used, such as the NCI CTC classification used in oncology studies, provisions should be made regarding the reporting of events of defined grading (e.g. ≥ 3) as serious.

AEs with changes in severity: If an AE changes in severity, this will be captured as one AE with the highest severity grade recorded.

- **Seriousness**

  For definition of seriousness criteria refer to section 9.3.1. For a serious AE all seriousness criteria that apply have to be reported. Reporting requirements by the investigator are detailed in Appendix 2.

  If a list of always serious terms is to be used in the study, this should be mentioned here, as well as its use by the investigator. For example a PT-based auto-seriousness in the eCRF, or an urgent query process once a verbatim is coded to a PT on the list.

- **Action Taken with Study Medication**

  The action taken with study medication as a result of the AE has to be documented. In the situation that the AE leads to permanent discontinuation of the study medication, this meets the definition of an AE leading to subject's withdrawal from the study, which is an immediately reportable AE (IRAE). Reporting requirements by the investigator are detailed in section Appendix 2.

- **Treatment for the AE**

  It has to be specified in the eCRF if counteractive treatment was given for the AE. Any treatment for an AE, whether pharmacological or other (e.g. surgical) treatment, has to be recorded in the eCRF.

- **Outcome**

  The following categories are used:

  - Resolved
    - Indicates that the event has fully resolved.
  - Resolving
    - Indicates that the event is in the process of recovery but has not yet fully resolved.
  - Not resolved
    - Indicates that the event is ongoing and there has been no recovery.
  - Resolved with sequelae
    - Indicates that there is a residual, possibly permanent consequence of the event (e.g. residual hemiparesis subsequent to stroke).
  - Fatal
    - Indicates that the subject died due to the event. The outcome "fatal" applies only to the event(s) that were the cause(s) of death. For other AEs that were ongoing at the time of death, the outcome must not be "fatal" but "not resolved".

- **Causal Relationship of AE**

  The causal relationship with the study medication has to be reported for each AE. It refers to the presence or absence of a reasonable possibility of a causal relationship between the study medication and the AE. The investigator is asked to use medical judgment and take into account the nature of the AE, subject's

medical history, temporal relation, response to withdrawal or interruption of study drug (dechallenge), response to re-introduction of study drug (rechallenge), any alternative explanations such as underlying or concomitant diseases, concomitant drugs, study procedures.

The following categories are used:

- Related: There is a reasonable possibility of a causal relationship between the study medication and the AE.
- Not related: There is no reasonable possibility of a causal relationship between the study medication and the AE.

For serious and other immediately reportable AEs the investigator is asked to specify if there are alternative and/or additional explanations for the occurrence of the event, e.g. concomitant drugs, study procedures, or concomitant/underlying disease and should provide this information already with the initial case report.

- **Concomitant medication**

Concomitant medication will be documented according to categories of medicinal products which are normally used in clinical studies as NIMPs (European Commission, 18/03/2011):

(1) Rescue medication
(2) Challenge agents
(3) Concomitant medicinal products systematically prescribed to the study patients
(4) Background treatment

Definitions adapted from the Guidance on IMPs and NIMPs (European Commission, 18/03/2011):

- **Rescue medication**

Rescue medications are medicines identified as those that may be administered to the patients when the efficacy of the IMP is not satisfactory, or the effect of the IMP is too great and is likely to cause a hazard to the patient, or to manage an emergency situation. Rescue medication allows patients to receive effective treatment, e.g. where a standard treatment is available.

- **Challenge agents**

Challenge agents are usually given to study subjects to produce a physiological response that is necessary before the pharmacological action of the IMP can be assessed.

- **Concomitant medicinal products systematically prescribed to the study patients**

This type of NIMP is given to clinical study participants as required in the protocol as part of their standard care for a condition which is not the indication for which the IMP is being tested, and is therefore not the object of the study.

- **Background treatment**

This type of medicinal product is administered to each of the clinical study subjects, regardless of randomization arm, to treat the indication which is the object of the study. Background treatment is generally considered to be the current standard care for the particular indication. In these studies, the IMP is given in addition to the background treatment and safety and efficacy are assessed. The protocol may require that the IMP plus the background treatment is compared to an active comparator or to placebo plus background treatment.

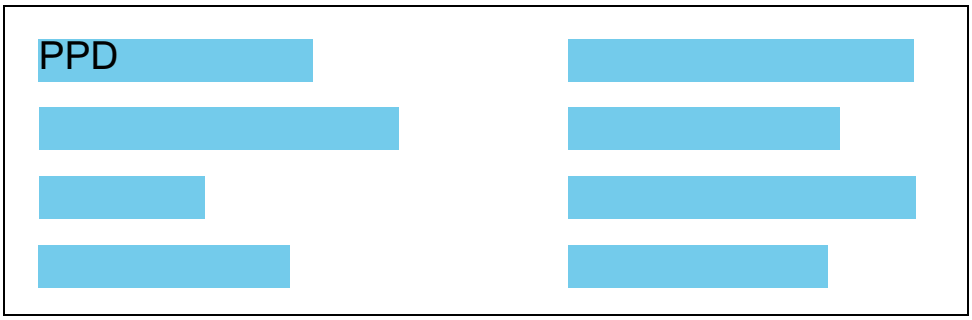
Appendix 2: Reporting Procedures

Reporting procedure:

All IRAE information has to be recorded in the IRAE/SAE form and reported to PPD Corporate Drug Safety (CDS) immediately (i. e. within 24 hours) by e-mail or fax (see addresses below in the box) after the investigational site becoming aware of the IRAE.

In addition, this IRAE has to be recorded on the AE page of the eCRF and the following eCRF pages have to be updated or completed at the same time as necessary: Study drug documentation, subject demographics, medical history, concomitant medication, and study completion/termination (in case of an AE leading to withdrawal).

Entry of an IRAE/SAE into the eCRF will trigger an alert message to PPD and Biotest CDS.



For questions regarding IRAEs including SAEs or to notify the sponsor of an IRAE including SAE in the event of technical failure of the e-mail or fax system, the investigator should contact PPD

Whenever follow-up information becomes available to a previously recorded IRAE/SAE, this has to be captured in the IRAE/SAE form and should be send by e-mail or fax together with any supporting documents (e.g. medical records, autopsy report, ECG or laboratory reports) as part of the follow-up information accompanied by a cover page within max. 24 hours of the investigator becoming aware of the follow-up information to the reporting contact above.

In addition, the new information should be captured in the eCRF on the AE page within max. 24 hours after becoming aware of the follow-up information.

The investigator has to undertake active follow-up for subjects with IRAE/SAEs. The investigator shall respond to queries raised by the sponsor with regard to IRAE/SAEs within the timelines stipulated in the query, and provide all necessary information as requested. In case of a fatal or life-threatening SAE, the sponsor will contact the investigator urgently to obtain required additional information within one business day. If supporting documents are requested by the sponsor (e.g. copies of medical records, laboratory reports, ECG tracings, autopsy report), the investigator must ensure that subject identifying data are obliterated prior to sending to the sponsor. The supporting documents should carry the subject ID for identification.

If required the investigator is responsible to inform local IECs/IRBs of safety reports in compliance with applicable regulatory requirements. Copies of all correspondence

relating to reporting of safety reports to IEC/IRB should be maintained in the Investigator Site File/ Regulatory Binder.

The sponsor is responsible for fulfilling all obligations regarding notification of regulatory authorities, ethics committees according to applicable regulatory requirements, in regard to expedited reporting (e.g. serious unexpected suspected adverse reactions) and periodic reporting (e.g. development Safety Update Report). In addition, the sponsor is responsible for information of investigators according to the current legislation.