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

Summary

EudraCT number	2011-004154-25
Trial protocol	IT DE BG
Global end of trial date	18 May 2020

Results information

Result version number	v1 (current)
This version publication date	11 September 2021
First version publication date	11 September 2021

Trial information

Trial identification

Sponsor protocol code	984

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02065882
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Biotest AG
Sponsor organisation address	Landsteinerstraße 5, Dreieich, Germany, 63303
Public contact	Corporate Clinical Research & Development, Biotest AG, 0049 6103801492, andrea.wartenberg-demand@biotest.com
Scientific contact	Corporate Clinical Research & Development, Biotest AG, 0049 6103801497, andrea.wartenberg-demand@biotest.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-001931-PIP16-02
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	02 July 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	18 May 2020
Global end of trial reached?	Yes
Global end of trial date	18 May 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To investigate the 14 day single-dose pharmacokinetics of BT524 following intravenous infusion in patients with congenital fibrinogen deficiency (afibrinogenemia or severe hypofibrinogenemia).

Protection of trial subjects:

The study was conducted in accordance with the ICH-GCP guidelines, the most recent version of the Declaration of Helsinki, and with local regulatory requirements.
Children and adolescents (≥ 6 to < 18 years) were to be enrolled, only after completion of dosing interval and the associated 7-day dosing-free safety interval of the first 10 adult patients enrolled into the study and after the Data Monitoring Committee (DMC) had reviewed the data from these 10 adult patients. Subsequently, after the first 20 patients ≥ 6 to ≤ 75 years had finished PK/PD part I, 3 additional patients < 6 years were planned to be enrolled in study part I and subsequently in the part II. Prior to enrolment of any children < 6 years into the study the DMC had to review and to assess all available safety and PK/PD data from adults and children ≥ 6 years enrolled in the study at that time. Implementation of Stopping rule: The DMC was expected to review all safety relevant information for each participating subject individually with the purpose to identify safety issues that were pertinent to the decision whether the study could be continued as intended or whether the safety relevant methods and procedures needed to be adjusted.

Background therapy:

None

Evidence for comparator:

None

Actual start date of recruitment	11 March 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Lebanon: 39
Country: Number of subjects enrolled	Egypt: 12
Country: Number of subjects enrolled	Tunisia: 13
Country: Number of subjects enrolled	Bulgaria: 2
Country: Number of subjects enrolled	Germany: 1
Worldwide total number of subjects	67
EEA total number of subjects	3

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	4
Children (2-11 years)	23
Adolescents (12-17 years)	9
Adults (18-64 years)	31
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

First Patient enrolled March 2013, last Patient completed May 2020

Pre-assignment

Screening details:

Male or female aged 0 to 75
Diagnosis: Known congenital afibrinogenemia or severe congenital hypofibrinogenemia

Pre-assignment period milestones

Number of subjects started	35[1]
Number of subjects completed	27

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Consent withdrawn by subject: 2
Reason: Number of subjects	screen failures: 5
Reason: Number of subjects	No IMP available: 1

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: The study was divided into part I and part II. Patients in part I who received treatment and completed part I were subsequently enrolled in part II. 35 patients were enrolled in part I, thereof 27 patients were enrolled in part II. In addition, 32 patients were directly enrolled in part II, without participation in PK part I. Overall, 67 patients were enrolled in this study (35 patients in part I and additional 32 patients in part II).

Period 1

Period 1 title	PK Part I
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	BT524

Arm description:

IV administration of BT524 (fibrinogen concentrate from human plasma)

Arm type	Intervention
Investigational medicinal product name	BT524 (fibrinogen concentrate from human plasma)
Investigational medicinal product code	BT524
Other name	Fibrinogen concentrate
Pharmaceutical forms	Powder for solution for injection/infusion
Routes of administration	Injection , Infusion , Intravenous use

Dosage and administration details:

The dosage and duration of the substitution therapy depended on the severity of the disorder, location and extent of the bleeding and the patient's clinical condition. Besides, dosage was based on individual body weight (BW) and individual fibrinogen baseline level. Similar dosage strategy was applied to patients
aged < 6 years, as for patients aged ≥ 6 to ≤ 75 years. The dosage regimen for surgical interventions and spontaneous bleedings targeted (functional) fibrinogen levels recommended by the core Summary of Product Characteristics (SmPC) for human fibrinogen products.

PK Part I: 70 mg/kg BW, single IV infusion

Number of subjects in period 1[2]	BT524
Started	27
Completed	27

Notes:

[2] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: Baseline characteristics are only available separate for treated patients in study part I (n=27) and for treated patients in study part II (n=36).

Period 2

Period 2 title	Part II
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	BT524

Arm description:

IV administration of BT524 (fibrinogen concentrate from human plasma)

Arm type	Intervention
Investigational medicinal product name	BT524 (fibrinogen concentrate from human plasma)
Investigational medicinal product code	BT524
Other name	Fibrinogen concentrate
Pharmaceutical forms	Powder for solution for injection/infusion
Routes of administration	Infusion , Injection , Intravenous use

Dosage and administration details:

The dosage and duration of the substitution therapy depended on the severity of the disorder, location and extent of the bleeding and the patient's clinical condition. Besides, dosage was based on individual body weight (BW) and individual fibrinogen baseline level. Similar dosage strategy was applied to patients
aged < 6 years, as for patients aged ≥ 6 to ≤ 75 years. The dosage regimen for surgical interventions and spontaneous bleedings targeted (functional) fibrinogen levels recommended by the core Summary of Product Characteristics (SmPC) for human fibrinogen products.

Part II: Variable dose, as required IV infusion

Number of subjects in period 2	BT524
Started	27
Completed	36
Not completed	23
Consent withdrawn by subject	1
Adverse event, non-fatal	1

Study termination due to local authority decision	3
Screen failure	7
Without bleeding event	11
Joined	32
New recruitment directly in study part II	32

Baseline characteristics

Reporting groups	
Reporting group title	PK Part I
Reporting group description:	
Demographic data were documented at screening. The analysis was performed in the Safety Analysis Set (SAF I) for all patients completed part I (n=27).	

Reporting group values	PK Part I	Total	
Number of subjects	27	27	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	3	3	
Children (2-11 years)	6	6	
Adolescents (12-17 years)	3	3	
Adults (18-64 years)	15	15	
From 65-84 years	0	0	
85 years and over	0	0	
Gender categorical Units: Subjects			
Female	13	13	
Male	14	14	

Subject analysis sets	
Subject analysis set title	SAF I
Subject analysis set type	Safety analysis
Subject analysis set description:	
The safety analysis set I (SAF I) comprises of all patients who were exposed to BT524 in part I of the study.	
Subject analysis set title	SAF II
Subject analysis set type	Safety analysis
Subject analysis set description:	
The safety analysis set II (SAF II) comprises of all patients who were exposed to BT524 in part II of the study.	
Subject analysis set title	PK Set
Subject analysis set type	Full analysis
Subject analysis set description:	
The Pharmacokinetic analysis set (PK) consists of all patients of part I with PK data.	

Reporting group values	SAF I	SAF II	PK Set
Number of subjects	27	36	27
Age categorical Units: Subjects			
In utero	0	0	0

Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	3	1	3
Children (2-11 years)	6	11	6
Adolescents (12-17 years)	3	4	3
Adults (18-64 years)	15	20	15
From 65-84 years	0	0	0
85 years and over	0	0	0
Gender categorical			
Units: Subjects			
Female	13	14	13
Male	14	22	14

End points

End points reporting groups

Reporting group title	BT524
Reporting group description: IV administration of BT524 (fibrinogen concentrate from human plasma)	
Reporting group title	BT524
Reporting group description: IV administration of BT524 (fibrinogen concentrate from human plasma)	
Subject analysis set title	SAF I
Subject analysis set type	Safety analysis
Subject analysis set description: The safety analysis set I (SAF I) comprises of all patients who were exposed to BT524 in part I of the study.	
Subject analysis set title	SAF II
Subject analysis set type	Safety analysis
Subject analysis set description: The safety analysis set II (SAF II) comprises of all patients who were exposed to BT524 in part II of the study.	
Subject analysis set title	PK Set
Subject analysis set type	Full analysis
Subject analysis set description: The Pharmacokinetic analysis set (PK) consists of all patients of part I with PK data.	

Primary: Single-dose PK of FiAg: Terminal Elimination Half-life (t1/2)

End point title	Single-dose PK of FiAg: Terminal Elimination Half-life (t1/2)[1]
End point description: Terminal Elimination Half-live (t1/2) was assessed after a single IV infusion of 70 mg/kg body weight of BT524. t1/2 of fibrinogen antigen was determined from samples taken at several time points during the 14 day sampling period. t1/2 was derived from time-concentration profiles using adapted methodology (non-compartmental analysis, compartment analysis, or population modeling, as appropriate/ required).	
End point type	Primary
End point timeframe: Pre-dose, end of infusion (EoI), 0.5 h, 1 h, 2 h, 4 h, 8 h, 24 h, 48 h, 96 h, 168 h, 240 h and 336 h post-EoI.	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Analysis of the study data for the primary endpoint was descriptive only. PK parameters were summarized by descriptive statistics. No confirmatory testing was performed on the PK parameters in part I.

End point values	BT524	PK Set		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	27	27		
Units: hours				
arithmetic mean (standard deviation)	67.9 (± 15.3)	67.9 (± 15.3)		

Statistical analyses

No statistical analyses for this end point

Primary: Single-dose PK of FiAg: Time to Maximum Concentration (tmax)

End point title	Single-dose PK of FiAg: Time to Maximum Concentration (tmax)[2]

End point description:

Time to reach Maximum Concentration (tmax) was assessed after a single IV infusion of 70 mg/kg body weight of BT524.
Time of occurence of Cmax relative to dosing (Tmax) for fibrinogen antigen was determined from samples taken at several time points during the 14 day sampling period. Tmax was derived from time-concentration profiles using adapted methodology (non-compartmental analysis, compartment analysis, or population modeling, as appropriate/ required).

End point type	Primary

End point timeframe:

Pre-dose, end of infusion (EoI), 0.5 h, 1 h, 2 h, 4 h, 8 h, 24 h, 48 h, 96 h, 168 h, 240 h and 336 h post-EoI.

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Analysis of the study data for the primary endpoint was descriptive only. PK parameters were summarized by descriptive statistics. No confirmatory testing was performed on the PK parameters in part I.

End point values	BT524	PK Set		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	27	27		
Units: hours				
arithmetic mean (standard deviation)	0.843 (± 0.361)	0.843 (± 0.361)		

Statistical analyses

No statistical analyses for this end point

Primary: Single-dose PK of FiAg: Maximum Concentration (Cmax)

End point title	Single-dose PK of FiAg: Maximum Concentration (Cmax)[3]

End point description:

Maximum Concentration (Cmax) was assessed after a single IV infusion of 70 mg/kg body weight of BT524.
Maximum observed plasma concentration (Cmax) for fibrinogen antigen was determined from samples taken at several time points during the 14 day sampling period. Cmax was derived from time-concentration profiles using adapted methodology (non-compartmental analysis, compartment analysis, or population modeling, as appropriate/ required).

End point type	Primary

End point timeframe:

Pre-dose, end of infusion (EoI), 0.5 h, 1 h, 2 h, 4 h, 8 h, 24 h, 48 h, 96 h, 168 h, 240 h and 336 h post-EoI.

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Analysis of the study data for the primary endpoint was descriptive only. PK parameters were summarized by descriptive statistics. No confirmatory testing was performed on the PK parameters in part I.

End point values	BT524	PK Set		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	27	27		
Units: g/L				
arithmetic mean (standard deviation)	1.81 (± 0.423)	1.81 (± 0.423)		

Statistical analyses

No statistical analyses for this end point

Primary: Single-Dose PK for FiAg: Area Under the Curve (AUC) Calculated to the Last Measured Concentration (AUC0-tz)

End point title	Single-Dose PK for FiAg: Area Under the Curve (AUC) Calculated to the Last Measured Concentration (AUC0-tz)[4]

End point description:

AUC0-tz was assessed after a single IV infusion of 70 mg/kg body weight of BT524.
AUC0-tz: Area under the time course of the plasma concentrations calculated from time zero up to the last quantifiable plasma concentration for fibrinogen antigen (FiAg), was determined from samples taken at several time points during the 14 day sampling period. AUC0-tz was derived from time-concentration profiles using adapted methodology (non-compartmental analysis, compartment analysis, or population modeling, as appropriate/ required).

End point type	Primary

End point timeframe:

Pre-dose, end of infusion (EoI), 0.5 h, 1 h, 2 h, 4 h, 8 h, 24 h, 48 h, 96 h, 168 h, 240 h and 336 h post-EoI.

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Analysis of the study data for the primary endpoint was descriptive only. PK parameters were summarized by descriptive statistics. No confirmatory testing was performed on the PK parameters in part I.

End point values	BT524	PK Set		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	27	27		
Units: g*h/L				
arithmetic mean (standard deviation)	144 (± 38.9)	144 (± 38.9)		

Statistical analyses

No statistical analyses for this end point

Primary: Single-dose PK of FiAg: Area Under the Curve (AUC) From Time 0 to Infinity (AUC0-∞)

End point title	Single-dose PK of FiAg: Area Under the Curve (AUC) From Time 0 to Infinity (AUC0-∞)[5]

End point description:

Area Under the Curve (AUC) From Time 0 to Infinity (AUC0-∞) was assessed after a single IV infusion of 70 mg/kg body weight of BT524.
AUC0-∞: AUC from time 0 to infinity for fibrinogen antigen, was determined from samples taken at several time points during the 14 day sampling period. AUC0-∞ was derived from time-concentration

profiles using adapted methodology (noncompartmental analysis, compartment analysis, or population modeling, as appropriate/required).

End point type	Primary

End point timeframe:

Pre-dose, end of infusion (EoI), 0.5 h, 1 h, 2 h, 4 h, 8 h, 24 h, 48 h, 96 h, 168 h, 240 h and 336 h post-EoI.

Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Analysis of the study data for the primary endpoint was descriptive only. PK parameters were summarized by descriptive statistics. No confirmatory testing was performed on the PK parameters in part I.

End point values	BT524	PK Set		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	27	27		
Units: g*h/L				
arithmetic mean (standard deviation)	173 (± 45.4)	173 (± 45.4)		

Statistical analyses

No statistical analyses for this end point

Primary: Single-dose PK of FiAg: Mean Residence Time (MRT) Extrapolated to Infinity (MRT0-∞)

End point title	Single-dose PK of FiAg: Mean Residence Time (MRT) Extrapolated to Infinity (MRT0-∞)[6]

End point description:

Mean Residence Time (MRT) extrapolated to infinity (MRT0-∞) was assessed after a single IV infusion of 70 mg/kg body weight of BT524.
MRT0-∞: Mean Residence Time (MRT) extrapolated to infinity for fibrinogen antigen was determined from samples taken at several time points during the 14 day sampling period. MRT0-∞ was derived from time-concentration profiles using adapted methodology (non-compartmental analysis, compartment analysis, or population modeling, as appropriate/ required).

End point type	Primary

End point timeframe:

Pre-dose, end of infusion (EoI), 0.5 h, 1 h, 2 h, 4 h, 8 h, 24 h, 48 h, 96 h, 168 h, 240 h and 336 h post-EoI.

Notes:

[6] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Analysis of the study data for the primary endpoint was descriptive only. PK parameters were summarized by descriptive statistics. No confirmatory testing was performed on the PK parameters in part I.

End point values	BT524	PK Set		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	27	27		
Units: hours				
arithmetic mean (standard deviation)	133 (± 17.4)	133 (± 17.4)		

Statistical analyses

No statistical analyses for this end point

Primary: Single-dose PK of FiAg: Clearance (CL)

End point title	Single-dose PK of FiAg: Clearance (CL)[7]

End point description:

Clearance (CL) was assessed after a single IV infusion of 70 mg/kg body weight of BT524.
CL: Total clearance (CL) for fibrinogen antigen was determined from samples taken at several time points during the 14 day sampling period. CL was derived from time concentration profiles using adapted methodology (non-compartmental analysis, compartment analysis, or population modeling, as appropriate/ required).

End point type	Primary

End point timeframe:

Pre-dose, end of infusion (EoI), 0.5 h, 1 h, 2 h, 4 h, 8 h, 24 h, 48 h, 96 h, 168 h, 240 h and 336 h post-EoI.

Notes:

[7] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Analysis of the study data for the primary endpoint was descriptive only. PK parameters were summarized by descriptive statistics. No confirmatory testing was performed on the PK parameters in part I.

End point values	BT524	PK Set		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	27	27		
Units: L/h				
arithmetic mean (standard deviation)	0.0206 (± 0.00961)	0.0206 (± 0.00961)		

Statistical analyses

No statistical analyses for this end point

Primary: Single-dose PK of FiAg: Volume of distribution (Vdss)

End point title	Single-dose PK of FiAg: Volume of distribution (Vdss)[8]

End point description:

Volume of distribution at presumed steady-state (Vdss) per kg BW was assessed after a single IV infusion of 70 mg/kg body weight of BT524.
Volume of distribution at presumed steady-state (Vdss) per kg BW for fibrinogen antigen was determined from samples taken at several time points during the 14 day sampling period.
Vdss was derived from time concentration profiles using adapted methodology (non-compartmental analysis, compartment analysis, or population modeling, as appropriate/ required).

End point type	Primary

End point timeframe:

Pre-dose, end of infusion (EoI), 0.5 h, 1 h, 2 h, 4 h, 8 h, 24 h, 48 h, 96 h, 168 h, 240 h and 336 h post-EoI.

Notes:

[8] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Analysis of the study data for the primary endpoint was descriptive only. PK parameters were summarized by descriptive statistics. No confirmatory testing was performed on the PK parameters in part I.

End point values	BT524	PK Set		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	27	27		
Units: mL/kg				
arithmetic mean (standard deviation)	57.8 (± 19.1)	57.8 (± 19.1)		

Statistical analyses

No statistical analyses for this end point

Primary: Single-dose PK of FiAg: Incremental Recovery (IR)

End point title	Single-dose PK of FiAg: Incremental Recovery (IR)[9]

End point description:

IR was assessed after a single IV infusion of 70 mg/kg body weight of BT524.
IR is the dose-adjusted maximum fibrinogen increase in plasma within 4 hours after the end of infusion and reported as milligram per deciliter per milligram per kilogram [mg/dL]/[mg/kg].

End point type	Primary

End point timeframe:

Pre-infusion to 4 hours post-infusion.

Notes:

[9] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Analysis of the study data for the primary endpoint was descriptive only. PK parameters were summarized by descriptive statistics. No confirmatory testing was performed on the PK parameters in part I.

End point values	BT524	PK Set		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	27	27		
Units: (mg/dL)/(mg/kg)				
arithmetic mean (standard deviation)	2.63 (± 0.652)	2.63 (± 0.652)		

Statistical analyses

No statistical analyses for this end point

Primary: Single dose PK of FibAg: Classical in vivo recovery (CIR)

End point title	Single dose PK of FibAg: Classical in vivo recovery (CIR)[10]

End point description:

CIR was assessed after a single IV infusion of 70 mg/kg body weight of BT524.
Classical in vivo recovery (CIR) is the maximum fibrinogen increase in plasma within 4 hours after the end of infusion divided by the maximum theoretical fibrinogen increase (Maximum concentration0-4h /(dose/plasma volume)). A plasma volume of 45 mL/kg body weight will be used in these calculations.

End point type	Primary

End point timeframe:

Pre-infusion to 4 hours post-infusion.

Notes:

[10] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Analysis of the study data for the primary endpoint was descriptive only. PK parameters were summarized by descriptive statistics. No confirmatory testing was performed on the PK parameters in part I.

End point values	BT524	PK Set		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	27	27		
Units: percent volume/volume				
arithmetic mean (standard deviation)	118 (± 29.4)	118 (± 29.4)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

For Treatment emergent AEs (TEAEs): After administration of BT524 and until the last study visit (Day 49) in study part I and II. Non-TEAEs: after patient's signature of Informed Consent and before first administration of BT524 per study part.

Adverse event reporting additional description:

PK part I: TEAEs were reported from the time of single dose administration of BT524 for PK assessments to Day 49 (PK safety visit).
Part II: TEAEs were reported from the time of BT524 administration for treatment of a bleeding event to Day 49 (Safety visit for this bleeding event).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	03/2018

Reporting groups

Reporting group title	PK Part I
Reporting group description: -	
Reporting group title	Part II

Reporting group description: -

Serious adverse events	PK Part I	Part II	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 27 (7.41%)	7 / 36 (19.44%)	
number of deaths (all causes)	0	1	
number of deaths resulting from adverse events	0	1	
Injury, poisoning and procedural complications			
Extra dural hematoma			
subjects affected / exposed	0 / 27 (0.00%)	1 / 36 (2.78%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Traumatic haemorrhage			
subjects affected / exposed	0 / 27 (0.00%)	1 / 36 (2.78%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Deep vein thrombosis			

subjects affected / exposed	0 / 27 (0.00%)	1 / 36 (2.78%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Hypertensive Encephalopathy			
subjects affected / exposed	1 / 27 (3.70%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epilepsy			
subjects affected / exposed	0 / 27 (0.00%)	1 / 36 (2.78%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Iron deficiency anaemia			
subjects affected / exposed	0 / 27 (0.00%)	1 / 36 (2.78%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Pancreatitis			
subjects affected / exposed	0 / 27 (0.00%)	1 / 36 (2.78%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Menorrhagia			
subjects affected / exposed	0 / 27 (0.00%)	1 / 36 (2.78%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Portal vein thrombosis			
subjects affected / exposed	0 / 27 (0.00%)	1 / 36 (2.78%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Post streptococcal glomerulonephritis			

subjects affected / exposed	1 / 27 (3.70%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Haematoma muscle			
subjects affected / exposed	0 / 27 (0.00%)	1 / 36 (2.78%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in extremity			
subjects affected / exposed	1 / 27 (3.70%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	PK Part I	Part II	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	10 / 27 (37.04%)	25 / 36 (69.44%)	
Injury, poisoning and procedural complications			
Procedural haemorrhage			
subjects affected / exposed	0 / 27 (0.00%)	2 / 36 (5.56%)	
occurrences (all)	0	2	
Procedural pain			
subjects affected / exposed	0 / 27 (0.00%)	9 / 36 (25.00%)	
occurrences (all)	0	30	
Skin wound			
subjects affected / exposed	0 / 27 (0.00%)	2 / 36 (5.56%)	
occurrences (all)	0	2	
Subcutaneous haematoma			
subjects affected / exposed	1 / 27 (3.70%)	6 / 36 (16.67%)	
occurrences (all)	1	10	
Traumatic haematoma			
subjects affected / exposed	0 / 27 (0.00%)	3 / 36 (8.33%)	
occurrences (all)	0	3	

Vascular disorders Haematoma subjects affected / exposed occurrences (all)	 0 / 27 (0.00%) 0	 2 / 36 (5.56%) 3	
Nervous system disorders Headache subjects affected / exposed occurrences (all)	 1 / 27 (3.70%) 1	 2 / 36 (5.56%) 2	
General disorders and administration site conditions Pyrexia subjects affected / exposed occurrences (all) Swelling face subjects affected / exposed occurrences (all)	 1 / 27 (3.70%) 1 0 / 27 (0.00%) 0	 3 / 36 (8.33%) 3 3 / 36 (8.33%) 3	
Gastrointestinal disorders Gingival bleeding subjects affected / exposed occurrences (all) Toothache subjects affected / exposed occurrences (all)	 1 / 27 (3.70%) 1 2 / 27 (7.41%) 2	 2 / 36 (5.56%) 3 3 / 36 (8.33%) 3	
Respiratory, thoracic and mediastinal disorders Epistaxis subjects affected / exposed occurrences (all)	 0 / 27 (0.00%) 0	 4 / 36 (11.11%) 4	
Skin and subcutaneous tissue disorders Ecchymosis subjects affected / exposed occurrences (all)	 0 / 27 (0.00%) 0	 3 / 36 (8.33%) 3	
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) Back pain	 0 / 27 (0.00%) 0	 2 / 36 (5.56%) 2	

subjects affected / exposed	3 / 27 (11.11%)	4 / 36 (11.11%)	
occurrences (all)	4	5	
Haemarthrosis			
subjects affected / exposed	0 / 27 (0.00%)	2 / 36 (5.56%)	
occurrences (all)	0	2	
Osteorrhagia			
subjects affected / exposed	0 / 27 (0.00%)	3 / 36 (8.33%)	
occurrences (all)	0	9	
Pain in extremity			
subjects affected / exposed	0 / 27 (0.00%)	4 / 36 (11.11%)	
occurrences (all)	0	8	
Infections and infestations			
Rhinitis			
subjects affected / exposed	1 / 27 (3.70%)	2 / 36 (5.56%)	
occurrences (all)	1	2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
16 January 2013	Modification of the involved countries and sites. Date of first patient in. Introduction of two additional flowcharts for the newly defined subgroups of children with different BW: Children Group I (6 to 18 years, BW > 43 kg) and Children Group II (6 to 18 years, BW between 22 and 43 kg). Reduction of time points of blood draw in children Group I (> 43 kg BW) for the assessment of Coagulation, Hematology and Biochemistry. Reduction of time points of blood draw in children Group II (22-43 kg BW) for the assessment of Coagulation, Hematology and Biochemistry as well as of PK and PD. Addition of a new chapter concerning Pregnancy Reporting.
16 September 2013	Clinical Study Protocol Tunisia, only adults included in study 984
15 June 2014	Introduction of a DMC to approve the inclusion of children and adolescents after the 10th adult patient treated and to survey the study as a whole. Implementation of an appropriate procedure and a related stopping rule. Inclusion criterion 1 (now 1 and 2) and exclusion criterion 12 were modified to clarify the target population. Extension of study duration due to slow patient recruitment. Furthermore, study patients already on trial were offered to extend their study participation (in part II) until the last patient enrolled has finished study part II. Modified method for determination of Fibrinogen Antigen (Assay); ELISA changed to nephelometry. Assessments of risk and burden in children and adolescents and a justification regarding the risks and burden these age groups are exposed by the clinical trial. Implementation of risk minimization measures for all study patients as well as for the enrolment and treatment of children and adolescents. Determination of Fibrinogen inhibitory antibodies was stated more precisely. Addition of requirement to report the development of Fibrinogen inhibitory antibodies as SAEs.
15 July 2015	Treatment of at least 10 additional patients into part II (without part I PK/PD). Calculation of the BT524 dose to be administered to the patients was revised in regard to the specifications in the COA. Treatment of at least 10 additional patients into part II (without part I PK/PD). Implementation of the DMC Modified method for determination of Fibrinogen Antigen (Assay); ELISA changed to nephelometry Calculation of the BT524 dose to be administered to the patient was revised in regard to the specifications in the COA Implementation of risk minimization measures for all study patients Determination of fibrinogen inhibitory antibodies was stated more precisely. Addition of a requirement to report the development of fibrinogen inhibitory antibodies as SAEs.
15 March 2017	Based on the agreement of the PIP (EMEA-001931-PIP01-16) the extension of the ongoing study 984 was introduced. Detailed description of the inclusion and treatment of children aged 0 to < 6 years. Update of study synopsis and introduction of 6 additional flowcharts for the newly defined groups of children aged < 6 years (Pre-school Children Group III and Newborns/ Infants and Toddlers Group IV)

08 May 2018	Adaption of exclusion criterion 12 in order to clarify that this criterion is only applicable for patients in PK part I. Adaption of exclusion criterion 13 in order to harmonize the 'lower BW limit' (the 5th percentile of the normal range) between all children age groups. Information regarding the WHO Child Growth Standards was included in CSP appendix 20.2. Introduction of new sections 'Adverse Event of Special Interest (AESI)' and 'Follow-up of Adverse Events'. Correction of Sample Calculation as this section was adapted within amendment 3 (CSP Version 4.0) to the new patient numbers in error. The investigator was asked to classify any bleeding event post-dose as minor or major.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported