Statistical Analysis Plan

Part A, Part B, Part C and Part D Analysis

A SINGLE/MULTIPLE ASCENDING DOSE PHASE 1 STUDY OF THE SAFETY, TOLERABILITY, AND PHARMACOLOGIC ACTIVITY OF BT200 IN NORMAL HUMAN VOLUNTEERS

Protocol: BT200-01

NCT #04103034

Confidential

Sponsor: Band Therapeutics, LLC

Table of Contents

Document	
Study	BT200-01
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Revision History

Version	Date	Reason for Revision
FINAL 1.0	27-May-2020	First version;
FINAL 2.0	05-Jun-2020	Patient overview and demographic information tables added into the Topline Analyses
FINAL 3.0	17-Sep-2020	Analysis of BMI at screening and embolic and thrombotic events added, update of section 2.14 (Columns in tables), additional biomarkers Fibrin D-dimer and Prothrombin fragment F1.2 described, Topline Analyses for Parts B and C removed.

Approval

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List of Abbreviations

ADA	Anti-drug antibody
AE	Adverse Event
AGES	Austrian Agency for Health and Food Safety GmbH
aPTT	Activated partial thromboplastin time
BA	Bioavailability
BDRM	Blind Data Review Meeting
BMI	Body Mass Index
CAT	Calibrated Automated Thrombogram
CI	Confidence Interval
CSP	Clinical Study Protocol
CSR	Clinical Study Report
DSMB	Data and Safety Monitoring Board
EC	Ethics Committee
ELISA	Enzyme-linked immunosorbent assay
FIH	First-In-Human
GP1b	Glycoprotein Ib
IV	Intravenous
MAD	Multiple ascending dose
MedDRA	Medical Dictionary for Regulatory Activities
NHV	Normal healthy volunteer
PD	Pharmacodynamic(s)
PFA	Platelet Function Analyzer
PK	Pharmacokinetic(s)
PP	Per-Protocol
SAD	Single ascending dose
SC	Subcutaneous
SD	Standard deviation
SMQ	Standardized MedDRA Query
TLF	Tables, Listings and Figures
T_{max}	Time to Maximum Plasma Concentration
VWF	Von Willebrand Factor
VWF:RiCo	Von Willebrand Factor:ristocetin co-factor assay
WHO	World Health Organization

1. OVERVIEW

1.1 Study Objectives

1.1.1 Primary Objective

The primary objective of this study is to assess the clinical safety and tolerability of BT200 in normal human volunteers (NHVs).

1.1.2 Secondary Objective

The secondary objectives of this study are to assess the human pharmacokinetics (PK) of BT200.

1.1.3 Exploratory Objectives

The exploratory objectives of this study are to evaluate the human immunogenicity and Pharmacodynamics (PD) of BT200, as follows:

- To evaluate the presence of anti-drug antibodies (ADAs) against BT200
- To evaluate the human PD of BT200 with respect to von Willebrand Factor (VWF)-mediated platelet function
- To evaluate the human PK/PD relationship of BT200
- To evaluate potentially useful biomarkers for future clinical trials
- To investigate the mechanism of action of BT200 on the human coagulation system

1.2 Study Design

Study BT200-01 is a prospective, double-blind, randomized, placebo-controlled First-In-Human (FIH) study of BT200 in male and female NHVs with 4 sub-parts: Part A, a single ascending dose (SAD) study; Part B, a multiple ascending dose (MAD) study; Part C, a desmopressin challenge study; and Part D, a relative Bioavailability (BA) study.

Part A, the SAD study in NHVs, will be conducted according to an ascending dose cohort paradigm in which a unique cohort of NHVs will be treated at each single dose level. There will be 10 cohorts of NHVs (6:2 ratio of BT200:placebo; except for the sentinel pair [1:1 ratio]). Cohorts 1 through 10 will consist of 8 NHVs each, comprising 6 NHVs administered BT200 subcutaneous (SC) (0.18, 0.6, 1.8, 6.0, 12.0, 18.0, 24.0 by rapid SC injection, and 24.0, 36.0 mg, 48.0 mg by gradual SC infusion, respectively, for each cohort) and 2 NHVs administered placebo SC. Not all NHVs in a given cohort in Part A will be dosed on the same day: a sentinel pair (1 BT200, 1 placebo) will be dosed on the first day, then with a lag of at least 48 hours staggered groups roughly of 2 to 3 NHVs per day will be dosed thereafter. Cohorts 8-10 of Part A will be initiated only after submission and authorization of a Substantial Amendment to Ethics Committee (EC) and Austrian Agency for Health and Food Safety (AGES) summarizing the results of Cohorts 1-7.

Part B, the MAD study in NHVs, will also be conducted according to an ascending dose cohort paradigm. Part B will be initiated only after Substantial Amendment to EC and AGES has been submitted and authorized following completion of cohorts 8-10 of Part A and Part D. There will be 2 cohorts of NHVs, each consisting of 8 NHVs (6:2

ratio of BT200:placebo) in this part of the study. These cohorts will be administered an initial loading dose regimen of BT200 or placebo consisting of both a 2-hour IV infusion and an SC injection on Day 0, followed by 4 weekly (every 7 days) doses of BT200 or placebo by SC injection The dose levels in Part B are: a loading dose of 12.0 mg IV infused over 2 hours plus 12.0 mg SC injection followed by 4 maintenance doses of 12.0 mg SC injection in Cohort 13; a loading dose of 24.0 mg IV infused over 2 hours plus 24.0 mg SC injection followed by 4 maintenance doses of 24.0 mg SC injection in Cohort 14. Not all subjects in each of the cohorts of Part B will be dosed on the same day; rather, they will be dosed in staggered groups roughly of 2 to 3 subjects per day.

Part C, the desmopressin challenge will be initiated only after a Substantial Amendment to EC and AGES has been submitted and authorized following cohorts 8-10 of Part A and Part D. Part C will consist of a single cohort, Cohort 12, of 8 NHVs (6:2 ratio of BT200:placebo, plus desmopressin challenge) in this part of the study. Six subjects in Cohort 12 will be administered a single dose of 48.0 mg BT200 SC injection and 2 subjects administered a single dose of placebo on Day -4 as an SC injection All subjects will then be administered an intravenous (IV) infusion of 0.3 µg/kg desmopressin over 30 minutes on Day 0 approximately 96 hours after the single dose of BT200 or placebo SC (i.e., at the predicted time to maximum plasma concentration [T_{max}] for BT200).

Part D, the relative BA crossover, will be initiated only after a Substantial Amendment to EC and AGES has been submitted and authorized following cohorts 1-7 of Part A. Part D will consist of 1 cohort of NHVs, consisting of 8 NHVs (6:2 ratio of BT200:placebo) administered a single IV dose of BT200 of 24.0 and 2 NHVs administered a single dose of placebo IV over 24 hours on Day 0.. Part D could include NHVs who have previously participated in Part A.

Firstly Part A (cohorts 1-7), secondly Part A (cohorts 8-10) and Part D, and finally Part C and Part B will be conducted sequentially. There will be a DSMB safety review after dosing of NHVs in Cohorts 1-7 of Part A is completed before Cohorts 8-10 of Part A are initiated; again after Cohorts 8-10 of Part A and Part D before Part C and Part B is initiated. The safety data provided to the DSMB and the resulting DSMB opinion will be submitted as a Substantial Amendment to EC and AGES prior to initiating Cohorts 8-10 of Part A and Part D; again prior to initiating Part C and Part B.

1.3 Endpoints

1.3.1 Primary Endpoint

Overall safety and tolerability of BT200, assessed in terms of:

- Serious, drug-related adverse events (AEs)
- Premature terminations due to drug-related AEs
- Patterns of serious or non-serious, drug-related AEs, and/or clinically relevant laboratory abnormalities, vital signs, ECGs, or physical findings suggestive of one or more specific target organs for toxicity of BT200
- Clinically evident bleeding

1.3.2 Secondary Endpoints

Pharmacokinetic Endpoints:

- Measured concentration of BT200
- Derived PK parameters

1.3.3 Exploratory Endpoints

- Immunogenicity Endpoint:
  - ADAs against BT200
- Pharmacodynamic Endpoints:
  - Platelet Function Analyzer (PFA-100®)
  - VWF:ristocetin co-factor assay (VWF:RiCo)
  - Multiplate electrode platelet aggregometer (ristocetin)
  - Enzyme-linked immunosorbent assay (ELISA) for unbound VWF-A1 domain (REAADS®)
- Biomarker Endpoints:
  - VWF antigen and propeptide
  - Factor VIIIc activity (elagic acid activator)
  - Activated partial thromboplastin time (aPTT) FS (elagic acid activator)
  - Calibrated Automated Thrombogram (CAT) assay (Thrombinoscope®)

1.4 Sample Size Calculation

As this study is exploratory and descriptive in nature, no inferential statistical testing was planned and therefore an exact sample size requirement cannot be specified. The number of NHVs planned to be included is expected to be sufficient to fulfill the study's objectives, but not excessive.

Part A: 80 NHVs; Part B: 16 NHVs; Part C: 8 NHVs; Part D: 8 NHVs (including NHVs who may have previously participated in Part A).

1.5 Flowchart and Schedules of Assessments

Flowcharts for all study parts are provided in the Clinical Study Protocol (CSP), Section 'Study Diagram'.

Table 1: Study Procedures Part A (Weeks 1-14) (SAD)

Visit	Screening	V1								V2	V3	V4	V5	V6	V7	V8	PK and Immuno Sampling Visits
		Treatment								Post-treatment							
Day		D0							D1	D2	D3	D4	D7	D14	D21	D28	D42, D56
Time		-1h	0h	0.5h	1h	4h	8h	14h	24h	48h	72h	96h	168h				
Time Window	D-28 to D-1	±59'		±15'	±15'	±30'	±30'	±120'	±30'	±2h	±2h	±2h	±2h	±1d	±1d	±1d	±2d
Written Informed Consent	X																
Demographic Data	X																
Medical History	X																
Admit to Inpatient Unit		X															
Inclusion / Exclusion Criteria	X	X [1]															
Randomization		X															
Study Drug Administration			X														
Body Weight and Height [2]	X	X														X	
Physical Examination, Full	X												X			X	
Physical Examination, Brief		X							X	X				X	X		
Vital Signs (BP, HR, body temperature)	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	
Cardiac Evaluation (12-lead ECG)	X	X							X				X			X	
Serology for HIV, hepatitis B, and hepatitis C	X																
Hematology	X	X				X			X	X			X	X	X	X	
Coagulation	X	X				X			X	X			X	X	X	X	
Clinical Chemistry	X	X				X			X	X			X	X	X	X	
Urinalysis [3]	X	X							X	X			X	X	X	X	
PK Assessments		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X [4]
Immuno Assessments		X															X [4]
PD Assessments [5]		X		X	X	X	X	X	X	X	X	X	X	X	X	X	

Visit	Screening	V1								V2	V3	V4	V5	V6	V7	V8	PK and Immuno Sampling Visits
		Treatment								Post-treatment							
Day		D0							D1	D2	D3	D4	D7	D14	D21	D28	D42, D56
Time		-1h	0h	0.5h	1h	4h	8h	14h	24h	48h	72h	96h	168h				
Discharge from Inpatient Unit									X								
Concomitant Medications / Procedures	X	**Ongoing**															
Adverse Events	X	**Ongoing**															

Abbreviations: ’=minute(s); ADA=anti-drug antibody; BP=blood pressure; D=day; ECG=electrocardiogram; h=hour(s); HIV=human immunodeficiency virus; HR=heart rate; Immuno=immunogenicity; PD=pharmacodynamic(s); PK=pharmacokinetic(s); SAD=single ascending dose; V=visit

1. At -1h (ie, before BT200 injection) on Day 0, site personnel will perform a brief recheck of inclusion/exclusion criteria (excluding reassessments of laboratory parameters) to ensure that the subject remains eligible to participate in the study.
2. Body height will only be measured at Screening.
3. Dipstick urinalysis will be performed.
4. Late PK samples will be obtained at 6 and 8 weeks after the dose of study drug, whereas late immunogenicity samples will be obtained only at 8 weeks after the dose of study drug
5. PD assessments also include biomarker assays and an exploratory coagulation assay.

Note: Additional details regarding Part A laboratory blood sampling (hematology, coagulation, clinical chemistry, PK assessments, immunogenicity assessments, and PD assessments [including biomarker assays and an exploratory coagulation assay]) are provided in CSP Appendix 1: Laboratory Blood Sampling Supplement to Schedule of Assessments (Part A) and the laboratory manual.

Table 2: Study Procedures Part B Week 1 (MAD)

Visit	Screening	V1								V2	V3	V4
Day		Treatment										
		D0							D1	D2	D3	D4
Time		-1h	0h	0.5h	1h	4h	8h	14h	24h	48h	72h	96h
Time Window	D-28 to D-1	±59'		±15'	±15'	±30'	±30'	±120'	±30'	±2h	±2h	±2h
Written Informed Consent	X											
Demographic Data	X											
Medical History	X											
Admit to Inpatient Unit		X										
Inclusion / Exclusion Criteria	X	X										
Randomization		X										
Study Drug Administration [1]			X									
Body Weight and Height [2]	X	X										
Physical Examination, Full	X											
Physical Examination, Brief		X							X			X
Vital Signs (BP, HR, body temperature)	X	X		X	X	X	X	X	X	X	X	X
Cardiac Evaluation (12-lead ECG)	X	X							X			
Serology for HIV, hepatitis B, and hepatitis C	X											
Nasal swab screen for coronavirus	X											
Hematology	X	X				X			X			X
Coagulation	X	X							X			X
Clinical Chemistry	X	X							X			
Urinalysis [3]	X	X							X			
PK Assessments		X		X	X	X	X	X	X	X	X	X
Immunogenicity Assessments		X										
PD Assessments [4]		X		X	X	X	X	X	X	X	X	X
Discharge from Inpatient Unit [5]									X			

Visit	Screening	V1								V2	V3	V4
Day		Treatment										
		D0							D1	D2	D3	D4
Time		-1h	0h	0.5h	1h	4h	8h	14h	24h	48h	72h	96h
Concomitant Medications / Procedures	X	**Ongoing**										
Adverse Events	X	**Ongoing**										

Abbreviations: ’=minute(s); ADA=anti-drug antibodies; BP=blood pressure; D=day; ECG=electrocardiogram; h=hour(s); HIV=human immunodeficiency virus; HR=heart rate; MAD=multiple ascending dose; PD=pharmacodynamic(s); PK=pharmacokinetic(s); V=visit

1. Study drug will be administered after all other study procedures for this visit have been completed.
2. Body height will only be measured at Screening.
3. Dipstick urinalysis will be performed.
4. PD assessments also include biomarker assays and an exploratory coagulation assay.
5. Based on the results from Part A, it may become apparent that the overnight stay and Hour 14 blood sample time point in Part B are superfluous. In this case, at the discretion of the Principal Investigator, the Hour 14 time point procedures may be omitted and the subjects discharged after the Hour 8 time point procedures have been completed.

Note: Additional details regarding Part B laboratory blood sampling (hematology, coagulation, clinical chemistry, PK assessments, immunogenicity assessments, and PD assessments [including biomarker assays and an exploratory coagulation assay]) are provided in CSP Appendix 2: Laboratory Blood Sampling Supplement to Schedule of Assessments (Part B) and the laboratory manual.

Table 3: Study Procedures Part B Weeks 2-12 (MAD)

Visit	V5-8			V9-11	V12	PK and Immuno Sampling Visits
	Treatment			Post-treatment		
Day	D 7, D14, D21, D28			D35, D42, D49	D56	D70, D84
Time	-1h	0h	1h	0h	0h	±2d
Time Window	±59'		±30'			
Study Drug Administration		X				
Body weight	X				X	
Physical Examination, Full			X [1]		X [1]	
Physical Examination, Brief	X		X	X		
Vital Signs (BP, HR, body temperature)	X		X	X	X	
Cardiac Evaluation (12-lead ECG)	X				X	
Hematology	X			X	X	
Coagulation	X			X	X	
Clinical Chemistry	X			X	X	
Urinalysis [2]	X			X	X	
PK Assessments	X			X	X	X [3]
Immuno Assessments	X					X [3]
PD Assessments [4]	X			X	X	
Concomitant Medications / Procedures	**Ongoing**					
Adverse Events	**Ongoing**					

Abbreviations: '=minute; BP=blood pressure; D=day; ECG=electrocardiogram; h=hour; HR=heart rate; Immuno=immunogenicity; MAD=multiple ascending dose; PD=pharmacodynamic(s); PK=pharmacokinetic(s); V=visit

1. Full physical examination only on Days 28 and 56.
2. Dipstick urinalysis will be performed.
3. Late PK samples will be obtained at 6 and 8 weeks after the last dose of study drug, whereas late immunogenicity samples will be obtained only at 8 weeks after the dose of study drug.
4. PD assessments also include biomarker assays and an exploratory coagulation assay.

Note: Additional details regarding Part B laboratory blood sampling (hematology, coagulation, clinical chemistry, PK assessments, immunogenicity assessments, and PD assessments [including biomarker assays and an exploratory coagulation assay]) are provided in CSP Appendix 2: Laboratory Blood Sampling Supplement to Schedule of Assessments (Part B) and the laboratory manual.

Table 4: Study Procedures Part C Weeks 1-9 (Desmopressin Challenge)

Visit	Scr	V1	V2									V3	V4	V5	V6	V7	V8	V9	PK and Immuno SaV
		Treatment										Post-treatment							
Day		D -4	D0								D1	D2	D3	D4	D7	D14	D21	D28	D42, D56
Time		-96h	-1h	0h	0.5h	1h	2h	3h	4h	8h	14h	24h	48h	72h	96h	168h				
Time Window	D-28 to D-5	±1h	±59'		±15'	±15'	±15'	±15'	±30'	±30'	±120'	±30'	±2h	±2h	±2h	±2h	±1d	±1d	±1d	±2d
Written Informed Consent	X																			
Demographic Data	X																			
Medical History	X																			
Admit to Inpatient Unit			X																	
Inclusion / Exclusion Criteria	X		X																	
Randomization		X																		
Study Drug Administration		X																		
Desmopressin Administration				X																
Body Weight and Height [1]	X		X																X	
Physical Examination, Full	X														X			X		
Physical Examination, Brief			X									X					X	X		
Vital Signs (BP, HR, body temperature)	X		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Cardiac Evaluation (12-lead ECG)	X		X									X			X			X		
Serology for HIV, hepatitis B, and hepatitis C	X																			
Nasal swab screen for coronavirus	X																			

Visit	Scr	V1	V2									V3	V4	V5	V6	V7	V8	V9	PK and Immuno SaV
		Treatment										Post-treatment							
Day		D -4	D0								D1	D2	D3	D4	D7	D14	D21	D28	D42, D56
Time		-96h	-1h	0h	0.5h	1h	2h	3h	4h	8h	14h	24h	48h	72h	96h	168h				
Hematology	X	X	X			X	X	X	X	X		X				X			X	
Coagulation	X	X	X			X	X	X	X	X		X				X			X	
Clinical Chemistry	X	X	X									X				X			X	
Urinalysis [2]	X		X									X				X			X	
PK Assessments		X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X [3]
Immuno Assessments		X																		X [3]
PD Assessments [4]		X	X		X	X	X		X	X	X	X	X	X	X	X	X	X	X	
Discharge from Inpatient Unit												X								
Concomitant Medications / Procedures	X	**Ongoing**																		
Adverse Events	X	**Ongoing**																		

Abbreviations: ’=minute(s); BP=blood pressure; D=day; ECG=electrocardiogram; h=hour(s); HIV=human immunodeficiency virus; HR=heart rate; Immuno=immunogenicity; PD=pharmacodynamic(s); PK=pharmacokinetic(s); SaV=Sampling Visits; Scr=Screening; V=visit

1. Body height will only be measured at Screening.
2. Dipstick urinalysis will be performed.
3. Late PK samples will be obtained at 6 and 8 weeks after the dose of study drug, whereas late immunogenicity samples will be obtained only at 8 weeks after the dose of study drug.
4. PD assessments also include biomarker assays.

Note: Additional details regarding Part C laboratory blood sampling (hematology, coagulation, clinical chemistry, PK assessments, immunogenicity assessments, and PD assessments [including biomarker assays]) are provided in CSP Appendix 3: Laboratory Blood Sampling Supplement to Schedule of Assessments (Part C) and the laboratory manual.

Table 5: Study Procedures Part D Weeks 1-8 (Relative Bioavailability)

Visit	Screening	V1								V2	V3	V4	V5	V6	V7	V8	PK and Immuno Sampling Visits
		Treatment								Post-treatment							
Day		D0							D1	D2	D3	D4	D7	D14	D21	D28	D42, D56
Time		-1h	0h	0.5h	1h	4h	8h	14h	24h	48h	72h	96h	168h				
Time Window	D-28 to D-1	±59'		±15'	±15'	±30'	±30'	±120'	±30'	±2h	±2h	±2h	±2h	±1d	±1d	±1d	±2d
Written Informed Consent	X																
Demographic Data	X																
Medical History	X																
Admit to Inpatient Unit		X															
Inclusion / Exclusion Criteria	X	X															
Randomization		X															
Study Drug Administration			X[4]														
Body Weight and Height [1]	X	X														X	
Physical Examination, Full	X												X			X	
Physical Examination, Brief		X							X					X	X		
Vital Signs (BP, HR, body temperature)	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	
Cardiac Evaluation (12-lead ECG)	X	X							X				X			X	
Serology for HIV, hepatitis B, and hepatitis C	X																
Hematology	X	X							X				X			X	
Coagulation	X	X							X				X			X	
Clinical Chemistry	X	X							X				X			X	
Urinalysis	X	X							X				X			X	
PK Assessments		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X [2]
Immuno Assessments		X															X [2]
PD Assessments [3]		X		X	X	X	X		X	X	X	X	X	X	X	X	
Discharge from Inpatient Unit									X								

Visit	Screening	V1								V2	V3	V4	V5	V6	V7	V8	PK and Immuno Sampling Visits
		Treatment								Post-treatment							
Day		D0							D1	D2	D3	D4	D7	D14	D21	D28	D42, D56
Time		-1h	0h	0.5h	1h	4h	8h	14h	24h	48h	72h	96h	168h				
Concomitant Medications / Procedures	**X**		**Ongoing**														
Adverse Events	**X**		**Ongoing**														

Abbreviations: ’=minute(s); ADAs=anti-drug antibodies; BP=blood pressure; D=day; ECG=electrocardiogram; h=hour(s); HIV=human immunodeficiency virus; HR=heart rate; Immuno=immunogenicity; PD=pharmacodynamic(s); PK=pharmacokinetic(s); V=visit

1. Body height will only be measured at Screening.
2. Late PK samples will be obtained at 6 and 8 weeks after the dose of study drug, whereas late immunogenicity samples will be obtained only at 8 weeks after the dose of study drug.
3. PD assessments also include biomarker assays.

Note: Additional details regarding Part D laboratory blood sampling (hematology, coagulation, clinical chemistry, PK assessments, immunogenicity assessments, and PD assessments [including biomarker assays]) are provided in Appendix 4: Laboratory Blood Sampling Supplement to Schedule of Assessments (Part D) and the laboratory manual.

4. Continuous IV infusion over 24 hours beginning at Time 0.

2. GENERAL CONSIDERATIONS

2.1 Rationale

BT200 is a PEGylated aptamer that binds to the A1 domain of human VWF and thereby inhibits VWF binding to platelet glycoprotein Ib (GP1b), the first step in the cascade of platelet-mediated thrombogenesis. Study BT200-01 is a Phase 1 FIH study designed to assess the human safety, tolerability, pharmacokinetics, and pharmacologic activity of BT200 in NHVs. In order to ensure the well-being of study subjects, some key safety measures have been incorporated into the design of this study, including use of sentinel pairs of subjects and an independent Data and Safety Monitoring Board (DSMB). In order to assess the effect of elevated VWF levels (as might be encountered in patients in the future) on the BT200 concentration-effect relationship,1 single-dose cohort of BT200 administered together with a secretagogue for VWF (desmopressin) will be included as Part C. Finally, in order to assess the relative bioavailability of BT200 via SC vs. IV administration, a single dose IV cohort will be included as Part D. Based upon the PK and PD data observed in Parts A, C, and D the nominal dose levels specified in Part B may be adjusted by means of a Substantial Amendment to this protocol prior to initiation of dosing therein.

2.2 Conduct of Analysis

For Part A, B, C and D, a formal interim analysis is not planned. After all subjects have all visits of the respective study part performed, a topline analysis will be performed for Part A and D separately. Tables, Listings and Figures (TLFs) for the topline analysis can be found in Section 7.Topline analyses might be based on cleaned data for which no SDV was performed yet (due to Covid-19 pandemic, see Section 2.16). The final analysis of all study parts will be performed, when all study parts were fully SDVd, cleaned and once all external data are available and reconciled and the database is closed.

2.3 Statistical Software and Quality Control

All statistical analyses will be performed using SAS® version 9.3 or higher. Tables, figures and data listings will be generated in Microsoft® Word® as well as PDF® format.

Quality control of SAS® programs will include a review of the whole process of result generation:

- Review of all analysis SAS® programs
- Review of SAS® log for errors, warnings and other notes that could indicate mistakes in the programs
- Review of all tables, listings and figures for completeness and correctness

2.4 Applicable Standard Operating Procedures

The applicable Standard Operating Procedures (SOPs) of Assign DMB for this study are:

STAT03	Statistical Analysis Plan
STAT04	Interim Analysis
STAT05	Randomization and Unblinding
STAT06	Data Review Meeting

STAT07	Report Writing
SAS01	SAS General Principles
SAS04	Handling of Statistical Analyses
SAS06	CDISC_ADaM
SAS07	CDSC_Quality_Control

2.5 Blinding and Randomization

Subjects and study staff will be blinded to treatment assignment. Injections and infusions of BT200 or placebo will have a similar appearance. Unblinding for Part A and D will be performed after data entry for the respective study part is complete and database snapshot was performed for topline analysis. Unblinding for Part B and C will be performed after data entry for the respective study part is complete and database closure was performed.

In Part A, NHVs will be randomized to treatment with BT200 or placebo in a ratio of 3:1 in Cohorts 1 and 2, and in a ratio of 6:2 in Cohorts 3 to 10, except for the sentinel pair of subjects (1:1 ratio). For each of the remaining study parts (Parts B, C, and D), NHVs will be randomized to treatment with BT200 or placebo in a ratio of 6:2. If the site is able to recruit Asians in addition to Caucasians, a stratified randomization procedure will be performed according to Ethnicity. This stratification is not performed formally within the randomization list, but the sites instructed to not consider Asians for the sentinel pairs (to increase probability for Asians to not receive placebo).

2.6 Descriptive Analyses

Descriptive analyses of continuous variables (summary statistics) will be described with the number of non-missing observations, arithmetic mean, standard deviation (±SD), median, quartiles (Q1 and Q3) and range (minimum and maximum).

Categorical variables (frequency statistics) will be described with the number of non-missing observations and percentages (%). Percentages will be calculated on the total number of non-missing observations, if not stated otherwise.

2.7 Inferential Analyses

Two-sided 95% confidence intervals (CIs)will be calculated according to Altman will be calculated for certain safety tables (see Section 7).

2.8 Center and Country Effect

Not applicable. This is a single-center study that will be conducted at the Department of Clinical Pharmacology, Medical University of Vienna at the Vienna General Hospital (AKH/MUW) in Vienna, Austria.

2.9 Handling Missing Data

Generally, missing values will not be imputed and the analysis will be limited to observed values.

2.10 Protocol Deviations

For Part A and D, a Blind Data Review Meeting (BDRM) will be conducted prior to database snapshot for topline analysis. For Part B and C the BDRM will be conducted prior the database closure. BDRMs will be conducted on all data to review protocol deviations, to discuss specific unforeseeable data issues, and to allocate the subjects to the analysis sets. During the BDRM, two classifications will be performed:

1. Protocol deviations will be classified as not relevant or relevant deviations, based on the potential influence on the PK and PD analysis. Relevant protocol violations will include the following but are not limited to:
   - Violations of major inclusion or exclusion criteria
   - Wrong treatment administration
   - Other protocol deviations with expected substantial influence on PK analysis
2. Protocol deviations will be classified as important or not important with respect to the GCP (E3) definition (i.e. important protocol deviations are a subset of protocol deviations that may significantly impact the completeness, accuracy, and/or reliability of the study data or that may significantly affect a subject's rights, safety, or well-being).

Protocol deviation classifications will be made on a case by case decision in the BDRM. The associated decisions will be documented and approved in the BDRM Report.

Protocol violations classified as important and/or relevant will be described in the CSR (Clinical Study Report).

2.11 Medical Coding

Adverse events, medical history and concomitant procedures will be coded using MedDRA. Concomitant medications will be coded using WHO Drug Dictionary. Details are defined in the Coding Guideline. The used dictionary versions will be indicated in the respective tables and listings.

2.12 Analysis Populations

2.12.1 Safety Population

The Safety Population will include all randomized NHVs who received at least 1 dose of BT200/placebo. Subjects will be analyzed according to the treatment that they actually received. The Safety Population will be used for all safety endpoints.

2.12.2 Per-Protocol Population

The Per-Protocol (PP) Population will comprise all NHVs of the Safety Population, if the following criteria are additionally met:

- All of the major inclusion criteria, none of the major exclusion criteria are fulfilled.
- Absence of other relevant protocol violations such as wrong treatment received.

For each study part, a PP Population will be defined in the BDRM. The PP Population will represent the primary PK and PD analysis population.

2.13 Subject Data Listings

All subjects in the database will be included in listings if not stated otherwise. Data listings will include the subject number as identifier (and parameter and/or visit if available) and will be sorted by Dose cohort, subject ID (and parameter and/or visit if available). Every listing contains the column treatment group.

2.14 Columns in Tables

The following columns will be used for tables, if not stated otherwise:

- Part A: Pooled Placebo column (over all dose levels), Cohort 1 BT200, Cohort 2 BT200, Cohort 3 BT200, Cohort 4 BT200, Cohort 5 BT200, Cohort 6 BT200, Cohort 7 BT200, Cohort 8 BT200, Cohort 9 BT200 and Cohort 10 BT200.
- Part B:Pooled Placebo (over all dose levels), Cohort 13 BT200, Cohort 14 BT200 and Pooled BT200 (all subjects treated with BT200 over all dose levels).
- Part C: Cohort 12 BT200 and Placebo column.
- Part D: Cohort 11 BT200 and Placebo column.

In each analysis part, a column showing all subjects together will additionally used in the table summarizing the demographic information.

2.15 Changes in the Conduct of the Study or Planned Analysis

No changes to the statistical analysis as compared to CSP are planned.

2.16 Effect of Covid-19

Due to the Covid-19 pandemic no monitoring visits can be performed before database snapshot for topline analyses. Possible impact of Covid-19 pandemic and respective measures were discussed. Subject visits and time points will be partly affected by the pandemic. If visits can not be performed due to Covid-19 the visit will be documented as not performed in the eCFR with reason “COVID19”. Drop-outs due to Covid-19 will be documented in the eCRF on the end of study page with reason “other“ and specification “COVID19” as reason for early termination. No further effects are expected due to Covid-19. Statistical analysis will include a summary of drop-outs and early terminations due to Covid-19. In Part B and C, a screening for coronavirus by nasal swab testing will be performed at the screening visit. Subjects with positive coronavirus test will be excluded from the study. The results of the coronavirus screening will be tabulated and listed.

Unexpected Covid-19 effects (e.g. overviews on missing data, Covid-19 related protocol deviations, missed visits, visits out of time-window and changes in study processes) will be described in the Clinical Study Report.

3. OVERALL STUDY INFORMATION

Tables will be provided for the Safety Population, if not stated otherwise and selected tables will be repeated for the PP Population. The following information will be analyzed descriptively and corresponding details on the subject level will be provided in data listings:

- Patient overview
- Screening failures
- Violated inclusion/exclusion criteria (will only be listed)
- Subjects by dose level and overall
- Study visit information (incl. Admission/Discharge Inpatient Unit information)
- Missed visits due to Covid-19 (will be listed only)
- End of study information (incl. drop-outs due to Covid-19)
- Protocol deviations
- Coronavirus screening (only applicable for Part B and C)

Specifications of Tables, Listings and Figures (TLFs) are provided in Section 7.

4. BASELINE EVALUATION

Baseline data will be presented for Safety Population .

4.1 Data Points

Data will be analyzed from the screening visit and the randomization visit (if applicable) The following information will be analyzed descriptively and corresponding details on the subject level will be provided in data listings:

- Demographics (including body height [cm] and body weight [kg], Body Mass Index (BMI) [kg/m^2])
- Serology (will only be listed)
- Medical history overall and by SOC and PT
- Prior/Concomitant medications overall and by ATC level
- Prior/Concomitant procedures overall and by SOC and PT
- Childbearing-potential (will only be listed)

Vital signs, ECG and physical examination results will be analyzed in the safety section (see Section 6.4).
Specifications of TLFs are provided in Section 7.

4.2 Derivations and Definitions

- Medications stopped clearly prior to first study drug administration will be considered as prior medications, all other medications are considered to be concomitant. Medications with a missing or incomplete stop date where it cannot clearly be decided if the stop date was before or after Day 0 (Visit 1) will be considered as concomitant.
- Procedures stopped clearly prior to first study drug administration will be considered as prior procedures, all other procedures are considered to be concomitant. Procedures with a missing or incomplete stop date where it cannot clearly be decided if the stop date was before or after Day 0 (Visit 1) will be considered as concomitant.
- BMI [kg/m^2] is defined as the weight [kg] divided by the square of the body height [m]

5. PHARMACOKINETICS / PHARMACODYNAMICS / BIOMARKER / IMMUNOGENICITY

Pharmacodynamics, biomarker and immunogenicity analysis will be performed for the PP Population and the Safety Population.

5.1 Pharmacokinetics

Pharmacokinetics analysis will be performed by CERTARA and are not described in this Statistical Analysis Plan.

5.2 Pharmacodynamics

The following tables will be performed for PFA-100, VWF:RiCo [%], multiplate aggregometer and REAADS and corresponding details on the subject level will be provided in data listings:

- Absolute values by time point
- Absolute change from randomization by time point
- Relative change [%] from randomization by time point

The following figures will be provided for PFA-100, VWF:RiCo [%], multiplate aggregometer and REAADS separately:

- Absolute values by subject: For every subject separately, the time course over of the parameters mentioned above will be drawn, where the actual measurement time point since first dose will be shown on x-axis (hours) and the parameters values will be drawn on the y-axis.
- Absolute values by cohort: One graph will be drawn that includes the data of all cohorts. One line will be drawn per cohort, where the x-axis will show the planned time point of measurement (in hours) and the y-axis will show the mean value of the respective cohort incl. standard error. Measurements of all scheduled visits will be included, where the EOS visit will be treated as the last visit.

PD sampling results will be entered eCRF using a result specifier (i.e. <, ≤, >, ≥). For statistical analysis, values reported as <x, ≤x, >x or ≥x will be analyzed as x. E.g. <300, ≤300, >300 or ≥300 will be analyzed as value 300.

Details are specified in Section 7.

5.3 Biomarker

The following tables will be performed for VWF antigen [%], VWF propeptide [mIU/mL], Factor VIIIc activity [%], aPTT FS [sec], Thrombin generation CAT assay (Thrombinoscope) [nM], Fibrin D-dimer [mIU/mL] and Prothrombin fragment F1.2 [mIU/mL]. Corresponding details on the subject level will be provided in data listings:

- Absolute values by time point
- Absolute change from randomization by time point
- Relative change [%] from randomization by time point

The following figures will be provided for VWF antigen [%], VWF propeptide [mIU/mL], Factor VIIIc activity [%], aPTT FS [sec],Thrombin generation CAT assay (Thrombinoscope) [nM] and Fibrin D-dimer [mIU/mL] and Prothrombin fragment F1.2 [mIU/mL] separately:

- Absolute values by subject: For every subject separately, the time course over of the parameters mentioned above will be drawn, where the actual measurement time point will be shown on x-axis (hours) and the parameters values will be drawn on the y-axis.
- Absolute values by cohort: One graph will be drawn that includes the data of all cohorts. One line will be drawn per cohort, where the x-axis will show the planned time point of measurement (in hours) and the y-axis will show the mean value of the respective cohort incl. standard error. Measurements of all scheduled visits will be included, where the EOS visit will be treated as the last visit.

Details are specified in Section 7.

5.4 Immunogenicity

The following tables will be produced for immunogenicity and corresponding details on the subject level will be provided in data listings:

- ADA results (positive/negative/not reportable/NA) by time point

Details are specified in Section 7.

6. SAFETY ANALYSIS

All analyses will be performed for the Safety Population. Data from unscheduled visits will only be listed. Data from scheduled visits and early termination visits will be tabulated.

6.1 Extent of Exposure

Study drug administration will be listed.

For Part B, a cumulative dose level will be determined as the total amount of received study drug up to the current time point (loading dose and maintenance dose).

For Part C, Desmopressin administration will be listed additionally.

6.2 Adverse Events and Bleeding Events

Adverse Events (AEs) are documented in the eCRF section “Adverse Events” and Bleeding Events in the eCRF section “Bleedings”. AEs and bleeding events will be analyzed together.

6.2.1 Data Points

The following tables will be generated:

AE and bleeding event overview (e.g. any AE or bleeding event, any severe AE or bleeding event, any related AE or bleeding event, any hemorrhage (MedDRA SMQ), all embolic and thrombotic events (SMQ), Embolic and thrombotic events, arterial (SMQ), Embolic and thrombotic events, vessel type unspecified and mixed arterial and venous (SMQ), Embolic and thrombotic events, venous (SMQ))

-)
- AEs and bleeding events overall and by SOC and PT

- Related AEs and bleeding events overall and by SOC and PT
- Serious AEs and bleeding events overall and by SOC and PT
- Related serious AEs and bleeding events overall and by SOC and PT
- AEs and bleeding events by maximum severity
- Related AEs and bleeding events by maximum severity
- Serious AEs and bleeding events by maximum severity
- Related serious AEs and bleeding events by maximum severity
- AEs and bleeding events leading to permanently study drug discontinuation or leading to withdrawn from study
- Related AEs and bleeding events leading to permanently study drug discontinuation or leading to withdrawn from study
- Major bleeding events overall and by SOC and PT
- Total ISTH bleeding score (frequency table)
- Bleeding Assessment Score by symptom
- Maximum Bleeding Assessment Score
- AEs and bleeding events with missing assessments (will only be listed)

6.2.2 Definitions and Derivations

- AEs and bleeding events are considered as “related” if the causality to study drug is reported as “related” or “possible”.
- Tables showing AEs or bleeding events by causality, subjects will be counted only in the strongest relationship category but events will be counted in each category.
- In tables showing AEs or bleedings events by maximum severity, subjects will be counted only in the highest grading category but events will be counted in each category.
- An AE or bleeding event is considered as “leading to permanently study drug discontinuation” if “study drug permanently discontinued” is ticked for “action taken on study treatment”.
- An AE or bleeding event is considered as “leading to withdrawal from study” if for “Other action taken”, “withdrawn from study” is answered with “yes”.
- Missing assessments contains missing seriousness, severity and/or causality
- The Total ISTH Bleeding Score will be calculated as the sum of bleeding assessment scores (documented in the eCRF) overall symptoms of a subject. If a subject experienced a symptom more than once, the event with the higher bleeding score will be used.
- The SMQ code for Hemorrhage is 20000038 Haemorrhages (SMQ) which consists of SMQ codes 20000039 “Haemorrhage terms (excl laboratory terms)” and 20000040 “Haemorrhage laboratory terms”.
- The SMQ code for arterial embolic and thrombotic events is 20000082 “Embolic and thrombotic events, arterial (SMQ)”.

- The SMQ code for vessel type unspecified and mixed arterial and venous embolic and thrombotic events is 20000083 “Embolic and thrombotic events, vessel type unspecified and mixed arterial and venous (SMQ)”.
- The SMQ code for venous embolic and thrombotic events is 20000084 “Embolic and thrombotic events, venous (SMQ)”.

6.3 Laboratory Parameters

Laboratory data from scheduled visits and early termination visits will be tabulated. Listings will additionally include results from unscheduled visits.

The following parameters will be assessed in the study and will be included in the statistical analysis:

- Hematology
    - Hemoglobin
    - Hematocrit
    - Red blood cells
    - White blood cells
    - Lymphocytes
    - Monocytes
    - Neutrophils
    - Eosinophils
    - Basophils
    - Platelets
    - Reticulocytes
- Coagulation
    - Prothrombin time
- Clinical Chemistry
    - Sodium
    - Potassium
    - Calcium
    - Chloride
    - Aspartate aminotransferase
    - Alanine aminotransferase
    - Alkaline phosphatase
    - Lactate dehydrogenase
    - Gamma-glutamyltransferase
    - Bilirubin
    - C-reactive protein
    - Blood Urea Nitrogen
    - Creatinine

    - Glucose
- Urinalysis
    - Specific gravity
    - pH
    - Leukocytes
    - Nitrite
    - Protein
    - Glucose
    - Ketones
    - Urobilinogen
    - Bilirubin
    - Erythrocytes

Quantitative laboratory parameters (i.e., hematology, clinical chemistry, coagulation, pH, Specific Gravity) will be analyzed descriptively:

- Absolute values by parameter and time point (summary statistics)
- Absolute change from randomization by parameter and time point (summary statistics)
- Relative change from randomization by parameter and time point (summary statistics)
- Number of subjects with values above/below normal range by parameter and time point (frequency statistics)

Qualitative urinalysis parameters will be analyzed by tabulation of urinalysis result by parameter and time point (frequency statistics)

One set of data listings will show parameters outside normal range (hematology, coagulation, clinical chemistry, quantitative urinalysis parameters) and abnormal qualitative urinalysis values, respectively.

For every parameter, boxplots showing the absolute values by study day will be provided.

All parameters will be analyzed using the unit registered by study site in the eCRF. No unit conversion will be done.

6.4 Other Safety Parameters

Other safety data from scheduled visits will be tabulated as described below. Listings will additionally include results from unscheduled visits or early termination visit.

Results from vital signs (systolic blood pressure [mmHg], diastolic blood pressure [mmHg], heart rate [beats/min], body temperature [C] and body weight [kg]) and ECG will be tabulated descriptively by:

- Absolute values by parameter and time points (summary statistics)
- Absolute changes from randomization by parameter and time points (summary statistics)
- Number of subjects with clinically relevant vital signs results by parameter and time point (frequency statistics)

- ECG Interpretation (normal/abnormal/abnormal, clinically relevant/abnormal, not clinically relevant) by time point (frequency statistics)
- Physical examination results (normal/abnormal) by body system and time point (frequency statistics)

Absolute values of vital signs parameters and continuous ECG parameters will be provided by time point. The x-axis will show the study day. A separate figure will be provided for every parameter.
Details are specified in Section 7.

7. LIST OF TABLES, DATA LISTINGS AND FIGURES

The x in the numbering of the TLFs below has to be replaced by 1 for Part A, 2 for Part B, 3 for Part C and 4 for Part D.

7.1 List of Tables

No	Topline Analysis	Title	Content/Comment
Overall Study Information and Baseline Evaluation			
14.x.1.1.1	Yes	Patient Overview	• Number of subjects in Safety Population • Number of subjects in PP Population • Number of sentinel subjects (only applicable for Part A) • Number of randomized subjects • Screening of coronavirus (only applicable for Part B and C) Columns: Not randomized, column for each BT200 dose level and Placebo
14.x.1.1.2	No	Number of Screening Failures and Reasons	One column for all subjects
14.x.1.1.3	No	Subjects by Visit (Safety Population)	
14.x.1.1.4	No	End of Study Information (Safety Population)	• Visit attendance status • Primary reason for early termination • Early terminations due to Covid-19
14.x.1.1.5	No	Protocol Deviations (Safety Population)	• Any major protocol deviation • Major protocol deviations by category • Any minor protocol deviation • Minor protocol deviations by category
14.x.1.1.6	Yes	Demographic Information (Safety Population)	• Gender • Age [years] • Race • Ethnicity • Body height [cm] • Body weight [kg] • BMI [kg/m^2] at screening
14.x.1.1.7	No	Medical History Overall and by SOC and PT (Safety Population)	• Any medical history • By SOC and PT
14.x.1.1.8	No	Prior Medications Overall and by ATC Level (Safety Population)	• Any prior medication • By ATC level
14.x.1.1.9	No	Concomitant Medications Overall and by ATC Level (Safety Population)	• Any concomitant medication • By ATC level
14.x.1.1.10	No	Prior Procedures Overall and by SOC and PT (Safety Population)	• Any prior procedures • By SOC and PT
14.x.1.1.11	No	Concomitant Procedures Overall and by SOC and PT (Safety Population)	• Any concomitant procedures • By SOC and PT

14.x.1.2.3-14.x.1.2.5	No	Repeat tables 14.x.1.1.3-5 for PP Population	
Pharmacodynamics/Biomarker/Immunogenicity			
14.x.2.1.1	Yes	Multiplate Aggregometer [U]: Absolute values by time point (PP Population)	
14.x.2.1.2	No	Multiplate Aggregometer [U]: Absolute change from randomization by time point (PP Population)	
14.x.2.1.3	No	Multiplate Aggregometer [U]:Relative change [%] from randomization by time point (PP Population)	
14.x.2.1.4	Yes	PFA-100 [sec]: Absolute values by time point (PP Population)	
14.x.2.1.5	No	PFA-100 [sec]: Absolute change from randomization by time point (PP Population)	
14.x.2.1.6	No	PFA-100 [sec]: Relative change [%] from randomization by time point (PP Population)	
14.x.2.1.7	Yes	REAADS: Absolute values by time point (PP Population)	
14.x.2.1.8	No	REAADS: Absolute change from randomization by time point (PP Population)	
14.x.2.1.9	No	REAADS: Relative change [%] from randomization by time point (PP Population)	
14.x.2.1.10	Yes	VWF:RiCo [%]: Absolute values by time point (PP Population)	
14.x.2.1.11	No	VWF:RiCo [%]: Absolute change from randomization by time point (PP Population)	
14.x.2.1.12	No	VWF:RiCo [%]: Relative change [%] from randomization by time point (PP Population)	
14.x.2.1.13	Yes	VWF antigen [%]: Absolute values by time point (PP Population)	
14.x.2.1.14	No	VWF antigen [%]: Absolute change from randomization by time point (PP Population)	
14.x.2.1.15	No	VWF antigen [%]: Relative change [%] from randomization by time point (PP Population)	
14.x.2.1.16	Yes	VWF propeptide [mIU/mL]: Absolute values by time point (PP Population)	
14.x.2.1.17	No	VWF propeptide [mIU/mL]: Absolute change from randomization by time point (PP Population)	
14.x.2.1.18	No	VWF propeptide [mIU/mL]: Relative change [%] from randomization by time point (PP Population)	
14.x.2.1.19	Yes	Factor VIIIc activity [%]: Absolute values by time point (PP Population)	
14.x.2.1.20	No	Factor VIIIc activity [%]: Absolute change from randomization by time point (PP Population)	
14.x.2.1.21	No	Factor VIIIc activity [%]: Relative change [%] from randomization by time point (PP Population)	
14.x.2.1.22	Yes	aPTT FS [sec]: Absolute values by time point (PP Population)	
14.x.2.1.23	No	aPTT FS [sec]: Absolute change from randomization by time point (PP Population)	
14.x.2.1.24	No	aPTT FS [sec]: Relative change from randomization by time point (PP Population)	
14.x.2.1.25	Yes	Thrombin generation CAT assay [nM]: Absolute values by time point (PP Population)	

14.x.2.1.26	No	Thrombin generation CAT assay [nM]: Absolute change from randomization by time point (PP Population)	
14.x.2.1.27	No	Thrombin generation CAT assay [nM]: Relative change [%] from randomization by time point (PP Population)	
14.x.2.1.28	Yes	Fibrin D-dimer [mIU/mL]: Absolute values by time point (PP Population)	
14.x.2.1.29	No	Fibrin D-dimer [mIU/mL]: Absolute change from randomization by time point (PP Population)	
14.x.2.1.30	No	Fibrin D-dimer [mIU/mL]: Relative change [%] from randomization by time point (PP Population)	
14.x.2.1.31	Yes	Prothrombin fragment F1.2 [mIU/mL]: Absolute values by time point (PP Population)	
14.x.2.1.32	No	Prothrombin fragment F1.2 [mIU/mL]: Absolute change from randomization by time point (PP Population)	
14.x.2.1.33	No	Prothrombin fragment F1.2 [mIU/mL]: Relative change [%] from randomization by time point (PP Population)	
14.x.2.1.34	No	ADA results by time point (PP Population)	
14.x.2.2.1-14.x.2.2.34	No	Repeat tables 14.x.2.1.1-14.x.2.1.34 for Safety Population	
Safety Analysis			
AEs and Bleeding Events			
14.x.3.1.1	Yes	AE and bleeding event overview (Safety Population)	• Any AE or bleeding event • Any related AE or bleeding event • Any severe AE or bleeding event • Any related severe AE or bleeding event • Any serious AE or bleeding event • Any related serious AE or bleeding event • Any Hemorrhage (MedDRA SMQ) • Any AEs or bleeding events leading to permanently study drug discontinuation or leading to withdrawn from study • Any related AEs or bleeding events leading to permanently study drug discontinuation or leading to withdrawn from study (repeat contents for bleeding events) • Any Hemorrhage Event (MedDRA SMQ)

			• All embolic and thrombotic events (SMQ) • Embolic and thrombotic events, arterial (SMQ) • Embolic and thrombotic events, vessel type unspecified and mixed arterial and venous (SMQ) • Embolic and thrombotic events, venous (SMQ) Incl. 2-sided 95% CIs
14.x.3.1.2	Yes	AEs and bleeding events overall and by SOC and PT (Safety Population)	
14.x.3.1.3	Yes	Related AEs and bleeding events overall and by SOC and PT (Safety Population)	
14.x.3.1.4	Yes	Severe AEs and bleeding events overall and by SOC and PT (Safety Population)	
14.x.3.1.5	Yes	Related severe AEs and bleeding events overall and by SOC and PT (Safety Population)	
14.x.3.1.6	Yes	Serious AEs and bleeding events overall and by SOC and PT (Safety Population)	
14.x.3.1.7	Yes	Related serious AEs and bleeding events overall and by SOC and PT (Safety Population)	
14.x.3.1.8	Yes	AEs and bleeding events by maximum severity (Safety Population)	Incl. 2-sided 95% CIs
14.x.3.1.9	Yes	Related AEs and bleeding events by maximum severity (Safety Population)	Incl. 2-sided 95% CIs
14.x.3.1.10	Yes	Serious AEs and bleeding events by maximum severity (Safety Population)	Incl. 2-sided 95% CIs
14.x.3.1.11	Yes	Related serious AEs and bleeding events by maximum severity (Safety Population)	Incl. 2-sided 95% CIs
14.x.3.1.12	Yes	AEs and bleeding events leading to permanently study drug discontinuation or leading to withdrawn from study by SOC and PT (Safety Population)	
14.x.3.1.13	Yes	Related AEs and bleeding events leading to permanently study drug discontinuation or leading to withdrawn from study by SOC an PT (Safety Population)	
14.x.3.1.14	Yes	Bleeding Events by SOC and PT (Safety population)	Incl. 2-sided 95% CI
14.x.3.1.15	Yes	Major bleeding events overall and by SOC and PT (Safety Population)	
14.x.3.1.16	Yes	Total ISTH Bleeding Score (Safety Population)	
14.x.3.1.17	Yes	Bleeding Assessment Score by Symptom (Safety Population)	
14.x.3.1.18	Yes	Maximum Bleeding Assessment Score (Safety Population)	
Laboratory parameter			
14.x.3.1.19	Yes	Hematology and Coagulation: Absolute values by time point (Safety Population)	
14.x.3.1.20	Yes	Hematology and Coagulation: Absolute change from randomization by time point (Safety Population)	
14.x.3.1.21	Yes	Hematology and Coagulation: Relative change from randomization by time point (Safety Population)	

14.x.3.1.22	Yes	Hematology and Coagulation: Subjects outside normal range by time point (Safety Population)	
14.x.3.1.23	Yes	Clinical Chemistry: Absolute values by time point (Safety Population)	
14.x.3.1.24	Yes	Clinical Chemistry: Absolute change from randomization by time point (Safety Population)	
14.x.3.1.25	Yes	Clinical Chemistry: Relative change from randomization by time point (Safety Population)	
14.x.3.1.26	Yes	Clinical Chemistry: Subjects outside normal range by time point (Safety Population)	
14.x.3.1.27	Yes	Quantitative Urinalysis: Absolute values by time point (Safety Population)	
14.x.3.1.28	Yes	Quantitative Urinalysis: Absolute change from randomization by time point (Safety Population)	
14.x.3.1.29	Yes	Quantitative Urinalysis: Relative change from randomization by time point (Safety Population)	
14.x.3.1.30	Yes	Quantitative Urinalysis: Subjects outside normal range by time point (Safety Population)	
14.x.3.1.31	Yes	Qualitative Urinalysis by time point (Safety Population)	
14.x.3.1.32	Yes	Vital Signs: Absolute values by time point (Safety Population)	• systolic blood pressure [mmHg] • diastolic blood pressure [mmHg] • heart rate [beats/min] • body temperature [C] • body weight [kg]
14.x.3.1.33	Yes	Vital Signs: Absolute change from randomization by time point (Safety Population)	Content see Table 14.x.3.1.32
14.x.3.1.34	Yes	Subjects with clinically relevant vital signs by time point (Safety Population)	Content see Table 14.x.3.1.32
14.x.3.1.35	Yes	ECG: Absolute values by time point (Safety Population)	• PQ [ms] • QRS [ms] • QT [ms] • QTcF [ms] • P [ms] • RR [ms] • PP [ms] • P [degree] • QRS [degree] • T [degree]
14.x.3.1.36	Yes	ECG: Absolute change from randomization by time point (Safety Population)	Content see Table 14.x.3.1.35
14.x.3.1.37	Yes	Subjects with clinically relevant ECG values by time point (Safety Population)	Content see Table 14.x.3.1.35
14.x.3.1.38	Yes	ECG Interpretation by time point (Safety Population)	• normal • abnormal • abnormal, clinically relevant • abnormal, not clinically relevant
14.x.3.1.39	Yes	Physical Examination results by body system and time point (Safety Population)	• normal • abnormal

7.2 List of Data Listings

No	Topline Analysis	Title	Content/Comment
Overall Study Information and Baseline Evaluation			
16.2.x.1.1	No	Analysis Population Details	Actual dose cohort, Randomized dose cohort, Subject number, Sentinel (only applicable for Part A), Randomization performed, Date of randomization, Time of randomization, Reason not randomized, Safety Population, Reason not in Safety Population, PP Population, Reason not in PP Population
16.2.x.1.2	No	Screening Failures with Reasons	Subject number, Informed consent date, Subject's withdrawal of consent, In/Ex criterion fulfilled, Adverse event, Other, Specification other reason
16.2.x.1.3	No	Violated Entry Criteria	Subject number, Visit, Criterion ID not met, Criterion description
16.2.x.1.4	No	Visit Information and Admission/Discharge Inpatient Unit	Dose cohort, Subject number, Visit, Reason for unscheduled visit, Visit/Admission/Discharge date, Visit/Admission/Discharge time, Reason visit not performed, Reason outside time window, Specification other reason, Age
16.2.x.1.5	No	Missed Visits due to Covid-19	Dose cohort, Subject number, Visit, Reason for unscheduled visit, Visit date, Visit time, Reason visit not performed, Reason outside time window, Age
16.2.x.1.6	No	Protocol Deviations	Dose cohort, Subject number, PD category, Classification, Reason for classification, PD description
16.2.x.1.7	Yes	Study End Information	Dose cohort, Subject number, Visit attendance status, Date of discontinuation, Primary reason for early termination, Specification other reason, Reason for recommended withdrawal, Death date, Primary cause of death
16.2.x.1.8	Yes	Drop-outs due to Covid-19	Dose cohort, Subject number, Visit attendance status, Date of discontinuation, Primary reason for early termination, Specification other reason, Reason for recommended withdrawal, Death date, Primary cause of death
16.2.x.1.9	Yes	Demographic Data	Dose cohort, Subject number, Subject re-screened (only applicable for Part D), Subject number in Part A (only applicable for Part D), Date of informed consent, Year of birth, Age [years], Gender, Childbearing potential, Reason no childbearing potential, Specification other reason childbearing potential, Race, Specification other race, Ethnicity, Blood type, Rhesus factor, Body weight [kg] at

			screening, Body Height [cm], BMI [kg/m^2] at screening
16.2.x.1.10	No	Medical History	Dose cohort, Subject number, Condition, SOC, PT, Start date, End date, Ongoing at study end
16.2.x.1.11	No	Concomitant Medications	Dose cohort, Subject number, Medication/Therapy, ATC Level 2, ATC Level 3, Start date, End date, Ongoing at study end, Dose, Dose Unit, Dose Form, Frequency, Route, Indication category, prior/concomitant
16.2.x.1.12	No	Concomitant Procedures	Dose cohort, Subject number, Procedure, SOC, PT, Start date, End date, Ongoing at study end, Indication category, Indication, prior/concomitant
16.2.x.1.13	No	Serology	Dose cohort, Subject number, Visit, Serology sample collected, Reason not collected, Collection date, Collection time, Test name, Result, Not done
16.2.x.1.14	No	Screening for coronavirus by nasal swab testing (only applicable for Part B and C)	Dose cohort, Subject number, Sample collected, Reason not collected, Collection date, Collection time, Result
Pharmacodynamics/Biomarker/Immunogenicity			
16.2.x.2.1	Yes	Pharmacodynamics Results	Dose cohort, Subject number, Visit, Sampling Date/Time, Sample taken, Reason not done, Test, Result specification, Result, Unit, Absolute Change, Relative Change [%]
16.2.x.2.2	Yes	Biomarker Results	Dose cohort, Subject number, Visit, Sampling Date/Time, Sample taken, Reason not done, Test, Result specification, Result, Unit, Absolute Change, Relative Change [%]
16.2.x.2.2	Yes	Additional Biomarker Results	Dose cohort, Subject number, Visit, Parameter, Result, Unit, Absolute Change, Relative Change [%]
16.2.x.2.3	No	ADA Results	Dose cohort, Subject number, Nominal Day, Collection date, Collection time, Ave, Stdev, CV%, Reported Result
Safety Analysis			
16.2.x.3.1.1	Yes	Study Drug Administration	Dose cohort, Subject number, Visit, Study drug administered, Study drug administered as, Reason not administered, Administration Start Date, Administration Start Time, Administration End Date, Administration End Time, Location, Other Location, Dose level, Study drug administration performed according to protocol, Cumulative dose level (only applicable for Part B)
16.2.x.3.1.2	Yes	Desmopressin Administration (only applicable for Part C)	Dose cohort, Subject number, Desmopressin administered, Reason not administered, Administration Start Date, Administration Start Time, Administration End Date, Administration End Time, Administration dose (ug)

16.2.x.3.2	Yes	Adverse Events (Part I)	Dose cohort, Subject number, Source, Term, SOC, PT, Start date, Start time, Serious, Serious Criteria, Severity, Causality to study treatment, Causality to desmopressin (only applicable for Part C)
16.2.x.3.3	Yes	Adverse Events (Part II)	Dose cohort, Subject number, AE Term, Action taken on study treatment, Action taken on desmopressin (only applicable for Part C), Other action taken, Specification other action taken, Outcome, Recovering date, recovering time, Ongoing at final examination
16.2.x.3.4	Yes	Serious Adverse Events (Part I)	See Listing 16.x.3.1
16.2.x.3.5	Yes	Serious Adverse Events (Part II)	See Listing 16.x.3.2
16.2.x.3.6	Yes	Haemorrhage terms (SMQ) (Part I)	See Listing 16.x.3.1
16.2.x.3.7	Yes	Haemorrhage terms (SMQ) (Part II)	See Listing 16.x.3.2
16.2.x.3.8	Yes	Embolic and thrombotic events, arterial (SMQ) (Part I)	See Listing 16.x.3.1
16.2.x.3.9	Yes	Embolic and thrombotic events, arterial (SMQ) (Part II)	See Listing 16.x.3.2
16.2.x.3.10	Yes	Embolic and thrombotic events, vessel type unspecified and mixed arterial and venous (SMQ) (Part I)	See Listing 16.x.3.1
16.2.x.3.11	Yes	Embolic and thrombotic events, vessel type unspecified and mixed arterial and venous (SMQ) (Part II)	See Listing 16.x.3.2
16.2.x.3.12	Yes	Embolic and thrombotic events, venous (SMQ) (Part I)	See Listing 16.x.3.1
16.2.x.3.13	Yes	Embolic and thrombotic events, venous (SMQ) (Part II)	See Listing 16.x.3.2
16.2.x.3.14	No	Adverse Events with missing assessments (Part I)	See Listing 16.x.3.1
16.2.x.3.15	No	Adverse Events with missing assessments (Part II)	See Listing 16.x.3.2
16.2.x.3.16	Yes	Additional Assessments for Bleeding Events	Dose cohort, Subject number, Bleeding event, Bleeding event verbatim, Start date, Start time, Bleeding Assessment Score, ISTH clinical relevant major bleeding, Major bleeding criteria, ISTH clinical relevant non-major bleeding, Non-major bleeding criteria, End date, End time
16.2.x.3.17	Yes	Hematology and Coagulation Values Outside Normal Range	Dose Level, Subject number, Parameter, Visit, Lab performed, Reason not performed, Collection date, Collection time, same as visit/admission/discharge date, Test, Result, Unit, not done, Reason not done, Outside laboratory limits, Lower limit, Upper limit, Clinically relevant
16.2.x.3.18	Yes	Clinical Chemistry Values Outside Normal Range	See Listing 16.x.3.9
16.2.x.3.19	No	Quantitative Urinalysis Values Outside Normal Range	See Listing 16.x.3.9
16.2.x.3.20	No	Abnormal Qualitative Urinalysis Results	Dose level, Subject number, Parameter, Visit, Lab performed, Reason not performed, Collection date, Collection

			time, same as visit/admission/discharge date, Result, not done, Reason not done, Clinically relevant
16.2.x.3.21	No	Vital Signs	Dose level, Subject number, Visit, Vital signs collection, Reason not collected, Collection date, Collection time, same as visit/admission/discharge date, Test, Result, Clinically relevant, not done
16.2.x.3.22	No	ECG	Dose level, Subject number, Visit, ECG performed, Reason not performed, Date, Time, Same as visit/admission/discharge date, Test, Result, Abnormal, Clinically relevant, not analyzed/not available
16.2.x.3.23	No	Physical Examination	Dose level, Subject number, Visit, Extent of physical examination, Examination performed, Reason not performed, Examination Date, Examination Time, same as visit/admission/discharge date, Body system, Result, Specification other body system

7.3 List of Figures

No	Topline Analysis	Title	Content/Comment
PD / Biomarker			
14.x.2.1.29	Yes	Multiplate Aggregometer [U]: Absolute values by subject (PP Population)	
14.x.2.1.30	Yes	Multiplate Aggregometer [U]: Absolute values by cohort (PP Population)	
14.x.2.1.31	Yes	PFA-100 [sec]: Absolute values by subject (PP Population)	
14.x.2.1.32	Yes	PFA-100 [sec]: Absolute values by cohort (PP Population)	
14.x.2.1.33	Yes	REAADS: Absolute values by subject (PP Population)	
14.x.2.1.34	Yes	REAADS: Absolute values by cohort (PP Population)	
14.x.2.1.35	Yes	VWF:RiCo [%]: Absolute values by subject (PP Population)	
14.x.2.1.36	Yes	VWF:RiCo [%]: Absolute values by cohort (PP Population)	
14.x.2.1.37	Yes	VWF antigen [%]:Absolute values by subject (PP Population)	
14.x.2.1.38	Yes	VWF antigen [%]: Absolute values by cohort (PP Population)	
14.x.2.1.39	Yes	VWF propeptide [mIU/mL]: Absolute values by subject (PP Population)	
14.x.2.1.40	Yes	VWF propeptide [mIU/mL]: Absolute values by cohort (PP Population)	
14.x.2.1.41	Yes	Factor VIIIc activity [%]:Absolute values by subject (PP Population)	
14.x.2.1.42	Yes	Factor VIIIc activity [%]:Absolute values by cohort (PP Population)	
14.x.2.1.43	Yes	aPTT FS [sec]: Absolute values by subject (PP Population)	

14.x.2.1.44	Yes	aPTT FS [sec]: Absolute values by cohort (PP Population)	
14.x.2.1.45	Yes	Thrombinoscope [nM]: Absolute values by subject (PP Population)	
14.x.2.1.46	Yes	Thrombinoscope [nM]: Absolute values by cohort (PP Population)	
14.x.2.1.47	Yes	Fibrin D-dimer [mIU/mL]: Absolute values by subject (PP Population)	
14.x.2.1.48	Yes	Fibrin D-dimer [mIU/mL]: Absolute values by cohort (PP Population)	
14.x.2.1.49	Yes	Prothrombin fragment F1.2 [mIU/mL]: Absolute values by subject (PP Population)	
14.x.2.1.50	Yes	Prothrombin fragment F1.2 [mIU/mL]: Absolute values by cohort (PP Population)	
Safety Analysis			
14.x.3.1.40	Yes	Boxplots of hematology values by group and visit (Safety Population)	Separate figures for every group and every parameter
14.x.3.1.41	Yes	Boxplots of coagulation values by group and visit (Safety Population)	Separate figures for every group and every parameter
14.x.3.1.42	Yes	Boxplots of clinical chemistry values by group and visit (Safety Population)	Separate figures for every group and every parameter
14.x.3.1.43	Yes	Boxplots of urinalysis values by group and visit (Safety Population)	Separate figures for every group and every parameter
14.x.3.1.44	Yes	Vital signs values by group and visit (Safety Population)	Separate figures for every group and every parameter
14.x.3.1.45	Yes	ECG values by group and Visit (Safety Population)	Separate figures for every group and every parameter

8. SHELLS OF TABLES, DATA LISTINGS AND FIGURES

For this analysis, no table shells or mock tables are produced, but analysis drafts of TLFs will be generated based on dummy group allocation (dummy randomization list) and dummy immunogenicity data. These drafts will reviewed by the sponsor.