BT200-01

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

Protocol identification number:	BT200-01
EudraCT No.:	2019-001818-42
Protocol version:	FINAL VERSION 1.5.1, DATE 22-APR-2020
Test product:	BT200
Principal Investigator:	**Ao. Univ.-Prof. Dr. Ulla Derhaschnig**
Sponsor:	**Band Therapeutics, LLC**

BAND
THERAPEUTICS

Confidentiality

The contents of the protocol are confidential and may not be communicated verbally or in writing without permission from the study sponsor.

CONTACT ADDRESSES

Sponsor	Band Therapeutics, LLC 101 Hartwell Avenue, Suite 2 Lexington, MA 02421 USA Phone: + 1.781.918.6580 Email: jim.gilbert@bandtherapeutics.com
Sponsor's Medical Monitor	James C. Gilbert, MD Chief Executive Officer Band Therapeutics, LLC Phone (mobile): +1.617.281.3550 Email: jim.gilbert@bandtherapeutics.com
Principal Investigator:	Ao. Univ.-Prof. Dr. Ulla Derhaschnig Medical University of Vienna Department of Clinical Pharmacology Waehringer Guertel 18-20 1090 Vienna, Austria Phone: +43 1 40400 29810 Fax: +43 140400 29980 Email: ulla.derhaschnig@meduniwien.ac.at
Data Monitoring Committee	Univ.-Prof. Dr.med. univ. Dr. Heinz Burgmann, Chairman Department of Internal Medicine I, Div. of Infectious Diseases Währinger Gürtel 18-20 1090 Vienna, Austria Phone: +43 1 40400 44400
Project Management Data Monitoring	Celerion Hainburger Strasse 33 1030 Vienna| Austria Phone: +43 1 403 38 05 – 54 Fax: +43 1 403 38 05 -66 www.celerion.com
Data Management Statistics	Assign Data Management and Biostatistics GmbH Stadlweg 23 6020 Innsbruck Austria Ph: +43 512 890 064 121 Fax: +43 512 281 514
BT200 Bioanalysis	QPS 3 Innovation Way #240 Newark, DE 19711 USA Phone: +1. 302 369-5601
Pharmacokinetic and Pharmacodynamic Analysis	Certara 2000 Peel Street, Suite 570 Montréal, Québec H3A 2W5 Canada

	Tel: +1 514 789 2180
Immunogenicity (Anti-Drug Antibody) Analysis	STC Biologics 330 Nevada Street, Newton, MA 02460, USA Phone: +1 617 916-9659
Drug Supply	ABF Pharmaceutical Services GmbH Brunner Strasse 63/18-19 1230 Vienna Austria

Summary of Changes in Version 1.1 Relative to Version 1.0

- Reference to contraceptives in the description of permitted concomitant medications was deleted as Not Applicable given that the inclusion of women volunteers has been restricted to those who are post-menopausal or *status post* hysterectomy.
- Cohorts 8-10 of Part A will not be initiated before a Substantial Amendment summarizing the results of Part A Cohorts 1-7 has been submitted to EC and AGES and authorized.
- Information supporting the IV route of administration was added to Section 3.1.1, *Justification for Dose Regimen***.**

Summary of Changes in Version 1.2 Relative to Version 1.1

- Contact Information was updated with the correct new phone number for Band Therapeutics' company offices.
- The address for ABF Pharmaceutical Services GmbH was updated to correspond to the location of the company's new facility where BT200 packaging and labeling is now being performed.
- ABO blood group typing was added to the Screening Visit tests as an extra precaution so that in case a serious bleeding event should occur requiring urgent blood transfusion this information would already be available.
- ISTH Bleeding Score was added as a specific and standardized safety assessment in case of the occurrence of "clinically evident bleeding".
- A discrepancy between the Schedule of Events and the Lab Sampling table in Appendix 4 with respect to the timing of samples for anti-drug antibody testing in Part D was corrected.
- An error in the Study Diagram for Part A was corrected, now placing the DSMB review after Cohort 7 and before Cohort 8, as per agreement with AGES.

Summary of Changes in Version 1.3 Relative to Version 1.2

Emerging PK and PD data from Part A suggest that the SC bioavailability of BT200 in humans may be lower than predicted. To address this concern the following modifications of the Phase 1 plan have been introduced;

- In Part A (the Single Ascending Dose part of the study) the mode of study drug administration was changed from rapid SC injection to gradual SC infusion.
- In Part A two additional dose cohorts were added in order that:
    - the 24 mg dose could be repeated (in a new cohort of subjects) using the technique of gradual SC infusion;
    - the highest dose to be increased to 48 mg dose cohort (i.e., exceeding the previous top dose of 36 mg, which will be retained in the new version of the protocol).
- Part D (the IV crossover part of the study) was moved ahead of Part B (the Multiple Ascending Dose part of the study) in the order of clinical operations so that a definitive read-out of relative bioavailability of BT200 (SC versus IV) will be obtained prior to conduct of Part B in case modification of the dosing scheme for Part B should be required.
- Part C (the desmopressin challenge part of the study) was reduced from two to one cohort of subjects.
- A second DSMB review and Substantial Amendment based upon the results of the expanded Part A together with those of Part C and Part D will be performed prior to initiation of Part B.

In addition, clarification of the timing of post-dose immunogenicity samples in Parts A, B, C, and D was added to the corresponding tables of Study Procedures.

Summary of Changes in Version 1.4 Relative to Version 1.3

Emerging PK and PD data from the additional Part A cohorts introduced in the preceding amendment show a favorable trend toward increased SC bioavailability of BT200 after SC infusion relative to SC small volume bolus injection, but suggest that the dose needs to be increased further to achieve the therapeutic target concentration of BT200. In order to accomplish this two new Part A cohorts have been added, both with BT200 administration by the SC infusion technique.

- BT200 72 mg SC injection or infusion; N=8; 6:2 active:placebo randomization
- BT200 96 mg SC injection or infusion; N=8; 6:2 active:placebo randomization

1.5.1

The visit schedule and planned study assessments will remain the same as for all previous Part A cohorts DSMB review of safety after Part A cohorts 8-10 and Part D (the IV crossover cohort) will be completed prior to initiation of these two new Part A cohorts.

In order to optimize the route, dose, and timing of BT200 administration for Part C according to the emerging PK data from Part A, study drug administration in Part C, is being changed as follows:

- BT200 administration will now be done only by SC infusion;
- The dose of BT200 will now be 48 mg, not 24 mg;
- BT200 will now be administered 96 hours prior to desmopressin, not 24 hours.

Summary of Changes in Version 1.5.1 Relative to Version 1.4

Substantial Changes:

After reviewing the safety and pharmacodynamic results of Part A Cohorts 8-10 and Part D Cohort 11 the DSMB recommended not to escalate the dose of BT200 any further in healthy volunteers than the 48 mg dose that had been administered in Part A Cohort 10. Therefore, the following modifications to the study will be made via this amendment.

- Part A Cohorts 16 (72 mg) and 17 (96 mg) will not be implemented as planned in Version 1.4 of this study protocol. Part A will now be closed.
- With no further dose escalation there is no longer the need for another interim DSMB safety review before the initiation of Part B, the Multiple Ascending Dose component of this study.
- The dose regimens for Part B can now be finalized based upon the safety, pharmacokinetics, and pharmacodynamics observed in the completed Part A.
- Part B Cohort 13: BT200 12 mg IV plus 12 mg SC on Day 0, then 12 mg SC on Days 7, 14, 21, and 28
- Part B Cohort 14: BT200 24 mg IV plus 24 mg SC on Day 0, then 24 mg SC on Days 7, 14, 21, and 28
- Part B Cohort 15, the high dose cohort previously planned, will be eliminated.

Part C, the desmopressin challenge will still be performed as planned in Version 1.4 of this study protocol (with a single dose of 48 mg of BT200).

Miscellaneous Changes:

- One additional VWF-related biomarker, VWF propeptide, will be added to the laboratory analysis program for Part A, in order to clarify the mechanism underlying the observed, unexpected rise in VWF antigen after BT200 treatment. No additional blood sampling will be required as this assay can be performed with the unused PK back-up samples.
- A typographical error in the heading of Table 3 Study Procedures Part B was corrected.
- Screening for coronavirus by nasal swab testing was added to the Screening Visit procedures for Part B and Part C.

Approval of the Protocol

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

FINAL VERSION 1.5.1, DATE 22-APR-2020

Representative of the Sponsor: Dr. James Gilbert, Chief Executive Officer, Band Therapeutics, LLC

Signature

22 April 2020
Date (DD Month YYYY)

Principal Investigator: Ao. Univ.-Prof. Dr. Ulla Derhaschnig

Signature

Date (DD Month YYYY)

PROTOCOL SYNOPSIS

Title	A SINGLE/MULTIPLE ASCENDING DOSE PHASE 1 STUDY OF THE SAFETY, TOLERABILITY, AND PHARMACOLOGIC ACTIVITY OF BT200 IN NORMAL HUMAN VOLUNTEERS
Protocol Number	BT200-01
Version	DRAFT VERSION 1.5.1, Date 22-APR-2020
EUDRACT Number	2019-001818-42
Test Product	BT200
Phase	Phase 1
Indication	Stroke prevention in high-risk patients
Sponsor	Band Therapeutics, LLC 101 Hartwell Avenue, Suite 2 Lexington, MA 02421 USA Phone: + 1.781.918.6580 Email: jim.gilbert@bandtherapeutics.com
Sponsor's Medical Monitor	James C. Gilbert, MD Chief Executive Officer Band Therapeutics, LLC Phone: + 1.781.918.6580 Email: jim.gilbert@bandtherapeutics.com
Principal Investigator	Ao. Univ.-Prof. Dr. Ulla Derhaschnig Medical University of Vienna Department of Clinical Pharmacology Waehringer Guertel 18-20 1090 Vienna, Austria Phone: +43 1 40400 29810 Fax: +43 140400 29980 Email: ulla.derhaschnig@meduniwien.ac.at
Data Monitoring Committee	Univ.-Prof. Dr. Heinz Burgmann, Chairman Department of Internal Medicine I, Div. of Infectious Diseases Währinger Gürtel 18-20 1090 Vienna, Austria Phone: +43 1 40400 44400
Project Management Data Monitoring	Celerion Hainburger Strasse 33 1030 Vienna| Austria Phone: +43 1 403 38 05 – 54 Fax: +43 1 403 38 05 -66 www.celerion.com
Data Management Statistics	Assign Data Management and Biostatistics GmbH Stadlweg 23 6020 Innsbruck Austria Ph: +43 512 890 064 121

	Fax: +43 512 281 514
BT200 Bioanalysis	QPS 3 Innovation Way #240 Newark, DE 19711 USA Phone: +1. 302 369-5601
Pharmacokinetic and Pharmacodynamic Analysis	Certara 2000 Peel Street, Suite 570 Montréal, Québec H3A 2W5 Canada Phone: +1 514 789 2180
Immunogenicity (Anti-Drug Antibody) Analysis	STC Biologics 330 Nevada Street, Newton, MA 02460, USA Phone: +1 617 916-9659
Drug Supply	ABF Pharmaceutical Services GmbH Brunner Strasse 63/18-19 1230 Vienna Austria Phone: +43 1 8901200
Study Design	Prospective, double-blind, randomized, placebo-controlled First-In-Human (FIH) study in male and female normal human volunteers (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; • Part D, a relative bioavailability study.
Rationale	BT200 is a PEGylated aptamer that binds to the A1 domain of human von Willebrand Factor (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 subcutaneous (SC) vs. intravenous (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.
Anticipated Start Date	Q3/2019
Duration of Study	1.5 years
Proposed Country	Austria
Study Site	Medical University of Vienna Department of Clinical Pharmacology Waehringer Guertel 18-20

	1090 Vienna, Austria Phone: +43 1 40400 29810 Fax: +43 140400 29980 Email: klin-pharmakologie@meduniwien.ac.at
Planned Sample Size	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)
Primary Objective	The primary objective of this study is to assess the clinical safety and tolerability of BT200 in NHVs.
Secondary Objectives	The secondary objective of this study is to assess the human PK of BT200.
Exploratory Objectives	The exploratory objectives of this study are to evaluate the human immunogenicity and PD of BT200, as follows: • To evaluate the presence of anti-drug antibodies (ADAs) against BT200 • To evaluate the human pharmacodynamics (PD) of BT200 with respect to 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
Target Population	NHVs
Inclusion Criteria	To be eligible for this study, subjects must meet all of the following inclusion criteria: 1. Healthy male or female volunteers, age ≥ 18 years old at screening 2. If female, must be post-menopausal or s*tatus post* hysterectomy 3. Able to comprehend and to give informed consent 4. Able to cooperate with the Investigator, to comply with the requirements of the study, and to complete the full sequence of protocol-related procedures
Exclusion Criteria	Subjects meeting any of the following criteria will be excluded from the study: 1. Clinically significant medical history (including von Willebrand Disease, thrombocytopathy, or any type of bleeding diathesis) or ongoing chronic illness that would jeopardize the safety of the subject or compromise the quality of the data derived from his/her participation in this study 2. Clinically relevant abnormal findings on physical examination or clinically relevant laboratory abnormalities 3. History of infusion hypersensitivity reactions, significant drug allergy, or anaphylactic reactions 4. Substance abuse, mental illness, or any reason that makes it unlikely in the judgment of the Investigator for the subject to be able to comply fully with study procedures

	5. Use of medication during 2 weeks before the start of the study, which in the judgment of the Investigator may adversely affect the subject's welfare or the integrity of the study's results 6. Concurrent treatment with other experimental drugs or participation in another clinical trial with any investigational drug within 30 days or 5 elimination half-lives (whichever is longer) prior to treatment start

Treatments Administered	Part A: • Randomization ratio for BT200 to placebo = 6:2 (except for the sentinel pair, which will be at a ratio of 1:1) • Single SC doses of placebo or BT200 at the following BT200 dose levels per cohort: o Cohort 1: 0.18 mg (N=8) o Cohort 2: 0.6 mg (N=8) o Cohort 3: 1.8 mg (N=8) o Cohort 4: 6.0 mg (N=8) o Cohort 5: 12.0 mg (N=8) o Cohort 6: 18.0 mg (N=8) o Cohort 7: 24.0 mg (N=8) o Cohort 8: 24.0 mg by SC infusion (N=8) o Cohort 9: 36.0 mg by SC infusion (N=8) o Cohort 10: 48.0 mg by SC infusion (N=8) Cohorts 8-10 will be initiated only after submission and authorization of a Substantial Amendment to EC and AGES summarizing the results of Cohorts 1-7. . Part B: • Randomization ratio for BT200 to placebo = 6:2 • Loading and maintenance doses of placebo or BT200 via a 2-hour IV infusion and a SC injection at the following BT200 dose levels per cohort: o Cohort 13: Loading dose of 12.0 mg IV + 12.0 mg SC, followed by 4 weekly maintenance doses of 12.0 mg SC (N=8) o Cohort 14: Loading dose of 24.0 mg IV + 24.0 mg SC, followed by4 weekly maintenance doses of 24.0 mg SC (N=8) . Part C: • Randomization ratio for BT200 to placebo = 6:2, plus desmopressin challenge • Single doses of placebo or BT200 via SC injection at the following BT200 dose levels per cohort: o Cohort 12: BT200 + desmopressin challenge cohort: 48.0 mg (N=8) Single IV dose of desmopressin at the following dose level for all NHVs: o 0.3 µg/kg Part D: • Randomization ratio for BT200 to placebo = 6:2 • Single IV dose of placebo or BT200 at the following BT200 dose level for all NHVs: o Cohort 11: 24.0 mg (N=8) .

Treatment Schedule & Route of Administration	Part A: • All dose cohorts will receive a single SC dose of BT200 or placebo on Day 0 at Time 0 Cohorts 8-10 will be initiated only after submission and authorization of a Substantial Amendment to EC and AGES summarizing the results of Cohorts 1-7. Cohorts 16-17 will be initiated only after submission and authorization of a Substantial Amendment to EC and AGES summarizing the results of Cohorts 8-10 of Part A and Cohort 11 of Part D. Part B: • All dose cohorts will receive a total of 6 SC or IV doses of BT200 or placebo: o Loading dose regimen consisting of equal IV and SC doses on Day 0 at Time 0 o IV dose will be infused over 2 hours o Maintenance doses: 4 SC doses thereafter every 7 days Part C: • All subjects will receive only a single SC dose of BT200 or placebo on Day -4 • All subjects will receive desmopressin by IV infusion over 30 minutes on Day 0 at approximately 96 hours after the single SC dose of BT200 or placebo Part D: • One cohort will receive BT200 or placebo administered as an IV infusion over 24 hours
Investigational Medicinal Product	Test Product: • BT200 as a sterile solution for injection Comparator (Placebo): • Sterile saline for injection Non-investigational Medicinal Product (NIMP; Challenge Agent): • Desmopressin (MINIRIN® Injection) as a sterile solution for injection
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 assessed using the ISTH Bleeding Score (see Appendix 6)
Secondary Endpoints	Pharmacokinetic Endpoints: • Measured concentration of BT200 (and derived PK parameters)
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 • aPTT FS (elagic acid) • Thrombin generation Calibrated Automated Thrombogram (CAT) assay (Thrombinoscope®)
Statistical Considerations	Sample Size Calculation: As this study is exploratory and descriptive in nature, no inferential statistical testing is 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. Analysis Plan: For the analysis of AEs, summary tables will be generated for the incidence of AEs overall and by severity. The same will be calculated for serious adverse events (SAEs), related AEs, and related SAEs. The AE and SAE summary tables will provide the number and percentage of subjects with AEs and the 95% confidence intervals for the event rates. All safety analyses will be performed within the Safety Population. Pharmacokinetic sampling results (serum concentration of BT200) will be tabulated descriptively by sampling time point. The area under the curve from 0 to 24 hours ($AUC_{[0-24h]}$) and area under the curve from time 0 to time t ($AUC_{[0-t]}$) will be calculated via trapezoidal rule and will be tabulated together with the maximum plasma concentration (C_{max}) and time to maximum plasma concentration (T_{max}), descriptively. Details regarding further safety endpoints and the analysis of secondary or exploratory endpoints will be described in the Statistical Analysis Plan.
Interim Analysis	A complete interim analysis is not planned; however, the DSMB will review relevant safety data after Cohorts 1-7 of Part A prior to initiation of Cohorts 8-10 of Part A, and Part D; after Cohorts 8-10 of Part A and Cohort 11 of Part D and prior to initiation of Cohorts 16-17 of Part A and Cohort C;. The data prepared for DSMB review together with the resulting DSMB opinion will be provided to EC and AGES as part of a Substantial Amendment after Cohorts 1-7 of Part A prior to initiation of Cohorts 8-10 of Part A and Part D;; after Cohorts 8-10 of Part A and Part D prior to initiation of Part B.
Study Plan	First Subject In (FSI) to Part A: Q3/2019 Last Subject In (LSI) to Part B: Q3/2020 Last Subject Out (LSO): Q4/2020 Database Lock: Q1/2021 Clinical Study Report (CSR): Q2/2021

STUDY DIAGRAM

Figure 1 Study Diagram

The following is an idealized diagram of the study intended to show the sequence and relative timing of dosing in Parts A, B, C, and D. Note that for the sake of visual simplicity, this idealized diagram gives the appearance of simultaneous dosing within each cohort; it does NOT reflect the sentinel pair dosing scheme for Part A, nor the possibility that the remainder of each cohort will be broken into small groups, each of which might be dosed on consecutive days. The first DSMB and Regulatory interim review will occur after Cohorts 1-7 of Part A have been treated (shown in the diagram for Part A). A second DSMB and Regulatory interim review will occur after Cohorts 8-10 of Part A and Cohort 11 of Part D and a third DSMB and Regulatory interim review will occur prior to initiation of Part B (not shown).

STUDY PART A	Part A Study Duration (Relative Weeks)	W1	W2	W3	W4	W5	W6	W7	W8	DSMB #1 and Regulatory review	W9	W10	W11	W12	DSMB #2 and Regulatory review	End of Part A
Cohort [1]	Single Placebo or BT200 Dose SC [2] N=8 per Cohort															
1	0.18 mg SC injection	↓														
2	0.6 mg SC injection		↓													
3	1.8 mg SC injection			↓												
4	6.0 mg SC injection				↓											
5	12.0 mg SC injection					↓										
6	18.0 mg SC injection						↓									
7	24.0 mg SC injection							↓								
8	24.0 mg SC infusion										↓					
9	36.0 mg SC infusion											↓				
10	48.0 mg SC infusion												↓			

STUDY PART B	Part B Study Duration (Relative Weeks)		W1	W2	W3	W 4	W5	W 6	W7	W 8	W9	W10	W11	W12	W13	W14	End of Part B
Cohort [3]	Loading Placebo or BT200 Dose [2] N=8 per Cohort	Maintenance Placebo or BT200 Dose SC injection or IV [2]															
13	12.0 mg IV + 12.0 mg SC	12.0 mg	↓	↓	↓	↓	↓										
14	24.0 mg IV + 24.0 mg SC	24.0 mg			↓	↓	↓	↓	↓								

STUDY PART D	Part D Study Duration (Relative Weeks)	W1	W2	W3	W 4	W5	W 6	W7	W 8	End of Part D
Cohort [5]	Single Placebo or BT200 Dose IV [2] N=8									
11	24.0 mg	↓								

STUDY PART C	Part C Study Duration (Relative Weeks)	W1	W2	W3	W 4	W5	W 6	W7	W 8	End of Part C
Cohort [4]	Single Dose SC injection[2] N=8 per Cohort									
12	Placebo or BT200: 48.0 mg SC injection Desmopressin: 0.3 µg/kg IV	↓								

Abbreviations: ↓=dosing; DSMB=Data and Safety Monitoring Board; IV=intravenous(ly); N/A=not applicable; NHV=normal human volunteer; SC=subcutaneous(ly); W=week

1. Part A Cohorts will also include NHVs treated with placebo (N=2 for all Cohorts). Each cohort will include a sentinel pair, with a randomization ratio of 1:1 for BT200 to placebo. All dose cohorts will receive a single SC dose of BT200 or placebo on Day 0 of Week 1 (Cohort 1), Week 2 (Cohort 2), Week 3 (Cohort 3), Week 4 (Cohort 4), Week 5 (Cohort 5), Week 6 (Cohort 6), Week 7 (Cohort 7), Week 9 (Cohort 8), Week 10 (Cohort 9), Week 11 (Cohort 10),).
2. In this figure, BT200 doses are shown for each cohort.
3. Part B Cohorts will also include NHVs treated with placebo (N=2 for Cohorts 13 and 14). Both dose cohorts will receive total of 6 doses of BT200 or placebo, comprising the split IV + SC loading dose Day 0 and maintenance SC doses as follows: 4 doses every 7 days of Weeks 1 to 5 (Cohort 13)and Weeks 3 to 7 (Cohort 14).
4. Part C Cohorts will also include NHVs treated with placebo (N=2 for Cohort 12 [BT200 + desmopressin challenge] All subjects will receive only a single SC injection of BT200 or placebo on Day -4 of Week 1. All subjects will receive desmopressin by IV infusion over 30 minutes on Day 0 of Week 1 (Cohort 12) at approximately 96 hours after the single dose of BT200 or placebo.
5. Part D Cohort 11 will also include NHVs treated with placebo (N=2). This cohort will receive BT200 or placebo administered as an IV infusion over 24 hours on Day 0 of Week 1.