CLINICAL STUDY PROTOCOL

Protocol No. PRT-201-320

Multicenter, Double-Blind, Placebo-Controlled Study of Vonapanitase (PRT--201) Administered Immediately after Radiocephalic Arteriovenous Fistula Creation in Patients with Chronic Kidney Disease

Edition No. 05
09 May 2018

SPONSOR:

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SIGNATURE PAGE FOR INVESTIGATOR

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I have read and understand the protocol and agree to conduct the study as outlined. I understand that the information in this protocol is confidential and must not be disclosed, other than to those directly involved in the execution or the scientific/ethical review of the study, without written authorization from the Sponsor.

Investigator name, institution, address, and telephone number must be printed or typed.

Name:_____

Institution:_____

Address:_____

City, State:_____

Telephone:_____

Signature:_____Date_____

Protocol Summary

Name of Sponsor:	Proteon Therapeutics, Inc.
Study Number and Title:	PRT-201-320: Multicenter, Double-Blind, Placebo-Controlled Study of Vonapanitase (PRT-201) Administered Immediately after Radiocephalic Arteriovenous Fistula Creation in Patients with Chronic Kidney Disease
Clinical Phase:	Phase 3
Investigators and Study Centers:	The study will be conducted at approximately 40 sites.
Number of Patients:	Six hundred (600) patients with chronic kidney disease (CKD) will be treated.
Objective:	To assess the efficacy and safety of vonapanitase administered immediately after radiocephalic arteriovenous fistula (AVF) creation.
Endpoints:	The co-primary efficacy endpoints are secondary patency and AVF use for hemodialysis. Secondary patency is defined as the time from AVF creation until AVF abandonment. AVF use for hemodialysis is defined as the ability of the study AVF to be successfully cannulated and used for hemodialysis for a minimum of 90 days or at least 30 days prior to a patient's last visit, if hemodialysis had not been initiated at least 90 days prior to the last visit. Additional efficacy endpoints are unassisted AVF use for hemodialysis, primary unassisted patency, AVF maturation by ultrasound criteria, unassisted AVF maturation by ultrasound criteria, the rate of procedures performed to the AVF, and the rate of procedures to restore or maintain AVF patency. Safety endpoints are incidence of adverse events (AEs) that include clinically significant adverse changes in physical examination, duplex Doppler ultrasound, clinical laboratory evaluations, and immunogenicity testing results.
Methodology:	This is a randomized, double-blind comparison of vonapanitase versus placebo. Eligible patients are either receiving hemodialysis or expecting to initiate hemodialysis and require the creation of a radiocephalic AVF. Patients are randomized in a 2:1 ratio to either vonapanitase 0.03 mg or placebo. Patients are stratified based on hemodialysis status at the time of randomization. The study consists of a 4-week screening period, a 1-day treatment

	period, and up to 12 months of follow-up. Patients whose study AVF has not been abandoned at Month 12 will be enrolled into a registry and will remain in the registry for 2 years, or until the AVF has been abandoned, whichever comes first. Screening: At the beginning of the 4-week screening period patients will provide written consent and be assessed for eligibility. The assessments include: evaluation of inclusion/exclusion criteria, review of medical history, physical examination, and clinical laboratory evaluations including serum pregnancy testing in women of childbearing potential. Results from the screening visit and evaluations conducted as part of routine standard of care are used to determine study eligibility and are completed as close to the time of AVF creation as possible, but no longer than 28 days prior to the scheduled surgery. Treatment: On the day of surgery, the surgeon connects the end of a transected cephalic vein to the side of a radial artery in the arm, exposing approximately 3 cm of the outflow vein. The surgery to create the AVF will proceed according to the standard practice of the institution and surgeon. Immediately after creation of the radiocephalic AVF, the surgeon treats the exposed inflow artery, anastomosis, and outflow vein with the study drug for 10 minutes by administering a series of drops. Evaluation of the AVF is conducted prior to the patient leaving the recovery area. Follow-up: Patients return at Weeks 2 and 4, and Months 3, 6, 9, and 12 post surgery for clinical safety assessments and evaluation of the AVF and upper extremity. A duplex Doppler ultrasound is performed at Week 4 and Month 3. The Proteon Medical Monitor provides continuing review of safety data in a blinded manner throughout the trial. In addition, a Data Monitoring Committee (DMC), independent of Proteon and operating under a pre-specified charter, reviews accumulated safety data at an appropriate interval.
Main Criteria for Inclusion/ Exclusion:	**<u>Inclusion</u>**: 1. Age of at least 18 years. 2. Life expectancy of at least 6 months. 3. Diagnosis of CKD. 4. Planned creation of a new radiocephalic AVF (revision of an existing AVF is not eligible). 5. Ability to understand and comply with the requirements of the entire study and to communicate with the study team. 6. Written informed consent using a document that has been

	approved by the Institutional Review Board (IRB) or Independent Ethics Committee (IEC). 7. If female and of childbearing potential (premenopausal and not surgically sterile) must have a negative serum pregnancy test at the screening visit and be willing to use contraception from the time of the screening visit to 2 weeks following study drug administration. Acceptable methods of birth control include abstinence, barrier methods, hormones, or intra-uterine device. **Exclusion**: 1. Malignancy or treatment for malignancy within the previous 12 months with the exception of the following cancers if they have been resected: localized basal cell or squamous cell skin cancer, or any cancer *in situ.* 2. Presence of any significant medical condition that might significantly confound the collection of safety and efficacy data in this study. 3. Previous treatment with vonapanitase (PRT-201). 4. Treatment with any investigational drug within the previous 30 days or investigational antibody therapy within the previous 90 days prior to signing informed consent.
Product, Dose, and Mode of Administration:	Vonapanitase (PRT-201) is a recombinant human chymotrypsin-like elastase family member 1 (CELA1) elastase intended for local application immediately following surgical creation of a radiocephalic AVF. Vonapanitase is supplied as a lyophilized powder in a single use glass vial with a rubber stopper. The placebo is identical in appearance and composition to vonapanitase but lacks the active ingredient. The investigational drug is administered topically by the surgeon to the external surface of surgically exposed blood vessels as a single application.
Randomization:	Randomizations occur utilizing an interactive voice response system (IVRS) or interactive web response system (IWRS). Patients are randomized by site in a 2:1 ratio to either vonapanitase 0.03 mg or placebo, stratified by hemodialysis status at the time of randomization and balance will be maintained by blocking within site.
Duration of Treatment:	Single application administered over 10 minutes.

Statistical Methods:	Demographic data, medical history, and other baseline characteristics will be summarized by treatment received. Statistical comparisons between treatment groups will be performed to assess baseline imbalances. Safety evaluations will be based on AEs, clinically significant adverse changes in the patient's physical examination, duplex Doppler ultrasound, clinical laboratory evaluations, and immunogenicity testing results. The co-primary efficacy endpoints are AVF secondary patency and AVF use for hemodialysis. Secondary patency is defined as the time from AVF creation until AVF abandonment. AVF use for hemodialysis is defined as the ability of the study AVF to be successfully cannulated and used for hemodialysis for a minimum of 90 days or at least 30 days prior to a patient's last visit, if hemodialysis had not been initiated at least 90 days prior to the last visit. Additional efficacy endpoints are unassisted AVF use for hemodialysis, primary unassisted patency, AVF maturation by ultrasound criteria, unassisted AVF maturation by ultrasound criteria, the rate of procedures performed to the AVF, and the rate of procedures to restore or maintain AVF patency. Secondary patency time will be estimated by the 25^{th}, 50^{th} (median), and 75^{th} percentiles calculated by using the Kaplan-Meier life test methods to estimate the survival functions. A log-rank test will be used to test the equality of the survival curves between vonapanitase and placebo. A graph of the survival probability over time will be presented. The number and percentage of patients with AVF use for hemodialysis will be summarized by treatment group. Vonapanitase vs. placebo will be tested using a Chi-square test.

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LIST OF ABBREVIATIONS

AE	Adverse Event
AVF	Arteriovenous Fistula
CKD	Chronic Kidney Disease
CMS	Centers for Medicare and Medicaid Services
CRF	Case Report Form
CRO	Contract Research Organization
DMC	Data Monitoring Committee
EAS	Evaluable Analysis Set
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
FAS	Full Analysis Set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ITT	Intention to Treat
IV	Intravenous
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
KDOQI	Kidney Disease Outcomes Quality Initiative
MedDRA	Medical Dictionary of Regulatory Activities
mg	Milligrams
mL	Milliliters
mM	Millimolar
QA	Quality Assurance
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOP	Standard Operating Procedure
TMF	Trial Master File
USRDS	United States Renal Data System

1. BACKGROUND AND RATIONALE

An arteriovenous fistula (AVF), in particular a radiocephalic AVF, is the most desirable form of vascular access for hemodialysis. [1, 2] However, approximately 50% of AVFs will lose primary patency within the first year. [3-6] This is due primarily to neointimal hyperplasia, a form of vascular scarring, most commonly at the arteriovenous anastomosis and adjacent outflow vein, that leads to progressive lumen stenosis and manifests as diminished AVF blood flow, venous hypertension, and thrombosis. [7] Patency loss is addressed via interventional procedures such as thrombectomy and balloon angioplasty, and surgical revision. [8] Interventions to restore or maintain patency are characterized by poor post-intervention patency. [9] Approximately 50% of the AVFs require re-intervention within 1 year possibly due to vessel injury caused by the intervention. [10-12]

An AVF is abandoned when it can no longer be used for hemodialysis as it may be unable to provide adequate blood flow and/or it is deemed unsafe for the patient, and the associated problem cannot be corrected by an intervention, including medical, surgical, or radiological intervention, or rest. Abandonment is synonymous with secondary patency loss. [9] Approximately 25% of AVFs will lose secondary patency within the first year. [3, 6] Radiocephalic AVFs are even more likely to lose primary and secondary patency within the first year. [13]

Patency loss is a significant risk factor for non-use of the AVF for hemodialysis. Approximately 50% of all new AVFs will never become usable for hemodialysis. [5, 14] In patients on hemodialysis, this requires hemodialysis to occur through a hemodialysis catheter until another permanent hemodialysis access site can be established.

A local treatment that safely prolongs patency of a radiocephalic AVF would be welcomed by patients and health care providers. Successful treatment could increase the success of AVF surgery, increase the chance that patients would dialyze with an AVF, and reduce the number of procedures to the AVF.

1.1 DESCRIPTION OF INVESTIGATIONAL DRUG

Vonapanitase (VOE-nah-pan-uh-tayse) is the generic name (United States Annotated Name/International Nonproprietary Name) for the investigational drug under development. It has previously been referred to in other documentation by its company code name, PRT-201. The investigational drug consists of lyophilized vonapanitase or placebo. Each vial of vonapanitase contains 0.036 mg of protein. Reconstitution with 3 mL sterile water yields 0.012 mg/mL vonapanitase solution containing 10 mM sodium phosphate, 55 mM NaCl, 3% mannitol, 1% trehalose, and 0.01% polysorbate 80. The placebo is identical in appearance to vonapanitase but lacks the active ingredient.

At the time of dosing 2.5 mL (0.03 mg) is withdrawn and topically administered.

1.2 STUDY RATIONALE

Vonapanitase is a locally acting recombinant human elastase that in the appropriate dose and setting can enlarge blood vessels, increase blood flow, or inhibit neointimal hyperplasia. In an AVF Phase 2 study, patients undergoing creation of a radiocephalic AVF and treated with vonapanitase 0.03 mg experienced prolonged AVF primary unassisted patency (time from access creation to a first patency loss event), fewer procedures to restore or maintain patency, prolonged secondary patency, and increased proportion with AVF maturation (by ultrasound criteria) and use for hemodialysis compared with placebo treated patients. [13, 15] In a recently completed Phase 3 study (PRT-201-310) preliminary results showed patients undergoing creation of a radiocephalic AVF and treated with vonapanitase 0.03 mg experienced prolonged secondary patency and an increased proportion of patients using their fistula for hemodialysis. The radiocephalic AVF is the form of access recommended by the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (KDOQI) Guidelines [2] and preferred by clinicians. No dose-related increases in adverse events (AEs) were observed in the study. Based on the results of prior clinical studies, this phase 3 study will examine the effect of vonapanitase 0.03 mg on radiocephalic AVF secondary patency and AVF use for hemodialysis (co-primary efficacy endpoints), and other additional efficacy endpoints (unassisted AVF use for hemodialysis, primary unassisted patency, AVF maturation by ultrasound criteria, unassisted AVF maturation by ultrasound criteria, the rate of procedures performed to the AVF, and the rate of procedures to restore or maintain AVF patency).

2. STUDY OBJECTIVE

To assess the efficacy and safety of vonapanitase administered immediately after radiocephalic AVF creation.

3. INVESTIGATIONAL PLAN

Vonapanitase is a recombinant human elastase intended for local application immediately following surgery to create a radiocephalic AVF.

3.1 METHODOLOGY

This is a phase 3, randomized, double-blind comparison of vonapanitase versus placebo. Eligible patients are stratified by hemodialysis status and randomized in a 2:1 ratio to either vonapanitase 0.03 mg or placebo. Investigators at approximately 40 centers will enroll 600 patients with chronic kidney disease (CKD) who require the creation of a radial artery to cephalic vein (radiocephalic) AVF.

The study consists of a 4-week screening period, a 1-day treatment period, and up to 12 months of follow-up. Results from the screening visit and evaluations conducted as part of routine standard of care are used to determine patient eligibility and are completed as close to the time of

AVF creation as possible, but no longer than 28 days prior to the scheduled surgery (see Section 5.1). Significant medical events since Screening will be reviewed and recorded as part of the patient's medical history. Patient randomization will occur at the time of surgery utilizing an interactive voice response system (IVRS) or interactive web response system (IWRS).

In most cases, the AVF surgical procedure is conducted in an operating room as an outpatient procedure. The surgeon connects the end of a transected cephalic vein to the side of a radial artery in the arm, exposing approximately 3 cm of the outflow vein. The AVF surgery proceeds according to the standard practice of the institution and surgeon. Immediately after creation of the AVF, the surgeon treats the exposed inflow artery, anastomosis, and outflow vein topically with the study drug for 10 minutes by administering a series of drops. The intent is to keep the vessels wet for 10 minutes. After dosing, the surgeon irrigates the surgical site with generous amounts of saline before and after closing the surgical incision. Evaluation of the AVF site is conducted prior to the patient leaving the recovery area.

Additional clinical safety assessments and evaluation of the AVF occur at Weeks 2 and 4, and Months 3, 6, 9, and 12 post study drug administration. All AEs are collected until Week 4; AEs associated with the AVF extremity and all AEs that result in death are collected until Month 12.

Following the Month 12 visit, patients whose study AVF has not been abandoned will be enrolled into a registry in which clinical events and outcomes pertaining to the AVF treated with the study drug will be collected. Study staff will contact the patient, their physician(s), their dialysis unit or other sources as appropriate every 3 months to collect information about the initiation of hemodialysis and procedures performed on the AVF treated with the study drug. The patient will remain in the registry for 2 years, or until the AVF has been abandoned, whichever comes first.

An ultrasound will be performed at the Week 4 and Month 3 visits according to a standard duplex Doppler ultrasound protocol. A blinded central reader will assess outflow vein luminal diameters, blood flow volume, and hemodynamically significant lumen stenosis. Results from the central reader will not be shared with the clinical site.

The Proteon Medical Monitor will provide continuing review of safety data, in a blinded manner, throughout the trial. An independent Data Monitoring Committee (DMC) comprised of a biostatistician, and two medical doctors, at least one of whom is an expert in the field of hemodialysis access, will review accumulated blinded safety data once 150 patients have been treated and have completed the Week 4 visit.

4. STUDY POPULATION

4.1 GENERAL CONSIDERATIONS

Six hundred (600) patients will be treated at approximately 40 centers. Patients are recruited from the nephrology and vascular surgery practices and through the referral network at facilities

treating patients with CKD. Each participating facility is evaluated with respect to its ability to enroll the necessary patients. Strategies for patient recruitment and retention are discussed during routine monitoring visits. Men and women meeting all of the inclusion criteria and none of the exclusion criteria will be allowed to participate.

4.2 INCLUSION CRITERIA

1. Age of at least 18 years.
2. Life expectancy of at least 6 months.
3. Diagnosis of CKD.
4. Planned creation of a new radiocephalic AVF (revision of an existing AVF is not eligible).
5. Ability to understand and comply with the requirements of the entire study and to communicate with the study team.
6. Written informed consent using a document that has been approved by the Institutional Review Board (IRB) or Independent Ethics Committee (IEC).
7. If female and of childbearing potential (premenopausal and not surgically sterile) must have a negative serum pregnancy test at the screening visit (Visit 1) and be willing to use contraception from the time of the screening visit to 2 weeks following study drug administration. Acceptable methods of birth control include abstinence, barrier methods, hormones, or intra-uterine device.

4.3 EXCLUSION CRITERIA

1. Malignancy or treatment for malignancy within the previous 12 months with the exception of the following cancers if they have been resected: localized basal cell or squamous cell skin cancer, or any cancer *in situ.*
2. Presence of any significant medical condition that might significantly confound the collection of safety and efficacy data in this study.
3. Previous treatment with vonapanitase (PRT-201).
4. Treatment with any investigational drug within the previous 30 days or investigational antibody therapy within the previous 90 days prior to signing informed consent.

4.4 CONCURRENT MEDICATIONS

Concomitant medications should be recorded from the date of Screening (Visit 1) through Week 4 (Visit 4).

4.5 EXCLUDED MEDICATIONS

The following medications should not be applied topically in the surgical field or be contained in the lavage fluid during the creation of the AVF. These medications have been shown to inhibit the activity of vonapanitase.

- Procaine
- Bicarbonate solution
- Vancomycin

Intravenous (IV) vancomycin and topical lidocaine in normal saline, but not bicarbonate solution, are acceptable.

In addition, ultrasound acoustic gel has been shown to inhibit the activity of vonapanitase and should not be used in the surgical field. After the surgical incision is closed, ultrasound acoustic gel can be used.

5. STUDY SCHEDULE

The assessments to be performed during the study are outlined below. The day the patient receives study drug (the day of surgery to create the AVF) is considered "Day 1." Refer to Appendix A for the table describing the Schedule of Assessments.

5.1 SCREENING: VISIT 1 (UP TO DAY -28)

All patients sign written informed consent before any protocol-specific screening procedures are conducted. Results from the screening period and evaluations conducted as part of routine standard of care are used to determine study eligibility and are completed as close to the time of AVF creation as possible, but no longer than 28 days prior to the scheduled surgery.

All patients will have the following procedures completed in the screening period once written informed consent has been obtained:

1. Collection of demographic information, hemodialysis vascular access history, and medical history.
2. Collection of concomitant medication information.
3. Physical examination, including height and weight.
4. Collection of blood samples for anti-vonapanitase antibody detection (see Section 6.2.4) and clinical laboratory evaluations including a serum pregnancy test in women of childbearing potential (see Section 6.2.5 and Appendix B for details). Refer to the Laboratory Manual for collection, processing, and shipping information.

5.2 AVF SURGERY: VISIT 2 (DAY 1)

5.2.1 PRE-SURGERY

Any change in clinical condition since Screening (Visit 1) is assessed. Significant medical events since Visit 1 are recorded as part of the patient's medical history.

The patient is randomized at the time of surgery, utilizing an IVRS or IWRS.

5.2.2 SURGICAL PROCEDURES

In most cases, the AVF surgical procedure is conducted in an operating room as an outpatient procedure. The surgeon connects the end of a transected cephalic vein to the side of a radial artery in the arm, exposing approximately 3 cm of the outflow vein, with the intent of creating a fistula that would be cannulated below the elbow. The AVF surgery proceeds according to the standard practice of the institution and surgeon. The surgical parameters that are important to record during the intraoperative phase are described in the case report form (CRF) completion guidelines; source document worksheets are provided by Proteon to help facilitate data collection.

5.2.2.1 Study Drug Administration

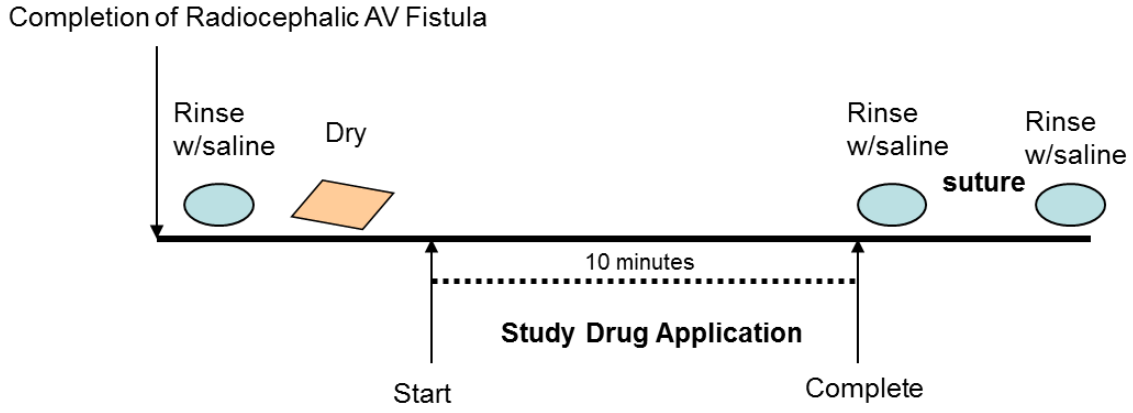
See Section 4.5 (Excluded Medications) for medications that should be avoided during surgery.

Procedures after AVF creation but before closure of incision:

1. The surgical site should be rinsed generously with saline.
2. The surgical site should be dry without ongoing bleeding during study drug administration.
3. Study drug, 2.5 mL of solution, is administered using a sterile syringe (3 mL suggested) fitted with a 22 gauge angiocatheter.
4. The surgeon administers the study drug in a series of drops to the exposed inflow artery (1 drop), anastomosis (1 drop), and the outflow vein (4 drops) every 20 seconds for 10 minutes, for a total of approximately 180 drops. After 5 minutes of dosing the surgeon should check that approximately 1.25 mL of dosing solution has been administered. The number of drops should be adjusted accordingly based on this check (i.e., extra drop(s) every 20 seconds if less than 1.25 mL was used in the first 5 minutes, or fewer drops if more than 1.25 mL was used).
5. The objective of study drug administration is to keep the vessels wet with the solution for the entire 10 minutes of treatment and to deliver the entire dose. Any dosing solution remaining in the syringe should be administered with the final application. If the drug pools around the AVF it does not need to be aspirated unless it is blood tinged since blood inhibits vonapanitase activity.

6. At the end of 10 minutes, the surgeon irrigates the surgical site with saline lavage continuously for 1 minute to remove any study drug.
7. The surgeon closes the incision per usual clinical practice and washes the incision and surrounding skin with saline.

Figure 1: Schematic of Study Drug Administration



5.2.3 POST-OPERATIVE ASSESSMENTS

Evaluation of the newly created radiocephalic AVF, including an assessment of AVF patency, is conducted according to routine surgical practice prior to the patient leaving the recovery area.

5.3 FOLLOW-UP: VISIT 3 /WEEK 2 (DAY 14 ± 3 DAYS)

The purpose of this visit is to perform protocol-specific safety assessments and to assess the short term effects of study drug administration and collect information regarding AVF patency and use for hemodialysis. The patient will have an AVF and upper extremity examination (see Section 6.2.1) and be asked for information about intercurrent medical events and changes in clinical condition since the day of surgery (Visit 2). Events that meet the definition of an AE should be fully documented in the patient's medical record. The following assessments are completed at this visit:

1. AVF and upper extremity examination (See Section 6.2.1).
2. Record procedures performed on the AVF since surgical creation.
3. Record AEs occurring since the last visit. Previously reported AEs that are ongoing are evaluated for status.
4. Record concomitant medications.

5. Collect blood samples for anti-vonapanitase antibody detection (see Section 6.2.4) and clinical laboratory evaluation (see Section 6.2.5 and Appendix B for details). Refer to the Laboratory Manual for collection, processing, and shipping information.

5.4 FOLLOW-UP: VISIT 4 /WEEK 4 (DAY 28 ± 3 DAYS)

The purpose of this visit is to perform protocol-specific safety assessments and collect information regarding AVF patency, maturation, and use for hemodialysis. The patient is asked for information about intercurrent medical events and changes in clinical condition since Week 2 (Visit 3). Events that meet the definition of an AE should be fully documented in the patient's medical record.

The following procedures are completed at this visit:

1. AVF and upper extremity examination (see Section 6.2.1).
2. Physical examination (see Section 6.2.1).
3. Record procedures performed on the AVF since surgical creation and date of successful initial cannulation, if applicable.
4. Record AEs occurring since the last visit. Previously reported AEs that are ongoing are evaluated for status.
5. Record concomitant medications.
6. Collect blood sample for anti-vonapanitase antibody detection (see Section 6.2.4 for details).
7. Duplex Doppler ultrasound performed according to a standard ultrasound protocol.

5.5 FOLLOW-UP: VISIT 5 / MONTH 3 (DAY 90 ± 14 DAYS)

The purpose of this visit is to perform protocol-specific safety assessments and to collect any information regarding AVF patency, maturation, and use for hemodialysis. The patient is asked for information about any intercurrent medical events and changes in clinical condition since their last visit. Events associated with the AVF extremity that meet the definition of an AE should be fully documented in the patient's medical record.

The following procedures are completed at this visit:

1. AVF and upper extremity examination (see section 6.2.1).
2. Record procedures performed on the AVF since surgical creation and date of successful initial cannulation, if applicable.
3. Record AEs associated with the AVF extremity occurring since the last visit. Previously reported AEs that are ongoing are evaluated for status.

4. Duplex Doppler ultrasound performed according to a standard ultrasound protocol.

5.6 FOLLOW-UP: VISIT 6 / MONTH 6 (DAY 180 ± 14 DAYS), VISIT 7 / MONTH 9 (DAY 270 ± 14 DAYS), AND VISIT 8 / MONTH 12 (DAY 360 ± 14 DAYS)

The purpose of these visits is to perform protocol-specific safety assessments and to collect any information regarding AVF patency and use for hemodialysis. The patient is asked for information about intercurrent medical events and changes in clinical condition that have occurred since their last visit. Events associated with the AVF extremity that meet the definition of an AE should be fully documented in the patient's medical record.

The following procedures are completed at this visit:

1. AVF and upper extremity examination (see Section 6.2.1).
2. Record procedures performed on the AVF since surgical creation and date of successful initial cannulation, if applicable.
3. Record AEs associated with the AVF extremity occurring since the last visit. Previously reported AEs that are ongoing are evaluated for status.
4. If a patient tests positive for anti-vonapanitase antibodies at the Week 4 visit (or at Week 2 without a Week 4 result), an additional blood sample is drawn at the Month 6 visit (See section 6.2.4 and the Laboratory Manual for collection, processing and shipping information).
5. If a patient tests positive for anti-vonapanitase antibodies at the Month 6 visit (or at Week 4 without a Month 6 test result), an additional blood sample is drawn at the Month 12 visit (See section 6.2.4 and the Laboratory Manual for collection, processing and shipping information).

5.7 HANDLING OF WITHDRAWALS

It is important to collect safety data on any patient who withdraws from the study before their last scheduled visit. A withdrawal is defined as a patient leaving the study with an AVF that has not been abandoned.

If voluntary withdrawal occurs, the patient should be asked to return for their next scheduled evaluation (e.g., next study visit) in order to complete an end-of-study evaluation, and be given appropriate care until the symptoms of any AE resolves or the patient's condition becomes stable. At minimum, the patient should be questioned over the telephone about any changes in clinical condition since their last visit, the status of any ongoing AEs, information regarding the initiation of hemodialysis, and procedures performed on the AVF.

Discontinuation because of an AE is of particular interest and every effort should be made to follow the patient until the event resolves, the patient's condition stabilizes or is fully

characterized, the event returns to baseline value (if a baseline value is available), or it is shown that the event is not attributable to the study drug or study conduct. Appropriate supportive and/or definitive therapy is administered as required.

5.8 HANDLING OF AVF ABANDONMENT

If a patient's study AVF is abandoned, the following visit schedule should be followed:

- If the study fistula is abandoned prior to Week 4 (Visit 4), the patient is expected to return for all office visits through Week 4 (Visit 4). If the fistula is thrombosed or ligated and abandoned prior to Week 4, an ultrasound is not required at the Week 4 visit. If the fistula is abandoned for another reason then an ultrasound is required at the Week 4 visit. The patient's participation will be considered complete at the Week 4 visit.
- If the study fistula is abandoned after Week 4 (Visit 4), the patient is expected to return for their next scheduled visit. If the decision to abandon the fistula is made at an office visit (i.e., patient comes in for the Month 3 visit and the investigator decides the fistula is not salvageable) then this will serve as their final office visit and the end-of-study evaluations can be completed. The patient's participation will be considered complete.

5.9 KIDNEY TRANSPLANTATION

If a patient receives a kidney transplant before Week 4 (Visit 4), the patient is expected to return for all office visits through Week 4 (Visit 4). If a patient receives a kidney transplant after Week 4 (Visit 4), the patient is expected to return for their next scheduled visit. All ultrasounds should be performed as scheduled. Patients who receive a kidney transplant will not be followed in a registry.

5.10 LONG-TERM OUTCOMES AND PHARMACOECONOMIC ANALYSES

Patients signing informed consent will have agreed to the collection of long-term clinical outcome information and the sharing of identifying information (Social Security Number or Health Insurance Claim/Beneficiary Identification Code) with the Centers for Medicare and Medicaid Services (CMS) and/or the United States Renal Data System (USRDS), unless otherwise stated or agreed upon in the ICF. Each patient's study information will be linked with information from a CMS and/or USRDS database. The linked information will be de-identified and used to analyze long-term outcomes not directly captured in the study (e.g., hospitalizations, and procedures after study completion) and to conduct pharmacoeconomic analyses of the costs associated with vascular access management, including access creations, patency loss events, and abandonments.

In addition, patients will have agreed to the long term collection of data pertaining to the AVF treated with the study drug in a registry for 2 years. Following the Month 12 visit, patients whose study AVF has not been abandoned will be enrolled into a registry in which clinical events and

outcomes pertaining to the AVF treated with the study drug will be collected. Clinical site staff will contact the patient, the hemodialysis unit, or a relevant physician every 3 months (± 14 days) to collect information on the date of successful initial cannulation of the study AVF, current use of the study AVF for hemodialysis, reasons for non-use, and procedures performed on the study AVF (e.g., thrombectomy, angioplasty). Information will be collected for 2 years or until the AVF is abandoned, whichever comes first.

6. PROCEDURES AND EVALUATIONS

6.1 ASSESSMENT OF EFFICACY

The co-primary efficacy endpoints are AVF secondary patency and AVF use for hemodialysis. Secondary patency is defined as the time from AVF creation until AVF abandonment. AVF use for hemodialysis is defined as the ability of the study AVF to be successfully cannulated and used for hemodialysis for a minimum of 90 days or at least 30 days prior to a patient's last visit, if hemodialysis had not been initiated at least 90 days prior to the last visit. Additional efficacy endpoints are unassisted AVF use for hemodialysis, primary unassisted patency, AVF maturation by ultrasound criteria, unassisted AVF maturation by ultrasound criteria, the rate of procedures performed to the AVF, and the rate of procedures to restore or maintain AVF patency.

6.1.1 AVF DISPOSITION

Disposition of the study AVF is recorded following surgery and at Weeks 2 and 4, and at Months 3, 6, 9, and 12. AVF disposition includes whether or not the study AVF is patent, the patient is on hemodialysis, central venous catheter use, the study AVF is being used for hemodialysis or reason not being used, the date of first successful cannulation, and most recent Kt/V or URR, as available.

Data on AEs of thrombosis, and procedures performed on the study AVF (e.g., angiography, thrombectomy, angioplasty) including the clinical reason the patient was referred for a procedure are collected at all follow-up visits.

Use of the AVF for hemodialysis is defined as the ability of the study AVF to be successfully cannulated and used for hemodialysis with two needles for a minimum of 3 months. If a patient does not initiate hemodialysis at least 3 months before their last office visit then the AVF must have been in use for at least 1 month and still be in use at their last office visit to meet the definition of usable.

6.1.2 ABANDONMENT

Abandonment of the study AVF is evaluated at Weeks 2 and 4 and at Months 3, 6, 9, and 12. Abandonment is defined as a fistula that can no longer be used for hemodialysis as it may be unable to provide adequate blood flow and/or it is deemed unsafe for the patient, and the

associated problem cannot be corrected by an intervention, including medical, surgical, or radiological intervention, or rest. [9] If a patient's study AVF requires a surgical revision whereby the anastomosis treated with the study drug is taken down and a new anastomosis is created, the fistula should be considered abandoned for the purposes of the study. The follow-up visit schedule outlined in Section 5.8 should be followed.

6.1.3 ULTRASOUND EVALUATION

AVF maturation is evaluated by ultrasound according to a standard ultrasound protocol at Week 4 (Visit 4) and Month 3 (Visit 5). All ultrasound examinations will be sent to a core imaging lab for review by an experienced ultrasound expert (VasCore, Massachusetts General Hospital, Boston, MA USA). The core imaging laboratory will remain blinded to the study treatment during ultrasound analysis.

6.2 ASSESSMENT OF SAFETY

Safety evaluations are based on clinical examination of the AVF and upper extremity, AEs, physical examination, duplex Doppler ultrasound, clinical laboratory evaluation, and immunogenicity testing results. Safety measurements are described below.

6.2.1 AVF AND UPPER EXTREMITY EXAMINATION

AVF patency is evaluated by clinical examination immediately following surgery and at Weeks 2 and 4, and Months 3, 6, 9, and 12. The examination of the AVF is performed by a qualified member of the study team. The examination of the AVF includes an evaluation of the thrill and pulse at the anastomotic site, the bruit 10 cm downstream from the anastomotic site, and outflow vein distension with the arm below and above the level of the heart. Clinically significant abnormal adverse physical findings of the AVF are noted as AEs.

Particular attention is given to evidence of vascular steal syndrome, excessive swelling, aneurysm, pseudoaneurysm, hematoma, seroma, infection, and abnormal wound healing. The following definitions are used for assessing patients enrolled into this protocol:

<u>Definitions and Classification:</u>

1. Vascular steal syndrome: cold and painful extremity distal to the AVF.
2. Aneurysm: a progressive pathological expansion of the AVF vein due to weakness, but not disruption, of the vein wall.
3. Pseudoaneurysm: an out-pouching of the AVF vein involving a defect in all three layers of the vein wall with bleeding that is contained by a blood clot or surrounding structures.
4. Hematoma: a localized mass of extravasated blood.
5. Seroma: a localized accumulation of serum.

6. Infection: infections will be classified as involving the skin (cellulitis), incision, or deep tissue. Deep tissue infections will include, but not be limited to, infected seromas, infected hematomas, and endovascular infections.
7. Abnormal wound healing: such as:
    - Inflammation (erythema, warmth, induration, or tenderness).
    - Excessive scar tissue (i.e., keloid formation).
    - Lack of direct union between opposing edges of the incision.

6.2.2 ADVERSE EVENTS

Monitoring of treatment emergent AEs is conducted throughout the study. All AEs, regardless of causality, are collected through Week 4 (Visit 4). After Week 4 and for up to Month 12 (Visit 8), only AEs associated with the AVF extremity and AEs resulting in death are collected, regardless of causality.

All AEs that are not resolved by Month 12 (Visit 8) or not resolved upon discontinuation of the patient's participation in the study are to be followed until any of the following occurs:

- The event resolves.
- The patient's condition stabilizes or is fully characterized.
- The event returns to baseline value (if a baseline value is available), or it is determined that the event is not attributable to the study medication or study conduct.

Definitions, documentation, and reporting of AEs are described in detail in Section 8.

6.2.3 MEDICAL HISTORY AND PHYSICAL EXAMINATION

A medical history is obtained through review of the patient's medical records and personal interview in order to assess the patient's eligibility.

A physical examination is performed at Screening (Visit 1) and Week 4 (Visit 4); clinically significant adverse changes from baseline are recorded as AEs.

6.2.4 SPECIAL ASSAYS OR PROCEDURES

A blood sample of 5 mL is drawn at Screening (Visit 1), Week 2 (Visit 3) and Week 4 (Visit 4) for anti-vonapanitase antibody detection. These samples will be processed according to the instructions provided in the Central Laboratory Manual.

Patients who demonstrate anti-vonapanitase antibodies at Week 4 (or at Week 2 without a Week 4 result) are asked to provide an additional blood sample for testing at Month 6. Patients who continue to test positive at Month 6 (or at Week 4 without a Month 6 result), are asked to provide an additional blood sample at Month 12.

Provisions for the storage and future use of the samples will be described in the informed consent form (ICF). No genetic testing is performed with this archived blood sample.

6.2.5 CLINICAL LABORATORY EVALUATION

Blood samples do not have to be obtained following fasting. Blood samples will be drawn at Screening (Visit 1), and Week 2 (Visit 3); labeled, processed, and shipped overnight to the central laboratory for testing. Instructions for the collection, processing, and shipping of samples will be provided in the Laboratory Manual.

Blood for serum pregnancy will be drawn in females of childbearing potential at Screening. Refer to Appendix A for the Schedule of Assessments and Appendix B for information regarding the specific laboratory tests.

Clinical laboratory values that are outside the normal limits are considered abnormal. Abnormal clinical laboratory values will be noted as clinically significant or non-clinically significant by the Investigator. Non-clinically significant is defined as those abnormalities unlikely to indicate a significant medical condition or are consistent with the patient's underlying medical condition and do not warrant any further investigation or treatment. All new clinically significant abnormalities not present at baseline will be reported as AEs.

6.2.6 DUPLEX DOPPLER ULTRASOUND

Duplex Doppler ultrasound examinations at Week 4 (Visit 4) and Month 3 (Visit 5) will be sent to a blinded central reader. Instructions for the acquisition and transmission of ultrasound examinations will be provided in the Ultrasound Guidelines.

6.2.7 UNSCHEDULED ASSESSMENTS

The Investigator may, at his/her discretion, arrange for a patient to have an unscheduled assessment(s). This may include repeated screening assessments if a surgery date is rescheduled out of the visit window, assessments to further evaluate a patient experiencing an AE considered by the Investigator to be possibly related to the use of study drug or collect information about AVF patency and use for hemodialysis. The CRF pages specific for unscheduled assessments must be completed at the time of the unscheduled visit.

7. INVESTIGATIONAL DRUG

7.1 IDENTITY OF INVESTIGATIONAL DRUG

Vonapanitase is a recombinant human elastase for clinical use. It is supplied by Proteon Therapeutics. For further detail, refer to the PRT-201 (vonapanitase) Investigator's Brochure.

7.2 PLACEBO

The placebo is identical in appearance and composition to vonapanitase but lacks the active ingredient. It is supplied by Proteon.

7.3 FORMULATION, PACKAGING, AND LABELING

Vonapanitase is supplied as a lyophilized powder in a single use 10 mL glass vial with a rubber stopper. Each vial contains 0.036 mg of protein. Proteon will also supply 5 mL vials of sterile water. Reconstitution with 3 mL sterile water yields a 0.012 mg/mL vonapanitase solution containing 10 mM sodium phosphate, 55 mM NaCl, 3% mannitol, 1% trehalose, and 0.01% polysorbate 80. Two and a half milliliters (2.5 mL) is used in the application. Further detail is provided in the Pharmacy Manual.

7.4 PATIENT RANDOMIZATION AND BLINDING

Both randomization and blinding techniques are used in this study to minimize bias. A computer generated randomization schema is centrally available via an IVRS or IWRS. The IVRS/IWRS is accessed by individuals who have been issued a username and password. Patient randomization is performed at the time of surgery. Patients will be randomized by site and stratified by hemodialysis status at the time of randomization and balance will be maintained by blocking within site.

7.5 UNBLINDING

In the case of a medical emergency where, in the Investigator's judgment, the patient's safety may be compromised without immediate knowledge of the exact treatment received, the Investigator can contact the Medical Monitor at Proteon Therapeutics to unblind a single patient treatment assignment.

Medical Monitor: Marco Wong, M.D, PhD
Telephone No.: 1-816-536-3770
Proteon Therapeutics, Inc.
Email: MWong@ProteonTx.com

7.6 PRODUCT SHIPPING, STORAGE, AND STABILITY

The Investigator acknowledges that the study drug supplies are investigational and as such must be handled strictly in accordance with the protocol and container label. The investigational drug must be stored frozen at -15°C to -35°C in a secure area with limited access.

The investigational drug is distributed from a drug repository and shipped in specialized insulated shippers that do not require dry ice or in insulated shippers packed with dry ice to maintain the shipper's internal temperature of -15°C to -35°C. Each shipment will include a TempTale to monitor the temperature throughout the shipping period, and a shipment

verification form that should be completed, signed and dated, and returned to the drug distribution center or designee. This form will capture discrepancies in the number of vials received, damage to the packaging or any indication of tampering, and the TempTale information. The original form should be maintained at the clinical center with the other drug inventory and distribution records.

The initial shipment of investigational drug will be sent on or about the date of the site initiation visit, or equivalent, and will be coordinated with the Investigational Pharmacy, where applicable. Plans for how the investigational drug will be distributed including participation of the drug repository and distribution center, frequency of product distribution, amount of product shipped, and plans for return of used and unused product will be provided in the Pharmacy Manual.

The expiry date for study drug is included on the product labeling.

7.7 DOSAGE, PREPARATION, AND ADMINISTRATION OF INVESTIGATIONAL DRUG

Investigational drug will be administered only to eligible patients under the supervision of the Investigator or identified sub-Investigator(s). Eligible patients will be randomized in a 2:1 ratio to either vonapanitase 0.03 mg or placebo. The investigational drug will be reconstituted with 3 mL of sterile water and gently swirled to ensure the investigational drug is completely dissolved. The study drug solution should be clear and colorless. Detailed investigational drug preparation instructions will be provided in the Pharmacy Manual.

Papaverine is often used during the surgical creation of an AVF. Care should be taken to ensure that prior to study drug administration the study drug solution does not come into contact with papaverine or any supplies containing or exposed to papaverine. Exposing the study drug solution to papaverine before study drug administration may cause the study drug solution to become cloudy. If the study drug solution ever appears cloudy, it should not be used for dosing. Discard any cloudy study drug solution and obtain a replacement. It is acceptable for the study drug solution to come into contact with papaverine in the surgical site.

The investigational drug will be administered in a volume of 2.5 mL topically using a sterile syringe fitted with a 22 gauge angiocatheter. The surgeon will administer a series of drops of study drug to the external surface of the exposed inflow artery (1 drop), anastomosis (1 drop) and the outflow vein (4 drops) every 20 seconds for 10 minutes, for a total of approximately 180 drops. The objective is to keep the vessels wet with the solution for the 10 minutes of treatment. After 5 minutes of dosing the surgeon should check that approximately 1.25 mL of dosing solution has been administered. The number of drops should be adjusted accordingly based on this check (i.e., extra drop(s) every 20 seconds if less than 1.25 mL was used in the first 5 minutes, or fewer drops if more than 1.25 mL was used). The entire dose should be delivered. Any dosing solution remaining in the syringe should be administered with the final application. If the drug pools around the AVF it does not need to be aspirated unless it is blood tinged. At the

end of 10 minutes, the surgeon will irrigate the incision site with saline lavage continuously for 1 minute to remove the investigational drug. The surgeon will close the incision per usual clinical practice and wash the incision and surrounding skin with saline.

All persons handling study drug should avoid contact with the investigational drug solution. Any accidental exposure to the skin, eyes, and mucous membranes should be washed with copious amounts of water or saline for at least 1 minute.

7.8 DRUG ACCOUNTABILITY/RETENTION

Accountability for the study drug at the trial site is the responsibility of the Investigator. The Investigator will ensure that the study drug is used only in accordance with this protocol. Where allowed, the Investigator may choose to assign some of the drug accountability responsibilities to a pharmacist or other appropriate individual. Accountability records will include dates, quantities, patient identifiers, and the initials of the individual documenting the record. The institution is free to use its drug accountability system, unless otherwise specified by Proteon. These records will adequately document that the patients were provided the doses specified in the protocol and should reconcile all study drug received from Proteon. Proteon or its Contract Research Organization (CRO) designee will review drug accountability records at the site on an ongoing basis during on-site monitoring visits.

7.9 DRUG RETURNS AND DESTRUCTION

Used and unused vials of study drug will be stored until the study monitor conducts an on-site visit to perform a physical inventory and reconciliation of the drug accountability records. Proteon may allow study drug to be destroyed on-site if the site has a documented method of destruction. Please refer to the Pharmacy Manual for study specific details regarding vial destruction and return.

8. ADVERSE EVENTS

8.1 DEFINITION OF ADVERSE EVENT

An **adverse event** (AE) means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational drug, whether or not considered related to the investigational drug. This includes any newly occurring event or a previous condition that has increased in severity or frequency since the administration of the investigational drug.

8.2 RECORDING OF ADVERSE EVENTS AND OBSERVATION PERIOD

The Investigator should question the patient about AEs and intercurrent illnesses since his/her last visit and record the information in the patient's medical record. The questions should be generalized such as, "How have you been feeling since your last visit?" The presence or absence of specific AEs should not be solicited from patients. The onset and end dates, severity, and relationship to study drug must be recorded for each AE. When possible, signs and symptoms indicating a common underlying pathology should be noted as one comprehensive event or diagnosis.

AEs will be recorded between administration of the study drug and Week 4 (Visit 4). After Week 4 and for up to Month 12 (Visit 8), only AEs associated with the AVF extremity and AEs resulting in death will be collected. Medical events that occur between the signing of the informed consent and study drug administration will be considered part of the patient's medical history and recorded accordingly. Patients who experience AEs will be monitored with relevant clinical assessments and laboratory tests, as determined by the Investigator. Any action taken and follow-up results must be recorded in the patient's medical record. Follow-up laboratory results should be filed with the patient's medical records.

All AEs that are not resolved by the end of the study, or that were not resolved upon discontinuation of the patient's participation in the study, are to be followed until one of the following occurs: the event resolves, the patient's condition stabilizes or is fully characterized, or the event returns to baseline value (if a baseline value is available).

8.3 SERIOUS ADVERSE EVENT

8.3.1 REFERENCE SAFETY INFORMATION

The current version of the vonapanitase Investigator's Brochure should be referenced for all safety information pertaining to the study. Proteon will provide a current version of the Investigator's Brochure to all study Investigators.

8.3.2 SERIOUS ADVERSE EVENT DEFINITION

A **serious adverse event** (SAE) means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related, that results in one or more of the following outcomes:

1. Death.
2. A life-threatening AE. Life-threatening means that the patient was at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that, had it occurred in a more severe form, might have caused death.

3. In-patient hospitalization or prolongation of existing hospitalization. Hospitalization admissions and/or surgical operations scheduled to occur during the study period, but planned prior to study entry are not considered AEs if the illness or disease existed before the patient was enrolled in the study, provided that it did not deteriorate in an unexpected manner during the study (e.g., surgery performed earlier than planned).
4. A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
5. A congenital anomaly/birth defect.
6. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in in-patient hospitalization, or the development of drug dependency or drug abuse.

8.3.3 REPORTING PROCEDURES

All initial and follow-up SAE reports must be reported on the SAE form and a facsimile sent to the appropriate Safety Desk within 24 hours of the site being made aware of it. See contact information below:

Premier Safety Desk
SAE Fax No.: 1-215-972-8765
Email: globalpv-us@premier-research.com

Medical Monitor: Marco Wong, M.D, PhD
Telephone No.: 1-816-536-3770
Proteon Therapeutics, Inc.
Email: MWong@ProteonTx.com

A report of an SAE by telephone must always be confirmed by a written, more detailed report within 24 hours of the site being made aware of the event. The Investigator should provide the following written documentation at the time of notification, if available:

- SAE Reporting Form
- Concomitant medication pages
- Relevant diagnostic reports
- Relevant laboratory reports
- Admission notes

- Hospital discharge summary

Proteon will assume responsibility for appropriate reporting of AEs to regulatory authorities. Proteon will also report all SAEs that are unexpected and associated with the use of the study drug to investigational sites.

Follow-up data concerning SAEs (e.g., diagnostic test reports, physician's summaries, etc.) must be submitted to Proteon or designee as they become available, preferably electronically. It is the responsibility of the Investigator to promptly notify the IRB or IEC of all SAEs, as well as any unanticipated problems that involve significant risk to patients, as required by their IRB/IEC. A copy of the IRB/IEC notification should be placed in the site's regulatory binder.

The Principal Investigator will review each SAE and further evaluate the relationship of the AE to study drug and to the patient's underlying disease. Based on the Investigator's assessment of the AE, a decision will be made concerning the need for further action. The primary consideration governing further action is whether new findings affect the safety of other patients participating in the clinical study. If the discovery of a new AE related to the study drug raises concern over the safety of its continued administration to patients, Proteon will take immediate steps to notify the Food and Drug Administration (FDA) and all Investigators participating in vonapanitase clinical studies.

8.3.4 SERIOUS ADVERSE EVENT COLLECTION TIMEFRAME

All SAEs, regardless of relationship to the investigational product, will be reported between study drug administration and Week 4 (Visit 4). After Week 4 only AEs and SAEs associated with the AVF extremity, and those resulting in death will be collected.

8.3.5 PREGNANCY

Pregnancy by definition is not considered to be a SAE unless the criteria in Section 8.3 are met. However, pregnancy in patients that have received the study drug must be followed to assess congenital anomalies. For purposes of consistency, Proteon or its designated CRO representatives will record pregnancies in the SAE System; however, the event will then be downgraded if the outcome does not meet the SAE criteria. Pregnancy Questionnaires and Pregnancy Outcome forms are provided to each clinical study site in the Study Manual and should be forwarded to Proteon or designee.

8.4 SEVERITY

For both AEs and SAEs, the Investigator must determine the severity of the event using the following definitions:

Mild: The event does not interfere in a significant manner with the patient's normal functioning level. It may be an annoyance but does not cause any limitation in usual activity.

Moderate: The event produces some impairment of functioning but is not hazardous to health. It is uncomfortable or an embarrassment and may cause some limitation in usual activity.

Severe: The event produces significant impairment or incapacitation and is a definite hazard to the patient's health.

Life-threatening: The event places the patient, in the view of the Investigator, at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that had it occurred in a more severe form, might have caused death.

The term "severe" is used to describe the intensity (severity) of a specific event (as in mild, moderate, severe, or life-threatening myocardial infarction). Even though the event itself may be of relatively minor medical significance (such as a severe headache), this is not the same as "serious," which is based on patient/event outcome or action criteria as described above and is usually associated with events that pose a threat to a patient's life or functioning. A severe AE is not necessarily serious. For example, persistent nausea of several hours duration may be considered severe nausea but not meet the definition of a SAE. On the other hand, a stroke resulting in only a minor degree of persistent disability may be considered mild, but would be defined as a SAE based on the above noted criteria. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

8.5 CAUSALITY

Association of AEs and SAEs to the study drug will be made using the following definitions:

Unrelated: An AE that is not related to the use of the study drug.

Unlikely: An AE that is unlikely to be due to the use of the study drug. An alternative explanation, e.g., concomitant drug(s), concomitant disease(s), is plausible. A relationship to the study drug is improbable but not impossible.

Possible: An AE that conceivably could be due to the use of the study drug. An alternative explanation, e.g., concomitant drug(s), concomitant disease(s), is not conclusive. The relationship of the event in time follows a plausible temporal sequence from administration of the study drug so that a causal relationship cannot be excluded, but could have been produced by the patient's clinical condition or other therapy.

Probable: An AE that might be due to the use of the study drug. An alternative explanation is less likely, e.g., concomitant drug(s), concomitant disease(s). The relationship in time is suggestive and follows a reasonable temporal association with study drug administration. The reaction cannot be reasonably explained by the known characteristics of the patient's clinical state or other modes of therapy administered to the patient.

Related: An AE that is almost certainly related to the use of the study drug. The AE cannot be reasonably explained by an alternative explanation, e.g., concomitant drug(s), concomitant disease(s).

8.6 DEATHS AND LIFE-THREATENING EVENTS

An event leading to death from any cause or any life-threatening event must always be reported as an SAE within 24 hours of the clinical site learning of the event, regardless of whether or not related to the study drug (see Section 8.3).

8.7 UNEXPECTED ADVERSE EVENT

An AE is considered “unexpected” if it is not listed in the Investigator's Brochure or is not listed at the specificity or severity that has been observed. “Unexpected,” as used in this definition, also refers to AEs that are mentioned in the Investigator's Brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

8.8 DATA MONITORING COMMITTEE

An independent DMC will review accumulated blinded safety data after 150 patients have been treated and complete Week 4 (Visit 4). The DMC will review adverse event and clinically significant laboratory data in a blinded fashion and make a determination whether the data raise any vonapanitase related safety concern. The DMC must make a recommendation to continue, modify, or stop the study. If a potential safety issue is identified during the course of the study, these will be brought to the attention of the Committee Chair and additional meetings may be convened.

A charter for the DMC will be created that will define the membership, schedule of meetings, data required for each safety review, and requirements for documenting meeting discussions and outcome.

9. STATISTICAL ANALYSIS

A formal statistical analysis plan (SAP) will be developed that includes a detailed description of all planned analyses, pre-specified exploratory analyses, and any data handling conventions. Any deviations from the statistical methods described in the protocol and/or SAP will be documented in the clinical study report.

In general, continuous variables will be summarized using descriptive statistics including the number of observations, mean, standard deviation, minimum, median, and maximum values. Categorical values will be summarized using number of observations and percentages. Data presentations will include columns for placebo and vonapanitase 0.03 mg.

All statistical tests will be performed at the two-sided, 5% significance level, unless otherwise specified. All statistical testing will compare placebo versus vonapanitase unless otherwise specified.

The primary analysis will be performed once all patients have completed the Month 12 visit (Visit 8). The analysis of the registry data will be performed separately.

All data will be included in data listings.

9.1 SAMPLE SIZE

Final data from the PRT-201-310 study has been used to estimate the sample size and power for the co-primary endpoints of secondary patency and AVF use for hemodialysis. Six hundred (600) patients will be stratified based on hemodialysis status at study entry and randomly allocated by site in a 2:1 ratio to either vonapanitase 0.03 mg or placebo. When the total sample size is approximately 600 (400 vonapanitase and 200 placebo), a two-sided Fleming-Harrington weighted log-rank test with $\rho = 0$ and $\gamma = 0.35$ for equality of survival curves with a 0.05 significance level will have approximately 88% power to detect a 13% difference (61 vs. 74%) in the proportion of placebo compared to vonapanitase 0.03 mg treated patients with secondary patency at 12 months. [16] A piecewise exponential model with no treatment benefit during the first three months (i.e., survival at 3 months for both treatment groups is 88.4%) is assumed. A 15% drop out rate has been assumed in the calculations. The study will enroll over 24 months and each patient will be followed for a maximum of 12 months.

Assuming 25% of patients will have insufficient data to determine AVF use for hemodialysis a sample size of 450 will have 98% power to detect a 20% difference in the percentage of AVF use in placebo compared to vonapanitase 0.03 mg (44 vs. 64% AVF use), using a two sided chi-square test with an 0.05 significance level.

9.2 ANALYSIS SETS

The Full Analysis Set (FAS), based on Intention to Treat (ITT) methodology, will be defined as all randomized patients who have AVF surgery. Patients will be analyzed according to the randomized treatment assignment. Analyses of all efficacy endpoints will be performed using the FAS as the primary analysis set. Any patients who are randomized but not treated and have AVF surgery will only contribute data from Visits 1 and 2.

An Evaluable Analysis Set (EAS) will be defined as all randomized patients who received any amount of study drug and who do not have any protocol violations/deviations, or a technical failure of the surgery that could adversely affect the evaluation of the primary analysis. These patients will be identified prior to unblinding and the reason for any potential exclusion will be documented. Patients will be analyzed according to the treatment actually received. Analyses of the co-primary endpoints will be performed using the EAS as a sensitivity analysis.

The Safety Analysis Set will be defined as all randomized patients who received any amount of study drug. Patients will be analyzed according to the treatment actually received.

9.3 STATISTICAL METHODOLOGY

9.3.1 DEMOGRAPHICS AND BASELINE CHARACTERISTICS

Demographic data, medical history, and other baseline characteristics will be summarized by treatment received and included in the data listings. Statistical comparisons will be performed to assess baseline imbalances between treatment groups.

9.3.2 SAFETY ANALYSES

Safety evaluations are based on AEs, physical examination, duplex Doppler ultrasound, clinical laboratory evaluations, and immunogenicity testing results.

9.3.2.1 Adverse Events

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) AE dictionary. Treatment emergent AEs, defined as AEs that occur after administration of the study drug, will be tabulated by body system, preferred term, and dose. Events will also be summarized by relationship to the study drug and severity (mild, moderate, severe, or life threatening). SAEs and events leading to study discontinuation will be summarized by body system, preferred term, and treatment group.

All AEs will be presented in the data listings.

9.3.2.2 Physical Examinations

Required components of the physical exam will be specified in the source worksheets. Clinically significant adverse changes from baseline will be reported as AEs. In addition to the physical examination at Screening (Visit 1) and Week 4 (Visit 4), an AVF and upper extremity examination will be performed immediately following surgery and at all follow-up visits. Details on the AVF and upper extremity examination may be found in Section 6.2.1. AVF procedure types and all angioplasty locations (angioplasty includes balloon angioplasty/fistulogram and surgical patch angioplasty) will be summarized by the total frequency of each as well as the number and percentage of patients receiving them in each treatment group. The clinical reasons the patients were referred for the first procedure to restore or maintain patency will be summarized and presented by decreasing order of frequency for the vonapanitase 0.03 mg group.

9.3.2.3 Duplex Doppler Ultrasound

The variables of lumen diameter and blood flow obtained through duplex Doppler ultrasound at Week 4 (Visit 4) and Month 3 (Visit 5) will be summarized and presented in the data listings and in tabular summaries by treatment group. The average value of multiple measurements will be used for summarization. Clinically significant adverse findings will be recorded as AEs.

9.3.2.4 Clinical Laboratory Evaluations

Clinical laboratory results will be summarized by treatment group at Screening (Visit 1) and Week 2 (Visit 3). The change from baseline in laboratory results will also be presented. All clinically significant adverse laboratory abnormalities will be reported as AEs and included in the summary of AEs. Out of range laboratory results will be listed.

All laboratory results will be presented in the data listings.

9.3.2.5 Anti-vonapanitase Antibody Detection

Results of anti-vonapanitase antibodies will be presented in the data listings.

9.3.3 EFFICACY ANALYSES

9.3.3.1 Primary Endpoints

The co-primary efficacy endpoints are secondary patency and AVF use for hemodialysis.

Secondary patency is defined as the time from AVF creation until AVF abandonment. A patient who does not have an abandoned AVF at Month 12 (Visit 8) or end of study will be censored at the last visit date the AVF was known not to be abandoned.

Secondary patency time is estimated by the 25^{th}, 50^{th} (median), and 75^{th} percentiles calculated by using the Kaplan-Meier life test methods to estimate the survival functions. A Fleming-Harrington weighted log-rank test with $\rho = 0$ and $\gamma = 0.35$ will be used to test the equality of the survival curves between vonapanitase and placebo. A 95% confidence interval for the median will be calculated. A graph of the survival probability over time will be presented. As a sensitivity analysis, the hazard ratio and 95% confidence interval, using a Cox proportional-hazards model will also be calculated. The analysis of secondary patency will be performed in the FAS. Analysis of secondary patency will also be performed in the EAS as a sensitivity analysis. As appropriate based on the proportional hazards assessment, restricted means or proportional hazards modeling may be employed to identify and adjust for any covariates potentially associated with secondary patency. The data from the models will be for descriptive purposes only. The Fleming-Harrington weighted log rank test in the FAS will be considered the primary analysis for secondary patency.

AVF use for hemodialysis is defined as the ability of the study AVF to be successfully cannulated and used for hemodialysis for a minimum of 90 days or at least 30 days prior to a patient's last visit, if hemodialysis had not been initiated at least 90 days prior to a patient's last visit. If AVF use is not defined as above, non-use of the AVF for hemodialysis is defined as an abandoned fistula prior to use; or if hemodialysis is recorded on 2 consecutive visits and there is no cannulation date or duration of use is less than 90 days. The patients who are not categorized as having use or non-use of the AVF have insufficient data to determine AVF use for hemodialysis and will be categorized as having indeterminate use. The number and percentage of

patients with AVF use or non-use for hemodialysis will be summarized by treatment group in the group of FAS patients who are not considered indeterminate. Vonapanitase vs. placebo will be tested using a Chi-square test. Analysis of AVF use will also be performed in the EAS as a sensitivity analysis.

9.3.3.2 Additional Efficacy Endpoints

Additional efficacy endpoints are unassisted AVF use for hemodialysis, primary unassisted patency, AVF maturation by ultrasound criteria, unassisted AVF maturation by ultrasound criteria, the rate of procedures performed to the AVF, and the rate of procedures to restore or maintain AVF patency.

9.3.3.2.1 Unassisted AVF Use for Hemodialysis

Unassisted AVF use for hemodialysis is defined as AVF use without prior procedures to restore or maintain patency.

The number and percentage of patients with unassisted AVF use for hemodialysis will be summarized by treatment group. Vonapanitase versus placebo will be tested using a chi-square test. The analysis of unassisted AVF use will be performed in the FAS.

9.3.3.2.2 Primary Unassisted Patency

AVF primary unassisted patency is defined as the time from AVF creation until the first occurrence of either access thrombosis or procedure to restore or maintain AVF patency. A patient who has a patent AVF at Month 12 or end of study will be censored at the last visit date where the AVF was known to be patent.

Primary unassisted patency time is estimated by the 25^{th}, 50^{th} (median), and 75^{th} percentiles calculated by using the Kaplan-Meier life test methods to estimate the survival functions. A log-rank test will be used to test the equality of the survival curves between vonapanitase and placebo. A 95% confidence interval for the median will be calculated. A graph of the survival probability over time will be presented. A hazard ratio and 95% confidence interval, calculated using a Cox proportional-hazards model including treatment as the covariate will assess the magnitude of the treatment effect. Proportional hazards modeling may be employed to identify and adjust for any covariates potentially associated with primary unassisted patency. The data from the proportional hazards models will be for descriptive purposes only. The analysis of primary unassisted patency will be performed in the FAS. Analysis of primary unassisted patency will also be performed on the EAS as a sensitivity analysis.

9.3.3.2.3 AVF Maturation

AVF maturation by ultrasound criteria is defined by two definitions:

1. As average cephalic vein luminal diameter ≥ 6 mm and outflow vein volume blood flow ≥ 600 mL/min by ultrasound. [2]
2. As average cephalic vein luminal diameter ≥ 4 mm and outflow vein volume blood flow ≥ 500 mL/min by ultrasound. [1]

The number and percentage of patients with AVF maturation will be summarized by treatment group at Week 4 (Visit 4) and Month 3 (Visit 5). Vonapanitase versus placebo will be tested using a chi-square test. Definition 2 at the Month 3 visit is considered primary for analysis. Unassisted AVF maturation is defined as AVF maturation by ultrasound criteria without prior primary unassisted patency loss. The number and percentage of patients with unassisted AVF maturation will be analyzed similarly. AVF maturation and unassisted AVF maturation by ultrasound criteria will be performed in the FAS. This analysis will also be performed on the EAS as a sensitivity analysis.

9.3.3.2.4 Procedure Rate

The procedure rate is defined as the total number of procedure days divided by time on study per person year of follow up. A Wilcoxon rank sum test will be used to compare the treatment groups. The rate of procedure days overall and the rate of procedure days to restore or maintain AVF patency will be performed in the FAS.

9.3.3.3 Multiplicity Adjustments

Multiplicity, with respect to the co-primary endpoints, will be managed with the Hochberg procedure. If both endpoints have a p-value ≤ 0.05 both will be considered statistically significant. If one endpoint has a p-value > 0.05 the other endpoint will be considered statistically significant only if its p-value is ≤ 0.025. If both p-values are > 0.05 neither will be considered statistically significant.

Multiplicity adjustments for other endpoints will be described fully in the SAP.

9.3.4 CLINICAL ENDPOINT REVIEW

Prior to database lock, a clinical expert in the field of hemodialysis vascular access will review all study patients' CRFs and procedure reports to confirm that the patients are appropriately defined with regard to the primary and secondary patency efficacy endpoints by reviewing applicable CRFs and procedure reports to ensure that appropriate documentation of clinical dysfunction has been recorded. A charter for this process will be created that will define the review process and the requirements for documentation of review.

10. ADMINISTRATIVE REQUIREMENTS

10.1 GOOD CLINICAL PRACTICE

The study will be conducted in accordance with the current Good Clinical Practice/International Conference on Harmonization (GCP/ICH) Guidelines and relevant regulatory requirement(s). Compliance with this standard provides public assurance that the rights, safety, and well-being of study patients are being protected consistent with the principles that have their origin in the Declaration of Helsinki and that the clinical study data are credible. The Investigator will be thoroughly familiar with the appropriate use of the study drug as described in the protocol and Investigator's Brochure. Essential clinical documents will be maintained to demonstrate the validity of the study and the integrity of the data collected. A Trial Master File (TMF) will be established at the beginning of the study, maintained for the duration of the study, and retained according to appropriate regulations.

10.2 ETHICAL CONSIDERATIONS

The study will be conducted in accordance with ethical principles that have their origin in the Declaration of Helsinki. The IRB/IEC will review all appropriate study documentation in order to safeguard the rights, safety, and well-being of the patients. The study will only be conducted at sites where IRB/IEC approval has been obtained. The protocol, Investigator's Brochure, informed consent, advertisements (if applicable), written information given to the patients (including patient information material), safety updates, annual progress reports, and any revisions to these documents will be provided to the IRB/IEC by the Investigator.

10.3 PATIENT INFORMED CONSENT AND INFORMATION

Prior to entry in the study, the Investigator must explain to potential study patients or their legally acceptable representative, the study and the implications of participation. Patients will be told that their participation is voluntary and they may withdraw consent to participate at any time. Patients will be told that their records may be accessed by competent authorities and authorized Proteon personnel or its representatives without violating the confidentiality of the patient, to the extent permitted by the applicable law(s) and/or regulations. In addition to signing the ICF, the patient or legally acceptable representative will be required to authorize access to the patient's protected health information by signing a separate authorization meeting the requirements of the Health Insurance Portability and Accountability Act of 1996. Each patient (or their legally authorized representative) must **sign and date** the ICF (and other locally required documents) after the nature of the study has been fully explained but prior to performing any study-related activities. The patient (or their legally acceptable representative) will be given sufficient time to read the ICF and to ask questions. After having obtained consent, a copy of the informed consent document must be given to the patient. In case the patient is unable to read, an impartial witness must attest to the informed consent. Patients who are unable

to comprehend the information provided can only be enrolled after consent of a legally acceptable representative.

The consent form that is used must be approved by both the reviewing IRB/IEC and by Proteon.

10.4 PATIENT CONFIDENTIALITY

The collection and processing of data from patients enrolled in this study will be limited to those data that are necessary to investigate the safety, quality, and utility of the investigational drug(s) used in this study and to conduct the other investigations described in this protocol, including the pharmacoeconomic analysis described in Section 5.10. These data will be processed with adequate precautions to ensure confidentiality.

In order to maintain patient privacy, CRFs, study drug accountability records, study reports, and communications will generally identify the patient by initials and the assigned patient number. The ICF will inform patients of any departures from this approach, such as the need to identify patients by social security number or Health Insurance Claim/Beneficiary Identification Code for purposes of the pharmacoeconomic analysis described in Section 5.10. The Investigator will grant monitor(s) and auditor(s) from Proteon, its CRO designee or business partners, and regulatory authority(ies) access to the patient's original medical records for verification of data gathered on the CRFs and to audit the data collection process. The patient's confidentiality will be maintained and will not be made publicly available except to the extent permitted by applicable laws and regulations.

10.5 PROTOCOL COMPLIANCE

The Investigator will conduct the study in compliance with the protocol provided by Proteon, and given approval by the IRB/IEC and the appropriate regulatory authority(ies). Modifications to the protocol should not be made without the approval of Proteon. Changes to the protocol will require written IRB/IEC approval prior to implementation, except when the modification is needed to eliminate an immediate hazard(s) to patients. The IRB/IEC may provide, if applicable regulatory authority(ies) permit, expedited review and approval for minor change(s) in ongoing studies that have the approval of the IRB/IEC. Proteon will submit all protocol modifications to the regulatory authority(ies) in accordance with the governing regulations.

When immediate deviation from the protocol is required to eliminate an immediate hazard(s) to patients, the Investigator will contact Proteon, if circumstances permit, to discuss the planned course of action. Any departures from the protocol must be fully documented in the patient's medical records and CRF.

10.6 STUDY MONITORING AND ON-SITE AUDITS

Monitoring and auditing procedures developed by Proteon or its CRO designee will be followed, in order to comply with GCP guidelines. Routine monitoring visits will be made to assure

compliance with the study protocol, to review and compare the patient's CRF or other data collection vehicle with source documents, to ensure adequate records of clinical supplies are maintained, and to assess the continued suitability of the investigational site. The Investigator agrees to allow the site monitors, and other authorized personnel or designees, access to the patient's medical records, regulatory binder, study binder, CRFs, and source documents as needed to assure the conduct of the study is within compliance.

Upon completion of the study the site monitor will make a final assessment of the conduct of the study and inventory all clinical supplies to be returned to Proteon or designee. Unused or used vials of study drug will be stored until the study monitor is able to perform a physical inventory and reconciliation with the drug accountability records. At the completion of this study, all unused or used vials must be returned to Proteon, or designee, or if authorized, disposed of at the study site and documented.

Regulatory authorities, the IRB or IEC and/or Proteon's quality assurance group, its CRO designee, or business partners may request access to all source documents, CRFs, and other study documentation for on-site audit or inspection. Direct access to these documents must be guaranteed by the Investigator, who must provide support at all times for these activities.

10.7 CASE REPORT FORM COMPLETION

Electronic case report forms (eCRFs) will be utilized for this study. It is the Investigator's responsibility to ensure the accuracy, completeness, legibility, and timeliness of the data reported in the patient's eCRF. Source documentation supporting the CRF data should indicate the patient's participation in the study and should document the dates and details of study procedures, AEs, and patient status. No data should be directly recorded into the eCRF without supporting source documentation.

The Investigator, or designated representative as noted in the site delegation log, should complete the eCRF as soon as possible after information is collected, preferably on the same day that a study patient is seen for an examination, treatment, or any other study procedure. Any outstanding entries must be completed immediately after the final examination. An explanation should be given for all missing data.

10.8 DATA QUALITY ASSURANCE

This clinical study will be monitored according to current Proteon or designated CRO Standard Operating Procedures (SOPs), GCP/ICH Guidelines, and all applicable regulatory requirements. Steps to be taken to assure the accuracy and reliability of data include the selection of qualified Investigators and appropriate study sites, review of protocol procedures and the administration of informed consent with the Investigator and associated site personnel prior to study start, periodic monitoring visits by Proteon personnel or its designated CRO representatives, and clinical site audits. During the study, the Investigator shall permit Proteon or its representatives to verify the

progress of the study on site as frequently as necessary. Qualified personnel will review CRF data or other appropriate data collection vehicles for accuracy and completeness remotely utilizing the electronic data capture (EDC) system and against source documents during on-site monitoring visits. Data discrepancies will be resolved with the Investigator or designees, as appropriate. The Investigator shall make the CRF, other data collection vehicles and source documents available, provide missing or corrected data, and sign the data collection tools. Data management and other qualified personnel will review CRF data for completeness, logical consistency, and safety; automated validation programs are used to help identify missing data, protocol violations, out-of-range data, and other data inconsistencies. Personal information will be treated as strictly confidential and will not be publicly available. The CRF must be amended after inconsistencies have been resolved.

An independent Quality Assurance (QA) department, Proteon business partner designees, and/or regulatory authorities may review this study. This implies that auditors/inspectors will have the right to inspect the investigational site(s) at any time during and/or after completion of the study and will have access to source documents, including the patient's medical file(s). By participating in this study, Investigators agree to this requirement. Measures will be undertaken to protect patient data handed over by the Investigator to Proteon and to inspectors against disclosure to unauthorized third parties and patient confidentiality will be maintained at all times.

10.9 STUDY COMPLETION OR PREMATURE CLOSURE

The Investigator will complete the study and submit the final eCRFs in satisfactory compliance with the protocol within approximately 2 weeks of study completion.

Proteon reserves the right to close the investigational site or terminate the study at any time. Reasons for the closure of an investigational site or termination of a study by Proteon may include:

1. Determination of unexpected, significant, or unacceptable risk to patients.
2. Failure to enter patients at an acceptable rate.
3. Insufficient adherence to protocol requirements.
4. Insufficiently complete and/or evaluable data.
5. Plans to modify, suspend, or discontinue the development of the study drug.

Should the study be closed prematurely, all study materials must be returned to Proteon.

10.10 RECORD RETENTION

A record of the eCRFs and all source documents (e.g., ICFs, laboratory reports, progress notes, medical history, physical and diagnostic findings, diagnoses and dates of therapy prior to and during this study, drug dispensing/disposition records) that support the data collected for each

patient must be retained in the files of the responsible Investigator for at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region; or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational drug. These documents should be retained for a longer period, however, if required by applicable regulatory requirements. The Investigator should take measures to prevent accidental or premature destruction of these records. Under no circumstances shall the Investigator re-locate or dispose of any study documents before having obtained Proteon written approval. If the Investigator withdraws from the responsibility of keeping the study records, custody must be transferred to a person willing to accept the responsibility. Proteon must be notified in writing if a custodial change occurs. If it becomes necessary for Proteon or a regulatory authority to review any documentation relating to this study, the Investigator must permit, with the approval of the patient, access to such records. Any difficulty in storing original records must be discussed with the study monitor prior to the initiation of the study.

11. USE OF INFORMATION AND PUBLICATION

All information regarding vonapanitase supplied by Proteon to the Investigator or generated by the Investigator in accordance with the conduct of the study is privileged and confidential information of Proteon. The Investigator agrees to use this information to accomplish the study and will not use it for other purposes without written consent from Proteon. It is understood that there is an obligation to provide Proteon with complete data obtained during the study. The information obtained from the clinical study will be used by Proteon in connection with the development of vonapanitase and may be disclosed by Proteon to regulatory authority(ies), other Investigators, corporate partners, or consultants as required.

The Investigator’s right and obligations with respect to publishing or otherwise presenting information regarding the study are detailed in the Publication provisions of the Clinical Study Agreement among the Investigator, the clinical site, and Proteon. The Investigator shall comply with such provisions.

12. REFERENCES

1. Allon M, Robbin ML. Increasing arteriovenous fistulas in hemodialysis patients: problems and solutions. *Kidney Int* 2002;62:1109–1124.
2. NKF-KDOQI. Clinical practice guidelines for vascular access. *Am J Kidney Dis* 2006a;48(suppl 1).
3. Pisoni RL, Young EW, Dykstra DM, et al. Vascular access use in Europe and the United States: Results from the DOPPS. *Kidney Int*. 2002;61:305-316.
4. Jackson RS, Sidawy AN, Amdur RL, et al. Angiotensin receptor blockers and antiplatelet agents are associated with improved primary patency after arteriovenous hemodialysis access placement. *J Vasc Surg* 2011;54:1706-12.
5. Ruddy JM, Brothers TE, Robison JG, Elliott BM. Increasing the proportion of autologous arteriovenous fistulas does not diminish fistula patency. *Vasc Endovascular Surg* 2011;45:51-4.
6. Schinstock CA, Albright RC, Williams AW, et al. Outcomes of arteriovenous fistula creation after the Fistula First Initiative. *Clinical J Am Soc Nephrol* 2011;6:1996-2002.
7. Roy-Chaudhury P, Sukhatme VP, Cheung AK. Hemodialysis vascular access dysfunction: a cellular and molecular viewpoint. *J Am Soc Nephrol* 2006;17:1112–1127.
8. Beathard GA. Management of complications of endovascular dialysis access procedures. *Semin Dial* 2003;16:309-313.
9. Lee T, Mokrzycki M, Moist L, et al. Standardized definitions for hemodialysis vascular access. *Semin Dial* 2011;24:1-10.
10. Asif A, Roy-Chaudhury P, Beathard GA. Early arteriovenous fistula failure: a logical proposal for when and how to intervene. *Clin J Am Soc Nephrol* 2006;1:332–339.
11. De Rango P, Parente B, Cieri E, et al. Percutaneous approach in the maintenance and salvage of dysfunctional autologous vascular access for dialysis. *J Vasc Access* 2012;13:381-7.
12. Heye S, Maleux G, Vaninbroukx J, et al. Factors influencing technical success and outcome of percutaneous balloon angioplasty in de novo native hemodialysis arteriovenous fistulas. *Eur J Radiol* 2012;81:2298-303.
13. Hye RJ, Peden EK, O'Connor TP, et al. Human type I pancreatic elastase treatment of arteriovenous fistulae in patients with chronic kidney disease. *J Vasc Surg* 2014; 60:454-461.
14. Dember LM, Beck GJ, Allon M, et al. Effect of clopidogrel on early failure of arteriovenous fistulas for hemodialysis: a randomized controlled trial. *JAMA* 2008;299:2164-2171

15. Peden EK, O'Connor TP, Browne BJ, et al. Arteriovenous fistula patency in the 3 years following vonapanitase and placebo treatment. J Vasc Surg 2016 http://dx.doi.org/10.1016/j.jvs.2016.08.101

16. Lin RS, León LF. Estimation of treatment effects in weighted log-rank tests. Contemporary Clinical Trials Communications. 2017; 8: 147-155.

Appendix A: Schedule of Assessments

Visit	Screen	Surgery	Follow-up					
			Week 2	Week 4	Month 3	Month 6	Month 9	Month 12
Visit Day[1]	**Day -28**	**Day 1**	**Day 14**	**Day 28**	**Day 90**	**Day 180**	**Day 270**	**Day 360**
Visit Number	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**
Informed Consent	X							
Incl/Excl Criteria	X	X						
Medical/Disease History	X	X						
Concomitant Medication	X	X	X	X				
Physical Examination	X			X				
Clinical Laboratory Evaluations[2]	X		X					
Anti-vonapanitase Antibody Sample[2]	X		X	X		X[3]		X[3]
Administer Study Drug		X						
Collection of Intraoperative Events		X						
AVF and Upper Extremity Examination[4]		X	X	X	X	X	X	X
Ultrasound				X	X			
Adverse Events Evaluation		X	X	X	X	X	X	X

1 Visit Day 14 is ± 3 days. Visit Day 28 is ± 3 days. Visit Days 90, 180, 270, and 360 are ± 14 days.

2 Blood samples will be drawn and processed locally and sent to a central laboratory for testing.

3 Patients who test positive for anti-vonapanitase antibodies at Week 4, or at Week 2 without a Week 4 test result will be asked to provide an additional blood sample for testing at Month 6. If the patient continues to test positive at Month 6, or was positive at Week 4 without a Month 6 test result, s/he will be asked to provide an additional blood sample at Month 12.

4 Data regarding procedures performed on the study fistula (e.g., angioplasty, thrombectomy) will be collected.

Appendix B: Laboratory Evaluations

Blood Chemistry

Albumin
Alkaline phosphatase
Alanine aminotransferase
Aspartate aminotransferase
Bilirubin
Blood glucose
Blood urea nitrogen
Calcium
Carbon dioxide
Cholesterol
Triglycerides
Chloride
Creatinine
Creatinine kinase
Gamma-glutamyl transferase
Lipase
Lactate dehydrogenase
Phosphate
Potassium
Sodium
Total serum protein
Uric acid

Hematology

Complete blood count
Hemoglobin
Hematocrit
White blood cell automated differential
Platelet count

Endocrinology

Serum beta-human chorionic gonadotropin **(at screening visit only in women of childbearing potential)**

Blood Sample

For anti-vonapanitase antibody testing

Coagulation Tests (at Screening Visit only)

Prothrombin time/
Activated partial thromboplastin time
International normalized ratio