Statistical Analysis Plan

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Approval

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Contents

List of Abbreviations and Definitions

ADE	Adverse device effect
AE	Adverse event
BD	Becton Dickinson and Company
BMI	Body Mass Index
CFR	Code of Federal Regulations
CI	Confidence Interval
CRBSI	Catheter-related Blood Stream Infection
CRF	Case Report/Record Form
DOPPS	Dialysis Outcomes and Practice Patterns Study
eCRF	Electronic Case Report Form
ESRD	End-Stage Renal Disease
EtO	Ethylene Oxide
FDA	Food and Drug Administration
HIPAA	Health Insurance Portability and Accountability Act
ICF	Informed Consent Form
IFU	Instructions for Use
ITT	Intent-to-Treat
IRB/EC	Institutional or Independent Review Board/Ethics Committee
KDOQI	Kidney Disease Outcomes Quality Initiative
mITT	Modified Intent-to-Treat
NKF	National Kidney Foundation
PP	Per-Protocol
SADE	Serious adverse device effect
SAE	Serious Adverse Event
SoA	Schedule of Activities
UADE	Unexpected Adverse device effect

1 Introduction

1.1 Background and Rationale

The Pristine™ Post-Market study is a prospective, multi-Center, single-arm clinical study to evaluate the safety and performance of the BD Pristine™ Long-Term Hemodialysis Catheter. This study will be conducted in conformance with the Declaration of Helsinki, applicable national privacy laws (e.g., Health Insurance Portability and Accountability Act (HIPAA) requirements in the U.S.), applicable Food and Drug Administration (FDA) regulations (21 Code of Federal Regulations (CFR) Parts 11, 50, 54, 56, and 812), Institutional Review Board (IRB) requirements, and International Organization for Standardization (ISO) 14155:2020 standards.

With introduction of hemodialysis as a feasible and effective treatment in the early 1940s, the grim outlook of death evolved to a prospect of survival for patients with advancing kidney failure. By reducing the time and effort required by the patient and caregivers, technological advancements have gradually transformed hemodialysis from an intensive bedside therapy to a more streamlined treatment, sometimes even self-administered in the comfort of patient's home. Standards have been established and guidelines were put in place to efficiently care for large numbers of patients with a balance of resources and patient time.

According to the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative, (2015 NKF KDOQI) over 400,000 patients are currently treated with hemodialysis in the United States, with Medicare spending reportedly approaching $90,000 per patient per year of care in 2012. In 2012, the European Renal Association - European Dialysis and Transplant Association reported a prevalence of 372 patients per million in the United Kingdom.

Appropriate care of hemodialysis patients requires constant maintenance of vascular access patency and function, to accommodate for a flow rate to the dialyzer that is adequate for the dialysis prescription. The failure of access is a major cause of morbidity for patients on hemodialysis therapy, with a number of reports indicating that a high percentage of hospitalizations for patients with chronic kidney disease were caused by vascular access complications. The United States Renal Data System (USRDS) reported that hemodialysis access failure was the most frequent cause of hospitalization for patients with stage 5 chronic kidney disease and, in some centers, it accounted for the largest number of hospital days. Ideally, vascular access has a long use-life, and has a low rate of complications. The surgically created arteriovenous fistula has shown the best 4- to 5-year patency rates and has required the fewest interventions compared with other access types. However, use of grafts and cuffed central venous catheters (CVCs) for permanent hemodialysis access is common, accompanied by an increased rate of access related complications.

Despite the burden of catheter-associated conditions and risks for patients, the use of cuffed tunneled central venous catheters is frequently vital as a standalone treatment modality of acute and chronic renal failure and serves as a bridge until recovery of renal function, maturation of fistula, or finding a donor organ. The need for better performing hemodialysis catheters still exists.

Catheter design can impact performance. Some hemodialysis catheters have side holes in their distal lumens. These side holes, which were intended to increase inflow and reduce risk of blockage, have been shown to be prone to clot formation. Under electron microscopy side holes have been shown to have rough edges where thrombi can attach. Due to the side holes flow, anticoagulant given at the end of dialysis may not be able to reach the tip of the catheter.

The Pristine™ Long-Term Hemodialysis Catheter, is an innovative split, symmetrical, side-hole–free tip. The Pristine™ Catheter's side-hole free tip is designed to help minimize thrombus adhesion that can be associated with hemodialysis catheters that have side holes.

In a previous feasibility study, the primary objective was to observe the performance of the Pristine™ Long-Term Hemodialysis Catheter in participants with End-Stage Renal Disease or Acute Renal Failure. The study was performed at a single investigation site in the Dominican Republic. Forty-five (45) participants (males or non-pregnant females with ESRD or ARF requiring hemodialysis treatment) received the current 15.5F Pristine™ catheter. The primary endpoint was primary patency, prespecified for evaluation at 30 days post-catheter implantation and was defined as a catheter that provided adequate hemodialysis (flow >300mL/min) without the need for additional interventions (i.e., TPA infusions or fibrin sheath stripping or catheter exchange) to maintain flow or correct device failure.

Participants were followed for 6 months post-catheter implantation at four sites that were affiliated with the placement institution. All catheters (n=44) were patent at 30 days post implantation. Primary patency at 60- and 180- days post procedure was 100.0% and 90.9%, respectively. The following adverse events (AE) were reported in accordance with MedDRA v. 22.1. There were 9 infections, 6 of which were reported as device-related and 3 (2 pneumonia and 1 abdominal abscess) were reported as not related to the study device. There were 2 cardiac disorders and 2 vascular disorders, none of which were reported as device related. There were 6 general disorder and access site conditions, 2 of which were reported as device related. There were 9 deaths reported in the study, none of which were reported as related to the device or procedure.

The purpose of this clinical investigation is to provide clinical evidence to further demonstrate reasonable assurance of safety and performance of the Pristine™ Long-Term Hemodialysis Catheter to provide immediate hemodialysis access. The Pristine™ Catheter has already been cleared by the FDA and is currently on the market in the United States.

1.2 Objectives

The objective of this study is to assess the safety and performance of the BD Pristine™ Long-Term Hemodialysis Catheter for attaining vascular access for hemodialysis. The information obtained from the study is intended to be reported in the device's labeling.

1.2.1 Primary Objectives

The primary objective is to assess the overall complication rate of the Pristine™ Catheter against an overall hemodialysis catheter complication rate derived from clinical literature.

1.2.2 Secondary Objectives

The second objective is to assess the short- and long- term safety and performance of the Pristine™ Catheter.

1.2.3 Exploratory Objectives

The exploratory objective is to determine and characterize the short- and long-term safety and performance of the device and ancillary kit components.

2 Study Description

2.1 Study Design

This is a prospective, multi-center, post market, single-arm study designed to assess the safety and performance of the Pristine™ Long-Term Hemodialysis Catheter. The primary objective of this study is to assess the overall complication rate of the Pristine™ Catheter against an overall hemodialysis catheter complication rate derived from clinical literature.

A total of 142 patients will be enrolled and have the Pristine™ Long-Term Hemodialysis Catheter placed. Under the current enrollment assumptions, up to 15 investigational sites in the United States (US) will participate. The

study will be enrolling male or non-pregnant female participants ≥18 years of age meeting study inclusion/exclusion and labeled indication for hemodialysis for adequate completion of study procedures and collection of data. Eligible participants will have End Stage Renal Disease requiring hemodialysis through a tunneled dialysis catheter. Follow-up for all enrolled participants will be performed at 1month, 3-months, 6-months, and 12-months post-Index Procedure. No site will be allowed to enroll more than 20% of the overall number of participants to ensure a reasonably well-balanced, multi-center study.

For this study, we have a combined Safety and Performance endpoint derived from the Dialysis Outcomes and Practice Patterns Study (DOPPS) data. Our combined Primary Endpoint will be overall complications including non-infectious and infectious at 3 months.

2.2 Study Population

Study population includes participants with end stage renal disease requiring hemodialysis through a tunneled dialysis catheter. All participants must meet all inclusion and exclusion criteria.

Participants will be recruited for enrollment in the study from each site's existing pool of patients. Enrollment of participants will continue until a total of 142 patients at up to 15 sites have been enrolled and undergo the placement procedure successfully of the BD Pristine™ Long-Term Hemodialysis Catheter. It is anticipated that enrollment will be approximately 12 months in duration. The following describes the clinical eligibility (inclusion and exclusion) criteria for this study:

Inclusion Criteria

To be eligible to participate in this study, an individual must meet all of the following criteria:

1. The participant or legally designated representative must voluntarily sign and date the approved Informed Consent Form (ICF) prior to collection of study-specific data or performance of study-specific procedures.
2. The participant must be willing and able to comply with protocol requirements, including all study visits and procedures.
3. The participant must be either a male or non-pregnant female ≥18 years of age.
4. The participant must have a diagnosis of End Stage Renal Disease with indication for a tunneled dialysis catheter creation.
5. Participant must require chronic hemodialysis treatments 3 times per week with intended use of the Pristine™ Long-Term Hemodialysis Catheter.
6. The participant meets the indications for hemodialysis use and does not meet any of the contraindications per the Pristine Instructions for Use (IFU).
7. The participant must have a patent jugular vein or subclavian vein.

Exclusion Criteria

A participant must NOT meet ANY of the following criteria to be enrolled in the study:

1. The participant has known central venous stenosis
2. Based on the local primary investigator's discretion, the patient would not be an appropriate study candidate.
3. The participant has already undergone an AVF or AVG procedure and is awaiting maturation.
4. The participant has an active infection at the time of study enrollment.

5. The participant has a presence of bacteremia or infection within 7 days prior to enrollment.
6. The participant has a history neutropenia or a history of severe immunodeficiency disease.
7. The participant has uncontrolled abnormal coagulation parameters and are at additional risk for clotting or excessive bleeding at time of enrollment per physicians' opinion.
8. The participant has a known allergy, intolerance or sensitivity to heparin, or previous incidence of heparin-induced thrombocytopenia.
9. The participant has a known allergy or hypersensitivity to any of the device materials or Ethylene oxide (EtO).
10. The participant has another medical condition or treatment, which in the opinion of the investigator, the participant may be non-compliant with the protocol, confound the data interpretation, or is associated with a life expectancy insufficient to allow for completion of study procedures and follow-up.
11. The participant is currently participating in an investigational drug or another device study that has not completed the study treatment or that clinically interferes with the study endpoints. Note: Studies requiring extended follow-up visits for products that were investigational but have since become commercially available, are not considered investigational studies.

2.3 Randomization and Blinding

Randomization and blinding are not applicable for this study.

2.4 Sample Size

The primary objective of the study is to show the overall complication rate for Pristine is non-inferior to the performance goal at 3 months. If successful, the next step is to show superiority of Pristine at 3 months.

Based on hypothesis test of Non-inferiority

- Assumptions:
  - The complication rate of our performance goal is estimated at 31.5 events per 1000 patient days with a 90 days follow-up based on DOPPS study data. The complication rate for Pristine is expected to be similar.
  - The performance goal is set at 36.5 events per 1000 days using a 5 events per 1000 days non-inferiority margin.
  - The attrition through 90 days is assumed to be 15%.
  - The Type 1 error is 0.025 (one-sided).
  - The Type 2 error is 0.2.
- Sample Size:
  - Total required exposure is 12765 patient days which translates to 142 participants with average exposure of 90 days (PASS 2019).

Based on hypothesis test of Superiority

- Assumptions:
  - The complication rate of our performance goal is estimated at 31.5 events per 1000 patient days with a 90 days follow-up based on literature review, which is set as the performance goal.
  - The complication rate for the Pristine™ Catheter is assumed to be 26.5 events per 1000 patient days.
  - The attrition through 90 days is assumed to be 15%.

- The Type 1 error is 0.025 (one-sided).

- Sample Size:
  - Total exposure of 12765 patient days (which translates to 142 participants with average exposure of 90 days) will provide 85% power of the test (PASS 2019).

2.5 Interim Analyses

An interim analysis will be conducted after all eligible patients have completed their 3-month follow-up visit. The Primary endpoint of combined complications will be analyzed and reported. Secondary endpoints will be reported with descriptive statistics.

2.6 Study Procedure

Individuals that consent to participate in the study will be considered ***enrolled***. Participants that fail to meet eligibility criteria post-consent and prior to undergoing device placement with the study device will be considered ***screen failures***.

After the PI, or authorized designee(s), has determined that the participant is eligible for participation, the participant may be enrolled and undergo the Pristine™ Catheter placement procedure. Enrolled participants will continue clinical participation through the 12-month follow-up period. Participants into whom the Pristine™ Catheter was not introduced should be treated per SOC and the reason documented on the appropriate eCRF. Participation for these participants will end at time of the index procedure.

The study procedures and visit schedules for enrolled subjects is shown in Table 1.

Table 1. Schedule of Activities

Procedure	Screening		Study Visits				
		Index Procedure Day 1	Follow-Up Visit 1 1 month (±7-days)	Follow-Up Visit 2 3-months (±15-days)	Follow-Up Visit 3 6-months (±15-days)	Follow-Up Visit 4 12-months (±30-days)	Unscheduled
In-Clinic Visit or Telephone Visit (Screening must be in-clinic visit)	x	x	x	x	x	x	x
Informed Consent	x						
Eligibility	x						
Demographics	x						
Physical Examination	x						
Medical History	x						
Dialysis History	x						
Procedure Overview		x					
Study Device Details		x					
Hemodialysis Catheter Assessment			x	x	x	x	x
Dialysis Session Logs			x	x	x	x	x
Device Deficiencies / Malfunctions		←	—	—	—	—	→
Re-Intervention Assessment		←	—	—	—	—	→
Adverse Event Assessment		←	—	—	—	—	→
Protocol Deviations	←	—	—	—	—	→	

2.7 Endpoints

2.7.1 Primary Endpoints

Primary Safety and Performance Endpoint

This study has a combined Safety and Performance endpoint derived from the Dialysis Outcomes and Practice Patterns Study (DOPPS) data. The combined Primary Endpoint will be overall complications including infectious and non-infectious complications at 3 months.

- Infectious Complications are defined as:

  Complications due to any documented diagnosis of access infection requiring medical intervention (managed in an outpatient or inpatient setting) or sepsis as diagnosis in the hospitalization file whether access related or not.

- Non-infectious complications are defined as:

  Complication due to any noninfectious cause (thrombosis of the access, fibrin material within or around a catheter, catheter migration, central vein stenosis or thrombosis) requiring a revision procedure to maintain patency or improve access performance (i.e., thrombolysis, angioplasty, or surgical correction) in an inpatient or outpatient setting or removal or abandonment with creation of a new access that was not due to an access-related infection).

2.7.2 Secondary Endpoints

The following secondary endpoints will be evaluated using descriptive statistics to provide further information related to the safety and performance of the Pristine™ Long-Term Hemodialysis Catheter. All secondary endpoints will be summarized with descriptive statistics.

- Rate of freedom from catheter-related bloodstream infection (CRBSI), defined by 2019 KDOQI Guidelines for CRBSI through 1-month, 3-months, 6-months, and 12-months post-index procedure.
- Rate of freedom from Device and/or Procedure-related adverse events, at 1-month, 3-months, 6-months, and 12 months post-index procedure.
- Rate of Technical Success, defined as the successful placement of the Pristine™ Long-term Hemodialysis Catheter, as assessed by the Investigator during the Index Procedure.
- Overall Participant Survival Rate at 1-month, 3-months, 6-months, and 12-months post-index procedure, defined as the proportion of participants that have not died from any catheter related complication.
- Overall Catheter Survival Rate at 1-month, 3-months, 6-months, and 12-months post-index procedure, defined as the proportion of Pristine™ Catheters that have not been removed for any cause.
- Overall Patency Rate, at 1-month, 3-month, 6-months, and 12-months post-index procedure, defined as the Pristine™ catheter having the ability to achieve a mean dialysis blood flow of ≥300mL/min without need for additional interventions.

2.7.3 Exploratory Endpoints

The following endpoints may be evaluated in an exploratory fashion. Data will be collected throughout the course of the investigation in support of this endpoint.

- Kit Component Safety and Performance, defined as the overall rate of the catheter's procedure kit component complications from time of procedure to discharge.

2.8 Acceptance Criteria

The Pristine™ Catheter will be considered as non-inferior to the competitor control devices if the following conditions are met:

The one-sided p-value is less than 0.025 with a 5 complications per 1000 patient days non-inferiority margin and a performance goal (PG) of 36.5 events per 1000 patient days.

3 Intended Statistical Software and Data Information

3.1 Intended Statistical Software

All data processing, summarization, and analyses will be performed using Statistical Analysis System (SAS), Version 9.4 software package.

3.2 Data Information

The input data will consist in several SAS files prepared by the Statistical Programming group and saved in H:\BDPI\BDPI21001-Pristine\Final\Data on SAS server.

4 Analysis Population Set(s)

4.1 Population Definitions

The following populations are defined:

Table 2: Analysis Population List

Population	Description
Enrolled	All participants who sign the ICF will be classified as enrolled.
Intent-to-Treat (ITT)	The ITT population will consist of all participants who have signed the ICF, met all inclusion/exclusion criteria, and had the procedure initiated. The ITT population includes the following three groups on the Subject Disposition CRF page: Eligibility met but device not inserted, Device inserted but subject did not undergo first dialysis session, and Treated with study device.
Modified Intent-to-Treat (mITT)	The mITT population will consist of all ITT participants treated with the study device. The mITT population includes subject treated with study device on the Subject Disposition CRF page.
Per-Protocol (PP)	A PP population may be created if there are participants who have any major deviations. The PP population will consist of any participants in the mITT population who do not have any major deviations. The deviations that are considered to have a "major" grade will be identified and summarized in Appendix 3 prior to data analyses.

All endpoints will be analyzed primarily based on the mITT population and ITT population where applicable. PP analyses may also be performed for the primary endpoints and will only serve as sensitivity analyses.

5 Statistical Analysis/Calculations

5.1 Derived Variables

Time to event= event date-procedure date

Note: Event can be an adverse event, an abandonment, a re-intervention etc.

5.2 Primary Endpoints

5.2.1 Definition

Primary Endpoint is the overall rate of infectious complications and non-infectious complications requiring revision to maintain patency and improve access performance at 3 months.

Infectious Complications

Complications due to any documented diagnosis of access infection requiring medical intervention (managed in an outpatient or inpatient setting) or sepsis as diagnosis in the hospitalization file whether access related or not.

Subject will be considered as having an infectious complication and will be counted as an event if the subject has experienced a device-related infection prior to the subject's end day of investigation period:

- **AE CRF Page**: Start Date of AE ≤ End Day of Investigation period **AND** Relationship to study Device: Equals 'Related' or 'Likely Related' **AND** Was event infectious: Equals Yes; subject will be considered as a failure at AE start date

Non-infectious complications

Complication due to any noninfectious cause (thrombosis of the access, fibrin material within or around a catheter, catheter migration, central vein stenosis or thrombosis) requiring a revision procedure to maintain patency or improve access performance (i.e., thrombolysis, angioplasty, or surgical correction) in an inpatient or outpatient setting or removal or abandonment with creation of a new access that was not due to an access-related infection.

Subject will be considered as having a non-infectious complication and will be counted as an event if the subject has experienced a device-related non-infectious AE resulting in a re-intervention prior to the subject's end day of investigation period:

- **AE CRF Page**: Start Date of AE ≤ End Day of Investigation period **AND** Relationship to study Device: Equals 'Related' or 'Likely Related' **AND** Was event infectious: Equals No **AND** Did AE Result in a Catheter Re-Intervention: Equals Yes; subject will be considered as a failure at AE start date

For each subject, the number of complications through the investigational duration is estimated as:

((Number of observed infectious complications+ Number of observed non-infectious complications) * 1000) / Length of investigation duration (Days)

Length of investigation duration (Days) is from the date of index procedure to the end day of each subject's investigation period (End day of investigation period – Date of index procedure + 1); the end day of investigational period will be the earliest occurrence date of the following three events:

- If a subject's Pristine™ Catheter is removed due to Kidney Transplant, Transferred to AVG/AVF, Peritoneal Dialysis, Withdrawal of Care, or Other reasons, then the date of removal will be used to calculate the length of investigation duration. That is:
  - ***Hemodialysis Catheter Re-Interventions CRF page****: Catheter removal Equals Yes AND Reason for catheter removal Equals: Kidney Transplant, Transferred to AVG/AVF, Peritoneal Dialysis, Withdrawal of Care, or Other; date of re-intervention is used in the estimation of investigation duration*

  Length of investigation duration (Days) = Removal date – date of index procedure +1

- If a subject discontinues early, then the discontinuation date will be used to calculate the length of investigation duration.

  Length of investigation duration (Days) = Discontinuation Date – Date of index procedure +1

- If the subject has not experienced any of the above events prior to the 3-months visit date, then the 3 months visit date will be used to calculate the length of investigation duration; in case of subject having the 3 months visit out of window and after day 105 or the subject misses the 3 months visit, then day 105 will be the end date of investigational period.

  Length of investigation duration (Days) = min((3 months visit date – date of index procedure +1), 105 days)

The analysis will be performed on the mITT population and repeated with per-protocol population as sensitivity analyses.

5.2.2 Hypothesis Testing

The primary endpoint is the overall rate of infectious complications and noninfectious complications requiring revision to maintain patency and improve access performance at 3 months. Based on the DOPPS study data, competitor control devices had an average incidence rate of 31.5 complications per 1000 patient days. To show noninferiority of the Pristine™ Catheter, a 5 complications per 1000 patient days non-inferiority margin is used to establish a performance goal (PG) of 36.5 events per 1000 patient days.

The Primary Patency endpoint will be evaluated by the following hypothesis:

H_0: The complication rate through 3 month is greater than or equal to 36.5 events per 1000 patients days at 3 months.

H_1: The complication rate through 3 month is less than 36.5 events per 1000 patient days at 3 months.

That is:

H_0: $\lambda \geq \lambda_0$

H_1: $\lambda < \lambda_0$

Where λ_0 is the PG of 36.5 events per 1000 patient days.

A one-sided p-value will be derived based on a Poisson distribution. The Pristine™ Catheter will be considered to have achieved the primary endpoint objective if the one-sided p-value is less than 0.025.

Conditioned on the success of the above test, a superiority test will be conducted to show that the Pristine™ Catheter is superior to the performance goal. The above test will be repeated with a PG of 26.5 events per 1000 patient days.

The analyses of the primary endpoint will be based on the mITT population and repeated with per-protocol population as sensitivity analyses. The analyses will be conducted after the last active treated subject completes their 3-month follow-up. The number of complications per 1000 patient days will be estimated by Poisson regression model with only the intercept term, and the estimate and 95% CI will be provided using the Wald method, and the p-value comparing to the PG will be calculated by a Chi-square test.

5.3 Secondary endpoints

5.3.1 Rate of freedom from catheter-related bloodstream infection (CRBSI) defined by 2019 KDOQI Guidelines for CRBSI.

Binary Analysis

Subject will be considered as having CRBSI for a given visit if the subject has experienced device-related bloodstream infection prior to the upper limit of visit window for the visit:

- **AE CRF Page**: AE start date <= upper limit of the visit window AND Relationship to study Device: Equals 'Related' or 'Likely Related' AND Was event infectious: Equals Yes AND Select Type of Infection: Equals Blood Stream and Were there clinical manifestation and at least 1 positive blood culture with no apparent source: Equals Yes; subject will be considered as a failure at the AE date

If the subject has not become failure and experience one of the following events prior to the lower limit of visit window, then subject will be considered as non-evaluable at the earliest occurrence of following event dates.

- Catheter has been removed due to Kidney Transplant, Transferred to AVG/AVF, Peritoneal Dialysis, Withdrawal of Care, or Other reasons
  Hemodialysis Catheter Re-Interventions CRF page*: Catheter removal Equals Yes AND Reason for*

catheter removal Equals: Kidney Transplant, Transferred to AVG/AVF, Peritoneal Dialysis, Withdrawal of Care, or Other
OR

- Subject has discontinued from the study.

Else subject will be considered as a success (freedom from CRBSI) for a given visit.

The rate of freedom from CRBSI will be reported with 95% confidence interval from the exact binomial method. The analysis will be performed on the mITT population through 1-month, 3-months, 6-months, and 12-months.

Kaplan-Meier (KM) Analysis

KM analysis will be used to estimate the time from the date of index procedure to the first CRBSI event and to determine the rate of freedom from CRBSI at 1-, 3-, 6-, and 12-months. CRBSI is considered as the event.

Subjects that have not reached CRBSI (event) will be censored or considered event free as described below.

- If the subject has experienced following events, subject will be censored at the earliest date of those events.
  - Catheter has been removed due to Kidney Transplant, Transferred to AVG/AVF, Peritoneal Dialysis, Withdrawal of Care, or Other reasons
  - Subject has discontinued from the study.

Note: How to assess the above events has been described in **Error! Reference source not found.**the Binary Analysis section.

- All the other subjects will be considered event free and will be censored on visit day (visit day can vary from lower limit to upper limit of visit window).

This endpoint will be evaluated on the mITT populations through 1-month, 3-months, 6-months, and 12-months.

5.3.2 Rate of freedom from Device and/or Procedure-related adverse events, at 1-month, 3-months, 6-months, and 12-months post-index procedure.

Binary Analysis

Subject will be considered as having device and/or procedure-related adverse events for a given visit if the subject has experienced device and/or procedure-related adverse events prior to the upper limit of visit window for the visit:

- **AE CRF Page**: AE start date <= upper limit of the visit window AND (Relationship to Device: Is 'Related' or 'Likely Related' OR Relationship to Procedure: Is 'Related' or 'Likely Related') ; subject will be considered as a failure at the AE date

If the subject has not become failure and experience one of the following events prior to the lower limit of visit window, then subject will be considered as non-evaluable at the earliest occurrence of following event dates.

- Catheter has been removed due to Kidney Transplant, Transferred to AVG/AVF, Peritoneal Dialysis, Withdrawal of Care, or Other reasons
  - ***Hemodialysis Catheter Re-Interventions CRF page****: Catheter removal Equals Yes AND Reason for catheter removal Equals: Kidney Transplant, Transferred to AVG/AVF, Peritoneal Dialysis, Withdrawal of Care, or Other*

  OR
- Subject has discontinued from the study.

If the subject has experienced any of the above non-evaluable events prior to the lower limit of visit window subject will be counted as a non-evaluable for a given visit. Else subject will be considered as a success (freedom from device and/or procedure-related adverse events) for a given visit.

The rate of freedom from device and/or procedure-related adverse events will be reported with 95% confidence interval from the exact binomial method. The analysis will be performed on the ITT population through 1-month, and mITT population through 1-month, 3-months, 6-months, and 12-months.

KM Analysis

KM analysis will be used to estimate the time from the date of index procedure to the first device and/or procedure-related adverse event and to determine the rate of freedom from CRBSI at 1-, 3-, 6-, and 12-months. Device and/or procedure-related adverse event is considered as the event.

Subjects that have not reached device and/or procedure-related adverse event will be censored or considered event free as described below.

- If the subject has experienced following events, subject will be censored at the earliest date of those events.
  - Catheter has been removed due to Kidney Transplant, Transferred to AVG/AVF, Peritoneal Dialysis, Withdrawal of Care, or Other reasons
  - Subject has discontinued from the study.

Note: How to assess the above events has been described in **Error! Reference source not found.**the Binary Analysis section.

- All the other subjects will be considered event free and will be censored on visit day (visit day can vary from lower limit to upper limit of visit window).

This endpoint will be evaluated on the mITT population through 1-month, 3-months, 6-months, and 12-months. This endpoint may be evaluated for ITT population through 1-month.

5.3.3 *Rate of Technical Success,* defined as the successful placement of the Pristine™ Long-Term Hemodialysis Catheter, as assessed by the Investigator during the Index Procedure.

Subject will be considered as having technical success if the subject has experienced successful placement of the catheter at the intended site during the procedure:

- **Procedure Overview Part-1 CRF Page**: Was there successful placement at the intended site of the Pristine™ Long-Term Hemodialysis Catheter: Equals Yes

The rate of technical success will be reported with 95% confidence interval from the exact binomial method. The analysis will be performed on the ITT population.

5.3.4 *Overall Participant Survival Rate* at 1-month, 3-months, 6-months, and 12-months post-index procedure, defined as the proportion of participants that have not died from any catheter related complication.

Binary Analysis

Subject will be considered as a failure of the endpoint for a given visit if the subject has experienced the death due to a catheter-related complication prior to the upper limit of visit window for the visit:

- **Disposition-End of Study CRF Page:** Date of Death <= upper limit of the visit window AND **AE CRF Page**: Relationship to Device: Is 'Related' or 'Likely Related' AND Does the Event Meet the Definition of an SAE: Is Yes AND Results in Death: Is Yes and subject will be considered as a failure at the Death date

If the subject has not become failure and experience one of the following events prior to the lower limit of visit window, then subject will be considered as non-evaluable at the earliest occurrence of following event dates.

- Catheter has been removed due to Kidney Transplant, Transferred to AVG/AVF, Peritoneal Dialysis, Withdrawal of Care, or Other reasons
  - ***Hemodialysis Catheter Re-Interventions CRF page****: Catheter removal Equals Yes AND Reason for catheter removal Equals: Kidney Transplant, Transferred to AVG/AVF, Peritoneal Dialysis, Withdrawal of Care, or Other*

  OR
- Subject has discontinued from the study.

If the subject has experienced any of the above non-evaluable events prior to the lower limit of visit window subject will be counted as a non-evaluable for a given visit. Else subject will be considered as a success of the endpoint for a given visit.

The overall participant survival rate will be reported with 95% confidence interval from the exact binomial method. The analysis will be performed on the mITT population through 1-month, 3-months, 6-months, and 12-months.

KM Analysis

KM analysis will be used to estimate the time from the date of index procedure to the date of death and to determine the overall participant survival rate at 1-, 3-, 6-, and 12-months. Catheter-related death is considered as the event.

Subjects that have not reached catheter-related death (event) will be censored or considered event free as described below.

- If the subject has experienced following events, subject will be censored at the earliest date of those events.
  - Catheter has been removed due to Kidney Transplant, Transferred to AVG/AVF, Peritoneal Dialysis, Withdrawal of Care, or Other reasons
  - Subject has discontinued from the study.

Note: How to assess the above events has been described in **Error! Reference source not found.**the Binary Analysis section.

- All the other subjects will be considered event free and will be censored on visit day (visit day can vary from lower limit to upper limit of visit window).

This endpoint will be evaluated on the mITT population through 1-month, 3-months, 6-months, and 12-months.

5.3.5 *Overall Catheter Survival Rate* at 1-month, 3-months, 6-months, and 12-months post-index procedure, defined as the proportion of Pristine™ Catheters that have not been removed for any cause.

Binary Analysis

Subject will be considered as a failure of the endpoint for a given visit if the subject has the catheter removed due to infection or catheter dysfunction prior to the upper limit of visit window for the visit:

- **Hemodialysis Catheter Re-interventions CRF Page**: Date of Re-Intervention: <= upper limit of the visit window AND Reason for catheter removal: Equals Infection/Catheter Dysfunction); subject will be considered as a failure at the re-intervention date

If the subject has not become failure and experience one of the following events prior to the lower limit of visit window, then subject will be considered as non-evaluable at the earliest occurrence of following event dates.

- Catheter has been removed due to Kidney Transplant, Transferred to AVG/AVF, Peritoneal Dialysis, Withdrawal of Care, or Other reasons
  - ***Hemodialysis Catheter Re-Interventions CRF page****: Catheter removal Equals Yes AND Reason for catheter removal Equals: Kidney Transplant, Transferred to AVG/AVF, Peritoneal Dialysis, Withdrawal of Care, or Other*

  OR
- Subject has discontinued from the study.

If the subject has experienced any of the above **non-evaluable** events prior to the lower limit of visit window subject will be counted as a non-evaluable for a given visit. Else subject will be considered as a success of the endpoint for a given visit.

The overall catheter survival rate will be reported with 95% confidence interval from the exact binomial method. The analysis will be performed on the mITT population through 1-month, 3-months, 6-months, and 12-months.

KM Analysis

KM analysis will be used to estimate the time from the date of index procedure to the date of catheter removal due to infection or catheter dysfunction and to determine the overall catheter survival rate at 1-, 3-, 6-, and 12-months. Catheter removal due to infection or catheter dysfunction is considered as the event.

Subjects that have not reached catheter removal due to infection or catheter dysfunction (event) will be censored or considered event free as described below.

- If the subject has experienced following events, subject will be censored at the earliest date of those events.
  - Catheter has been removed due to Kidney Transplant, Transferred to AVG/AVF, Peritoneal Dialysis, Withdrawal of Care, or Other reasons
  - Subject has discontinued from the study.

Note: How to assess the above events has been described in **Error! Reference source not found.**the Binary Analysis section.

- All the other subjects will be considered event free and will be censored on visit day (visit day can vary from lower limit to upper limit of visit window).

This endpoint will be evaluated on the mITT population through 1-month, 3-months, 6-months, and 12-months.

5.3.6 *Overall Patency Rate,* at 1-month, 3-months, 6-months, and 12-months post-index

procedure, defined as the Pristine™ catheter having the ability to achieve a mean dialysis blood flow of ≥300mL/min without need for additional interventions

Binary Analysis

Subject will be considered as loss of overall patency if subject has experienced one of the following events:

- Subject undergoes re-intervention and re-intervention date is after the first dialysis session date
    - **Hemodialysis Catheter Re-Interventions CRF**: Date of Re-intervention > **Procedure Overview Details-Part 2 CRF**: Date of first dialysis session and subject will be considered as a failure at re-intervention date
- Subject has not been able to maintain the patency since last visit
    - **Most Recent Dialysis Session Blood Flow Rate CRF**: Was the catheter able to maintain patency since the last visit (Have the ability to achieve a mean dialysis blood flow of >= 300mL/min)? No . The subject will be considered as a failure at Catheter Dysfunction Date

The subject will become a failure at the earlier occurrence of the above two events. If the subject has lost the overall patency prior to the upper limit of visit window subject will be counted as a failure for a given visit.

If the subject has not become failure and experience one of the following events prior to the lower limit of visit window, then subject will be considered as non-evaluable at the earliest occurrence of following event dates.

- Catheter has been removed due to Kidney Transplant, Transferred to AVG/AVF, Peritoneal Dialysis, Withdrawal of Care, or Other reasons
  Hemodialysis Catheter Re-Interventions CRF page*: Catheter removal Equals Yes AND Reason for catheter removal Equals: Kidney Transplant, Transferred to AVG/AVF, Peritoneal Dialysis, Withdrawal of Care, or Other*
  OR
- Subject has discontinued from the study.

If the subject has experienced any of the above **non-evaluable** events prior to the lower limit of visit window subject will be counted as a non-evaluable for a given visit; else subject will be considered as a success for a given visit.
The overall patency rate will be reported with 95% confidence interval from the exact binomial method. The analysis will be performed on the mITT population through 1-month, 3-months, 6-months, and 12-months.

KM Analysis

KM analysis will be used to estimate the time from the date of index procedure to the date of overall patency loss and to determine the overall patency rate at 1-, 3-, 6-, and 12-months. The loss of overall patency is considered as the event.

Subjects that have not reached overall patency loss (event) will be censored or considered event free as described below.

- If the subject has experienced following events, subject will be censored at the earliest date of those events.

- Catheter has been removed due to Kidney Transplant, Transferred to AVG/AVF, Peritoneal Dialysis, Withdrawal of Care, or Other reasons
- Subject has discontinued from the study.

Note: How to assess the above events has been described in **Error! Reference source not found.**the Binary Analysis section.

- All the other subjects will be considered event free and will be censored on visit day (visit day can vary from lower limit to upper limit of visit window).

This endpoint will be evaluated on the mITT population through 1-month, 3-months, 6-months, and 12-months.

5.4 Exploratory endpoints

The following endpoint may be evaluated in an exploratory fashion. Data will be collected throughout the course of the investigation in support of this endpoint.

Kit Component Safety and Performance, defined as the overall rate of the catheter's procedure kit component complications from time of procedure to discharge.

Subject will be considered as having a catheter's procedure kit component complication if the following event occurs:

- **Procedure Overview Part 1 CRF Page**: Were there any complications with any of the kit components: Equals Yes

The rate of catheter's procedure kit component complications with 95% confidence interval from the exact binomial method will be presented. All ITT subjects would be considered as evaluable for this endpoint and used in the denominator of rate estimation.

6 Summary of General Study Data

6.1 Subject Disposition

Subject disposition data is collected on the 'Subject Disposition' and 'Disposition – End of Study' CRF pages.

The summary of the number of subjects enrolled, screen failure, device inserted but subject did not undergo first dialysis session, treated with study device, eligibility met but device not inserted, eligibility met but procedure not initiated, completed the study, and discontinued from the study by reason of discontinuation will be provided. Screen failures will be summarized for each inclusion/exclusion criteria that were not met.

6.2 Protocol Deviations

The number of subjects with protocol deviations will be summarized with descriptive statistics by nature of the deviation. The major or minor deviations will be identified and classified as in Appendix 3 prior to data analyses of major reportings.

6.3 Demographics and Baseline Variables

Demographics and baseline characteristics will be summarized with descriptive statistics using the ITT population. Summary statistics for categorical variables will include frequency counts and percentages and for continuous variables will include mean, standard deviation, minimum, median, and maximum.

Demographics and baseline characteristics variables include:

- Age at screening (year)
- Sex (Male, Female)
- Race (American Indian or Alaskan Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Not Reported, and Unknown)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino, Not Reported, and Unknown)
- Baseline Weight
- Baseline Height
- Baseline Body mass index (BMI) calculated from weight and height.

Background disease characteristics including medical history and dialysis history will also be summarized.

6.4 Follow-up Visit Summary

Follow-up visit summary and listing will be presented for mITT population.

6.5 Index Procedure

Procedure overview details will be summarized for ITT population.

6.6 Hemodialysis Catheter Assessment

Summary of hemodialysis catheter assessments will be presented for mITT population at 1-, 3-,6-, 12- months. In the listing, assessments done at unscheduled visits will also be presented.

6.7 Most Recent Dialysis Session Blood Flow Rate

Dialysis session blood flow rates reported in scheduled and unscheduled visits will be presented in a listing for mITT population.

6.8 Hemodialysis Catheter Re-Interventions

Hemodialysis catheter re-interventions will be summarized for mITT population.

6.9 Device Deficiencies

All device deficiencies will be summarized by the failure code.

7 Safety Analysis

Collection of AEs will begin immediately following subject enrollment, during the index procedure through final subject follow-up visit or early termination.

An overall summary including the number and percentage of subjects with at least one AE, total number of AEs, total number of SAEs, total number of UADEs, AEs by relationship to the Device/Index Procedure, and AEs by severity of the event will be summarized for the ITT subjects. In addition, the following summary tables will be provided:

- Number of AEs by System Organ Class (SOC) and Preferred Terms (PT)
- Number of SAEs by System Organ Class (SOC) and Preferred Terms (PT)
- Number of AEs by relationship to Study Device by System Organ Class (SOC) and Preferred Terms (PT)
- Number of AEs by relationship to Procedure by System Organ Class (SOC) and Preferred Terms (PT)
- Number of AEs by severity by System Organ Class (SOC) and Preferred Terms (PT)

Listing of all AEs, SAEs, ADE, and UADEs will be provided.

8 Interim Analysis Plan

An interim analysis will be conducted after all eligible patients have completed their 3-months follow-up visit. The Primary endpoint of combined complications will be analyzed and reported. Secondary endpoints will be reported with descriptive statistics.

9 SAP Revision History

Version Number	Rationale for Change	Section or Page Affected	Description of Change
1.0	Original SAP		

10 Appendix

Appendix 1.1 Tables/Listing/Figures Shell for 3-Month Reporting

Appendix 1.2 Tables/Listing/Figures Shell for Final Reporting

Appendix 2 Derived Data Specification

Appendix 3 Deviations: Major/Minor Classification