Statistical Analysis Plan

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List of Abbreviations

ADE	Adverse Device Effect
AE	Adverse event
BD	Becton Dickinson and Company
BSI	Blood Stream Infection
CE	Certification Mark
CI	Confidence Interval
CLABSI	Central Line Associated Blood Stream Infection Defined as a primary BSI with use of a central vascular catheter in the 48 hours (two days) before the onset of the infection
CRBSI	Catheter-related Bloodstream Infection Defined as the presence of bacteremia originating from an intravenous catheter. [1]
CRF	Case Report/Record Form
CSA	Clinical Study Agreement
CV	Curriculum Vitae
DEHP	Diethylhexyl Phthalate
DMP	Data Management Plan
EDC	Electronic Data Capture
EEA	European Economic Area
EU	European Union
FDA	Food and Drug Administration
FDAAA	FDA Amendments Act of 2007
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IFU	Instructions for Use
IPA	Isopropyl Alcohol
IRB/EC	Institutional or Independent Review Board/Ethics Committee
IV	Intravenous
NDA	Non-disclosure Agreement
PI	Principal Investigator
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SIV	Site Initiation Visit
TMF	Trial Master File
UADE	Unexpected Adverse Device Effect
USADE	Unexpected Serious Adverse Device Effect
VAD	Vascular Access Device

1 Introduction

1.1 Background and Rationale

This study is designed to provide data utilizing the Becton Dickinson (BD) PureHub™ Disinfecting Cap for the purpose of providing clinical data required under European Union (EU) regulation 2017/745.

1.2 Objectives and Endpoints

Objectives	Endpoints
Primary Efficacy Objective	
To assess the rate of select performance measures of the BD PureHub™ Disinfecting Caps on swabbable needle-free connectors when used in a clinical environment.	▪ Attachment success rate of the BD PureHub™ Disinfecting Caps to a needle-free connector (successful attachment/ total number of attachments) ▪ Removal success rate of the BD PureHub™ Disinfecting Caps to a needle-free connector (successful removal/ total number of intended removals)
Primary Safety Objective	
To assess the incidence of BD PureHub™ Disinfecting Cap device-related adverse events.	▪ Rate of device-related adverse events
Informative Objectives	
To assess the frequency of BD PureHub™ Disinfecting Cap use To summarize the purposes for removal of the BD PureHub™ Disinfecting Cap from the needle-free connector To summarize the incidence of blood stream infection	▪ The number of BD PureHub™ Disinfecting Caps used per day/per study participant ▪ The purpose for each intended removal of the BD PureHub™ Disinfecting Cap from the needle-free connector ▪ Incidence of central line associated bloodstream infection (CLABSI) ▪ Incidence of bloodstream infections

2 Study Description

2.1 Study Design

This is a multi-center, single-arm, prospective post-market study that will enroll up to 175 participants in order to have 150 evaluable participants who have vascular access devices as part of their routine medical care. Data related to the safety and performance of the BD PureHub™ Disinfecting Cap will be captured when used as intended.

Participants will be screened against eligibility criteria and will be considered enrolled once the informed consent document is signed. Each study participant will have a BD PureHub™ Disinfecting Cap attached to each eligible needle-free connector to one or more VADs by a clinician. Clinicians will then be advised to place subsequent BD PureHub™ Disinfecting Caps as per the Instructions for Use through the course of the participant's IV therapy. During this time, attachment and removal success will be captured, as well as any device-related adverse events (AEs).

Participants will be followed from the time of enrollment until one week post VAD therapy, department/hospital discharge or 45 days post enrollment date, whichever comes first. Participants, with a VAD in place, who will be discharged from the hospital, but return regularly for catheter access to the site will remain in the study, either until the 45 days are reached or the VAD therapy is ended. If the catheter access will not be performed at the clinical trial site, the participant cannot continue in the study.

2.2 Study Population

Participants will be recruited from the patient population treated at the investigational sites. The inclusion/exclusion criteria are described in the protocol Section 5.

2.3 Randomization and Blinding

This is a single-arm study and randomization is not applicable.

2.4 Sample Size

Assuming the primary endpoints of successful insertion rate and successful removal rate are each 90%, a sample size of 150 participants with only 1 insertion/removal observed per participant would result in a 4.8% precision for each point estimate (i.e., the 95% confidence interval is the point estimate ±4.8%, using a simple asymptotic approach for confidence interval of one proportion). The precision margin will tighten as the number of line access per participant increases, for example, with an average of 4 insertions/removals per participant, the precision would be ±2.4%.

Additionally, with a sample size of 150, the probability of observing at least one rare AE/complication with a 1% rate (per participant) is 78% and the probability of observing at least one rare AE/complication with a 2% rate (per participant) is 95%.

2.5 Interim Analyses

No interim analysis is planned for the study.

2.6 Study Procedure

Participants will be screened against eligibility criteria and will be considered enrolled once the informed consent document is signed. Each study participant will have a BD PureHub™ Disinfecting Cap attached to each eligible needle-free connector to one or more VADs by a clinician. Clinicians will then be advised to place subsequent BD PureHub™ Disinfecting Caps as per the Instructions for Use through the course of the participant's IV therapy. During this time, attachment and removal success will be captured, as well as any device-related adverse events (AEs).

Participants will be followed from the time of enrollment until one week post VAD therapy, department/hospital discharge or 45 days post enrollment date, whichever comes first. Participants, with a VAD in place, who will be

discharged from the hospital, but return regularly for catheter access to the site will remain in the study, either until the 45 days are reached or the VAD therapy is ended. If the catheter access will not be performed at the clinical trial site, the participant cannot continue in the study.

2.7 Endpoints

Refer to Section 1.2.

2.8 Acceptance Criteria

There are no acceptance criteria for the study device.

3 Intended Statistical Software and Data Information

3.1 Intended Statistical Software

All the analyses will be performed using Statistical Analysis System (SAS) Version 9.4 or above or R.

3.2 Data Information

Derived data specification will be finalized prior to reporting.

4 Analysis Population Set(s)

4.1 Population Definitions

Enrolled: All participants who sign the ICF.

Evaluable: All enrolled participants who have at least 1 BD PureHub™ Disinfecting Cap applied.

5 Statistical Analysis/Calculations

5.1 Primary Performance Endpoints

The primary performance endpoints are:

- Attachment success rate of the BD PureHub™ Disinfecting Caps to a needle-free connector
- Removal success rate of the BD PureHub™ Disinfecting Caps to a needle-free connector

The attachment success will be performed on enrolled population with non-missing data on PureHub Initial Placement CRF page. The removal success will be performed on evaluable population.

If the clinician can successfully attach the first BD PureHub™ Disinfecting Cap, it is considered as attachment success. Attachment success will be based on count of "Yes" responses to the following fields in the CRF pages:

- PureHub Initial Placement page, Attachment success is "Yes"
- PureHub Maintenance page, Attachment success is "Yes"

The attachment success rate will be computed as the number of successful attachments divided by the total number of attachments. The total number of attachments can be calculated using the following CRF pages:

- PureHub Initial Placement page, Attachment success is "Yes" or "No"

- PureHub Maintenance page, Attachment success is “Yes” or “No”.

The removal success rate will be computed as the number of successful removals divided by the total number of removals.

Removal success will be based on counts of “Yes” response to “Removal success” question in the “PureHub Maintenance” CRF page. Total number of intended removals will be based on the number of times the “Removal Success” response is chosen (regardless of “Yes” or “No”).

95% confidence interval will be calculated for both rates using the Clopper-Pearson exact method.

5.2 Primary Safety Endpoints

The primary safety endpoint is the rate of device-related adverse events. It will be calculated as the number of participants with adverse events related to device divided by total number of participants. Adverse events related to device is determined by the responses to “Relationship to study device” on the “Adverse Events” log form:

- Likely Related
- Related

95% confidence interval will be calculated using Clopper-Pearson exact method. The analysis will be performed on the enrolled population.

5.3 Informational Endpoint(s)

The informational endpoints are:

- The number of BD PureHub™ Disinfecting Caps used per day/per study participant
- The purposes for each intended removal of the BD PureHub™ Disinfecting Cap from the needle free connector
- Incidence of central line associated bloodstream infection (CLABSI)
- Incidence of bloodstream infections

The calculation of number of PureHub caps used per day will be total number of caps used (including the ones attempted but didn’t attach) divided by number of days participants were in VAD therapy. If multiple VADs were removed, number of days will be last VAD removal date – PureHub initial placement date. If at least one VAD is not removed, the number of days will be the minimum of study duration (participant end of study date – PureHub initial placement date) and 45 days. The number of caps used will be from the following CRF pages:

- PureHub Initial Placement page, Number of caps used
- PureHub Maintenance page, Number of caps used

The purposes of removal of the BD PureHub™ Disinfecting Cap are identified on “PureHub Maintenance” log in response to “Removal reason” question. The percentage of each response will be provided, and the denominator will be the total number of intended removals.

Incidence of bloodstream infections can be identified on the CRF “Adverse Events” log form. If response to “In case of bloodstream infection, how was it confirmed” is not “Blood Stream Infection Not Present”, then subject had a bloodstream infection.

Central line associated bloodstream infection can be identified if the response to “Is the bloodstream infection central-line associated” is “Yes” on the CRF “Adverse Events” log form.

The analysis will be performed on the evaluable population. Descriptive statistics for the informational endpoints will be provided. Summary statistics for categorical variables will include frequency counts and percentages and for continuous variables will include mean, standard deviation, minimum, median, and maximum.

6 Summary of General Study Data

6.1 Subject Disposition

The summary of the number of subjects in the enrolled population, evaluable population, as well as those that completed the study, and withdrew from the study with reason for withdrawal will be provided. Screen Failures will be summarized for each inclusion/exclusion criteria that was not met. Summary table will also be provided by site.

6.2 Protocol Deviations

A protocol deviation is defined as an event where the Investigator or site personnel did not conduct the study according to the protocol requirements. Any and all protocol deviations must be documented regardless of whether medically justifiable, Sponsor-approved or taken to protect the subject in an emergency.

Details regarding protocol deviations will be listed for evaluable population.

6.3 Demographics and Baseline Variables

Demographics and baseline characteristics will be summarized with descriptive statistics for enrolled population. Summary statistics for categorical variables will include frequency and percentages, and for continuous variables will include mean, standard deviation (SD), minimum, median, and maximum.

The demographic variables will include:

- Age (at signing informed consent)
- Sex
- Race

6.4 Medical History/Baseline Assessments

Medical history including diagnosis for current admission and reported term for medical history will be tabulated and presented at participant-level for enrolled population.

Summary of baseline assessments includes:

- Type of VADs to be assessed per study participant
- VAD placement site location
- Number of lumens
- Type of dressing/securement
- Type and number of needle-free connector(s)
- Type and number of intravenous tubing/ extension set(s)
- Type and number of other add-on devices i.e. valves, stop cocks

6.5 Follow-up Visit Summary

Follow-up visit summary will be presented for the evaluable population.

6.6 Device Deficiency

Device deficiencies will be tabulated and presented on participant level for evaluable population. Details regarding device deficiencies will be listed.

7 Safety Analysis

An AE is defined as any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in participants, users or other persons, whether or not related to study device and whether anticipated or unanticipated (ISO 14155:2020). In this study, AE collection will be limited to those events judged to be related or likely related to the BD PureHub™ Disinfecting Cap and any events of bloodstream infection, including central line associated bloodstream infections (as defined in the List of Abbreviations).

An overall summary including the number and percentage of subjects with at least one AE, total number of AEs, total number of SAEs, AEs by relationship to the Study Device/Procedure, and AEs by severity of the event will be summarized for the enrolled population. In addition, AEs will be summarized by System Organ Class (SOC) and Preferred Term (PT):

- Number of AEs by SOC and PT
- Number of SAEs by SOC and PT
- Number of AEs by relationship to study device/procedure
- Number of AEs by severity by SOC and PT

A listing of all AEs, SAEs and UADEs will be provided for the enrolled population. An UADE is identified if answer to the question “Is the event expected” on the Adverse Events CRF page is “No”.

8 Interim Analysis Plan

No interim analysis is planned for the study.

9 References

None.

10 SAP Revision History

Version Number	Rationale for Change	Section or Page Affected	Description of Change
1.0	Original SAP		
2.0	Amendment	Section 5.3, page 8	Updated methodology for calculating number of caps per day
3.0	Amendment	Section 5.3, page 8	Updated methodology for calculating number of caps per day. The number of days for subject in study will be capped at 45 days.

11 Appendix

Appendix 1 Tables/Listing/Figures Shell for Final Reporting