TITLE PAGE

Protocol Title: A Post-Market Clinical Follow Up Study to Evaluate BD PureHub™ Disinfecting Cap Use on Needle-Free Connectors

Protocol Number: MDS-20PUREU001

Version Number: 2.5 PMCF – AT01

Study Device: BD PureHub™ Disinfecting Cap

Study Type: Post-Market Clinical Follow-up Study

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Version History

Version Number	Date	Type	Section	Change
1.0	04-Jun-2021	Initial release	N/A	N/A
1.1	30-Nov-2021	Local amendment: **Only applicable for UK**	N/A	No change for V2.3
1.2	21-Jan-2022	Local amendment: **Only applicable for Spain**	N/A	No change for V2.3
2.0	28-Feb-2022	**Local Amendment** PMCF – provision of study devices: Changing study from Observational to Interventional; reduction minimum VAD Therapy period	• Header Section • Sponsor Protocol Approval • Throughout the document • Synopsis – Participants • Synopsis • Section 2.3.1 Risk Assessment • Section 2.3.2 Benefit Assessment • Section 2.3.3 Overall Benefit: Risk Conclusion • Section 5.1 Inclusion Criteria	• Protocol Title: Change from "Observation" to "Post-Market Clinical Follow Up" Study • Change of Statistician • Reference to "observational" changed • Inclusion criterion 2: Expected minimum VAD therapy reduced from 7 to 3 days • Addition of anticipated study timelines • Adjustment of risk section to PMCF with interventional element • Adjustment of risk section to PMCF with interventional element, addition of clinical benefits • Adjustment of risk section to PMCF with interventional element • Inclusion criterion 2: Expected minimum VAD therapy reduced from 7 to 3 days • Information added • Information added

Version Number	Date	Type	Section	Change
			• Section 6.4 Device Labeling • Section 6.5 Treatment Allocation and measures to minimize bias • Section 7.1 Study duration • Section 9.1.1. Adverse Events • Section 11.5 Device accountability • Section 12.1 Control of Study products	• Updated timelines • "Procedure" added to AE definition • Information added • Clarification that Sponsor will provide marketed products as study devices
V2.1	15-Mar 2022	Local amendment: **Only applicable for BE**	• N/A	• Local Amendment BE01 – Not applicable for this version
V2.2	30-May 2022	Local amendment: **Only applicable for ES01**	• N/A	• Local Amendment ES01 – Not applicable for this version
V2.3	13JUL2022	Local Amendment: **Only applicable for ES02**	• Sponsor Protocol Approval • Synopsis & Section 5.2 – Exclusion Criteria	• Change of medical monitor, medical affairs representative, and statistician • Change of exclusion criterion 1 to allow for disinfecting cap placement within 12 hours prior to ICF signature
V2.4	11OCT2022	Local Amendment: **Only applicable for ES02**	• Sponsor Contact Details • Protocol • Section 7.1	• Update of Clinical Project Manager • Update of Format • Updated timelines

Version Number	Date	Type	Section	Change
V2.5	01DEC2022	Local Amendment: **Only applicable for AT01**	• Abbreviations • Inclusion criteria (Synopsis & Section 5.1) • Synopsis	• Update on Abbreviations • For AT01 LAR is not applicable • Update on Timelines & Investigational Sites

SPONSOR PROTOCOL APPROVAL

Signature below indicates approval of the protocol as written.

Individual or function	Name	Signature & Date
Business Unit Medical Affairs Medical Monitor	Klaus Hoerauf, MD, VP Medical Affairs, MDS	DocuSigned by: Klaus Hoerauf Signer Name: Klaus Hoerauf Signing Reason: I approve this document Signing Time: 05-Dec-2022 | 2:47:04 AM PST B5FBD0548E024978A2DD4D4C31387807 05-Dec-2022
Business Unit Medical Affairs	Kyle De Boer Ass. Director, Medical Affair	DocuSigned by: Signer Name: Kyle De Boer Signing Reason: I approve this document Signing Time: 05-Dec-2022 | 10:50:39 AM PST 410A0600E85445E0A128BBF68109C444 05-Dec-2022
Business Unit Regulatory Affairs	John Roberts Director, Regulatory Affairs, MDS	DocuSigned by: John W Roberts Signer Name: John W Roberts Signing Reason: I approve this document Signing Time: 07-Dec-2022 | 6:36:05 AM PST 8B97BB78BFBD4856ABBFB5B27C5A103E 07-Dec-2022
Global Clinical Development Clinical Operations	Stephan Hofmann Senior Clinical Project Manager, GCA	DocuSigned by: Signer Name: Stephan Hofmann Signing Reason: I approve this document Signing Time: 05-Dec-2022 | 12:54:43 AM PST 1CB1EEAF1E1A44D5AF29E7DECBB1D202 05-Dec-2022
Global Clinical Development Statistics	Minyi Ji Principal Statistician Statistics & Clinical Data, GCA	DocuSigned by: Minyi Ji Signer Name: Minyi Ji Signing Reason: I approve this document Signing Time: 05-Dec-2022 | 9:07:18 AM PST 75ABF8366EA849459E73690FD414E192 05-Dec-2022

PRINCIPAL INVESTIGATOR AGREEMENT PAGE

Investigator Responsibilities

1. Prior to participation in this study, the Investigator or Institution must sign the Clinical Study Agreement (CSA) and obtain written approval from the appropriate Institutional Review Board (IRB)/Ethics Committee (EC).
2. The Investigator must receive BD-sponsored training prior to site activation. The Investigator is responsible for ensuring that all Sub-Investigators and clinical staff are adequately trained prior to performing any data collection or study-related procedures.
3. The Principal Investigator shall ensure that the study is conducted in accordance with the study protocol, any modifications as requested by the IRB/EC, the signed CSA, the ethical principles of the Declaration of Helsinki, Good Clinical Practice (ICH E6) / ISO 14155, EU MDR (Council Regulation 2017/745 of 5 April 2017)), and applicable national/regional regulations and laws.
4. If applicable, ensure that written informed consent is obtained from each participant prior to the conduct of any study procedure, using the current IRB/EC approved Informed Consent Form.

I have read and understand the contents of this study protocol. I agree to follow and abide by the requirements set forth in this document. I agree to conduct the trial in accordance with the study protocol, the signed CSA, and Good Clinical Practice (GCP) as well as ISO regulations (e.g., ISO 14155:2020). I agree to participate in BD-Sponsored training prior to performing any data collection or study-related procedures.

Agreed to by (Investigator):

_____

Printed Name – Investigator

_____

Signature – Investigator

_____

Site Number

_____

Date

SUB-INVESTIGATOR AGREEMENT PAGE

Investigator Responsibilities

1. The Sub-Investigator must receive study specific training prior to performing any data collection or study-related procedures.
2. The Sub-Investigator shall conduct the study in accordance with the study protocol, any modifications as requested by the IRB/EC, the signed CSA, the ethical principles of the Declaration of Helsinki, Good Clinical Practice (ICH E6) / ISO 14155, EU MDR (Council Regulation 2017/745 of 5 April 2017)), and applicable national/regional regulations and laws.
3. If applicable, ensure that written informed consent is obtained from each participant prior to the conduct of any study procedure, using the current IRB/EC approved Informed Consent Form.

I have read and understand the contents of this study protocol. I agree to follow and abide by the requirements set forth in this document. I agree to conduct the trial in accordance with the study protocol, the signed CSA, and Good Clinical Practice (GCP) as well as ISO regulations (e.g., ISO 14155:2020). I agree to participate in BD-Sponsored training prior to performing any data collection or study-related procedures.

Agreed to by (Investigator):

_____

Printed Name – Investigator

_____

Signature – Investigator

_____

Site Number

_____

Date

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]
CSA	Clinical Study Agreement
CV	Curriculum Vitae
DEHP	Diethylhexyl Phthalate
DMP	Data Management Plan
eCRF	Electronic Case Report/Record Form
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
LAR	Legal Authorized Representative
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 PROTOCOL SUMMARY

1.1 Synopsis

<table>
<tr><td>Protocol Title</td><td colspan="2">A Post-Market Clinical Follow Up Study to Evaluate BD PureHub™ Disinfecting Cap Use on Needle-Free Connectors</td></tr>
<tr><td>Rationale</td><td colspan="2">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.</td></tr>
<tr><td rowspan="8">Objectives and Endpoints</td><td>Objectives</td><td>Endpoints</td></tr>
<tr><td colspan="2">Primary Efficacy Objective</td></tr>
<tr><td>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.</td><td>■ 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)</td></tr>
<tr><td colspan="2">Primary Safety Objective</td></tr>
<tr><td>To assess the incidence of BD PureHub™ Disinfecting Cap device-related adverse events</td><td>■ Rate of device-related adverse events</td></tr>
<tr><td colspan="2">Informative Objectives</td></tr>
<tr><td>To assess the frequency of BD PureHub™ Disinfecting Cap use</td><td>■ The number of BD PureHub™ Disinfecting Caps used per day/per study participant</td></tr>
<tr><td>To summarize the purposes for removal of the BD PureHub™ Disinfecting Cap from the needle-free connector</td><td>■ The purpose for each intended removal of the BD PureHub™ Disinfecting Cap from the needle-free connector</td></tr>
<tr><td>To summarize the incidence of blood stream infection</td><td>■ Incidence of central line associated bloodstream infection (CLABSI)
■ Incidence of bloodstream infections</td></tr>
</table>

Protocol Title	A Post-Market Clinical Follow Up Study to Evaluate BD PureHub™ Disinfecting Cap Use on Needle-Free Connectors
Design and Overview	A Post-Market Clinical Follow Up Study to Evaluate BD PureHub™ Disinfecting Cap Use on Needle-Free Connectors: This is a multi-center, prospective observational study of a minimum of 150 study participants who have vascular access devices (VADs) with needle-free connectors as part of their routine medical care. Patients will be followed from the time of enrollment through the duration of one week post VAD therapy, department/ hospital discharge if VAD therapy has ended, or 45 days post enrollment date, whichever comes first.
Study Device	BD PureHub™ Disinfecting Cap is comprised of a threaded plastic cap containing a porous pad pre-saturated with 70% Isopropyl Alcohol (IPA) and sealed with a multilayer foil film. BD PureHub™ Disinfecting Caps are intended to be used as a disinfecting device for swabbable needle-free luer connectors prior to access and to act as a physical barrier between line accesses.
Participants	Inclusion Criteria: 1. Has an eligible vascular access device with needle-free connectors in situ or will have one placed Note: This covers all needle-free devices, including central venous catheters, peripheral IV catheters and arterial VADs 2. Is expected to receive VAD therapy for a minimum of 3 days 3. Is expected to be available for regular observation from consent until end of study 4. Able and willing to provide informed consent or legal authorized representative (LAR)* authorized to give consent on behalf of the participant *LAR not applicable for AT01 Exclusion Criteria: 1. BD PureHub™ Disinfecting Cap or any other disinfecting cap in place for more than twelve (12) hours (>12 hours) prior to study participation 2. Presence of any infection, bacteremia, or septicemia is known or suspected 3. Any condition which, in the opinion of the Investigator, precludes the participant from participation in this study

Protocol Title	A Post-Market Clinical Follow Up Study to Evaluate BD PureHub™ Disinfecting Cap Use on Needle-Free Connectors
Intervention(s)/Procedure(s)	The BD PureHub™ Disinfecting Cap will be used for needle-free access of the vascular access device as necessary for each participant from enrollment through one week post VAD therapy, department/ hospital discharge if VAD therapy has ended, or 45 days post enrollment date, whichever comes first. During this time, attachment and removal success will be captured, as well as any device-related adverse events (AEs).
Investigational Sites	Up to 10 sites in the EU will participate in this study.
Data Monitoring Committee	A Data Monitoring Committee will not be used in this study.
Regulatory Status	The BD PureHub™ Disinfecting Cap is currently CE marked and marketed in the EEA under CE certificate 252.1127, CE mark #0050.
Anticipated Study Timelines	The enrollment of the study started on 31JAN2022. Last participant will leave the study approximately in Q2 2023.

Schema

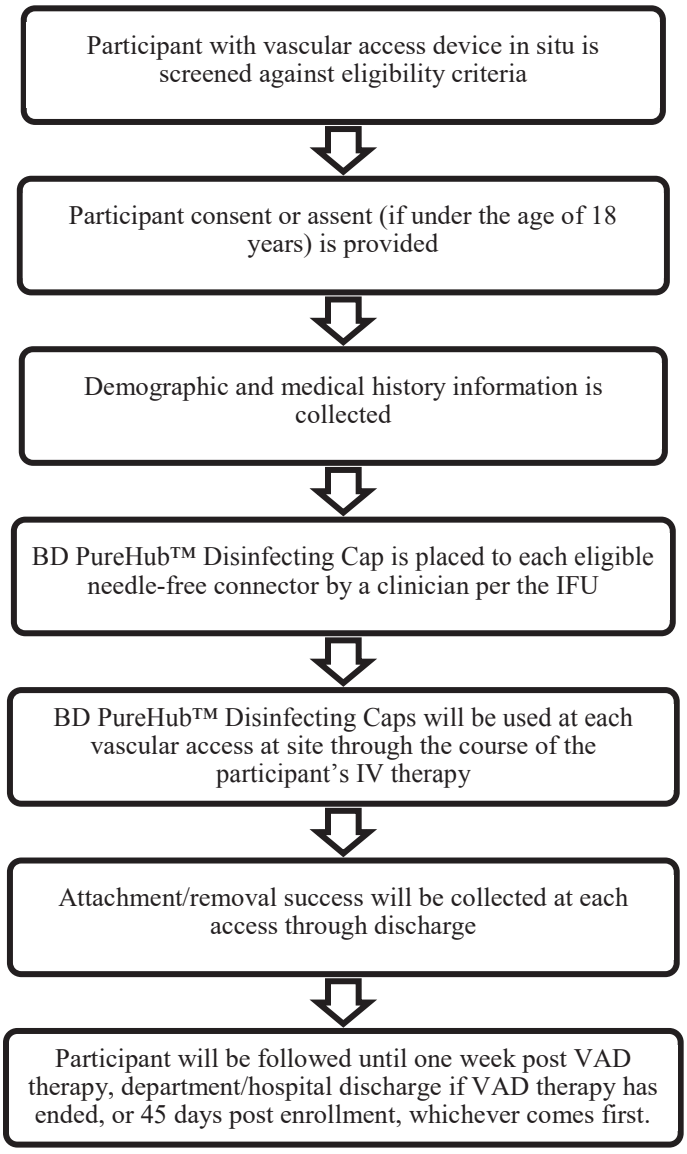
Participant with vascular access device in situ is screened against eligibility criteria
Participant consent or assent (if under the age of 18 years) is provided
Demographic and medical history information is collected
BD PureHub™ Disinfecting Cap is placed to each eligible needle-free connector by a clinician per the IFU
BD PureHub™ Disinfecting Caps will be used at each vascular access at site through the course of the participant's IV therapy
Attachment/removal success will be collected at each access through discharge
Participant will be followed until one week post VAD therapy, department/hospital discharge if VAD therapy has ended, or 45 days post enrollment, whichever comes first.

Table 1 – Schedule of activities

Procedure/Assessment	Baseline	**Initial PureHub Placement[1] Day 0**	**Each day** during VAD Therapy[2]	**7-day Follow Up** after VAD Therapy[4]	**End-of-study** 45-day FU or Department/ Hospital Discharge, whichever comes first[5]
Informed consent process, incl. Informed consent signature date	X				
Inclusion/Exclusion Criteria Check	X				
Patient in-hospital location information	X	(X)[7]	(X)[7]	(X)[7]	
Demographics	X				
Medical History	X				
VAD Information[3]	X	(X)[6]	X		
BD PureHub™ Placement Record number of eligible needle-free connectors per VAD • Placement of PureHub™ Caps • Record number of new caps used and location catheter line per day incl. primary reason for cap replacement • Document Yes or No if able to successfully attach a PureHub™ Disinfecting Cap per needle-free connector for each attachment. • Document number of attachments • Document Yes or No if able to successfully remove the BD PureHub™ Disinfecting Cap from the needle-free connector • Document number of intended removals		X	X		X
Device related Adverse Events assessment		X	X	X	X
Blood stream infection assessment		X	X	X	X
Device deficiency assessment		X	X		

1) Initial PureHub™ Placement can be performed on same day as Baseline, provided ICF has been signed.
2) Multiple Placements of PureHub™ Caps are possible per day
3) VAD Information: At baseline -VAD type, number of VADs, number of lumens per catheter, location of VADs, date of VAD placement, type and number of needle-free connectors per VAD, type of dressing; subsequent visits; type of dressing in case of changes, dressing changes, needle-free connector changes,
4) Only applicable for patients who continue to be hospitalized at the department/hospital and continue study participation
5) End of study is also applicable if the patient is discharged from department and cannot be followed up by the clinical investigation team at another department/ward
6) Baseline VAD Information at initial PureHub™ Placement day needs to be reconfirmed if the visit date is different to baseline date
7) Only in case participant is transferred to another department/ward and continues in the study, or participant is discharged home in-between hospital visits but the VAD is still in place.

2 INTRODUCTION

2.1 Background

Catheter-related blood stream infections (CRBSI) are bacterial infections that originate within a vascular access device (VAD). The International Society for Infectious Diseases report that CRBSIs account for 11% of all healthcare-associated infections and have an estimated attributable mortality rate between 12-25% (Lutwick and Bearman, 2019).

Introduction of bacteria into the bloodstream via the VAD can come from several sources, including contamination of the device prior to insertion, skin organisms, contamination of the infusate, and contamination of the catheter hub (Gahlot, 2014). There are multiple recommendations for CRBSI prevention that targets each of these potential origin points. For needleless connectors, the guidelines for the Prevention of Intravascular CRBSIs considers scrubbing the access port of needleless connectors with an appropriate antiseptic (including 70% IPA) a Category 1A recommendation (O'Grady et al, 2017). Standards of clinical practice published by Society for Healthcare Epidemiology of America (SHEA) and Infusion Nurses Society (INS) have included disinfection caps in their recommendations (Marschall et al, 2014; Infusion Nurses Society, 2021).

Alcohol-impregnated disinfectant caps were developed to simplify the disinfection process through passive disinfection. Furthermore, disinfectant caps act as a physical barrier between line accesses (Marschall 2014, Infusion Nurses Society, 2021). The BD PureHub™ disinfecting cap was designed for compatibility with market-leading needle-free connectors prior to access and maintains a physical barrier to contamination for up to seven days. The BD PureHub™ disinfecting cap disinfects with a sterilized 70% IPA solution, providing a > 4-log (99.99%) reduction in bacteria within 1 minute of application.

2.2 Rationale

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

2.3 Risk/Benefit Assessment

The BD PureHub™ Disinfecting Cap has been on the market in Europe since 2018 and as of July 2020, PureHub™ has been used in 122 institutions in EU and 131 institutions in US with more than 21.9 million units sold.

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of BD the PureHub™ Disinfecting Cap may be found in the Instructions for Use (IFU).

2.3.1 Risk Assessment

Potential risks for the BD PureHub™ Disinfecting Cap devices are based on items noted in the Instructions for Use and are not unique to this study.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention (s)		
The BD PureHub™ Disinfecting Cap has a potential for trace amounts of IPA to ingress from the disinfecting cap into the fluid path of the infusion therapy system.	A review of literature showed positive outcomes for the application as intended for the use of the BD PureHub™ Disinfecting Cap. A general patient benefit has been identified within the literature. However, one *in-vitro* study on another disinfecting cap found that use caused a change in the appearance of some E valves, and also allowed significant amounts of IPA to be injected. However, an assessment considering BD PureHub™ Disinfecting Cap found that the estimated ingress dose amount of BD PureHub™ disinfecting cap was determined to be below the BD derived acceptable exposure limit of IPA secondary to potential ingress.	A caution statement "The safety of 70% Isopropyl Alcohol caps has not yet been directly established in clinical use scenarios with neonates" has been added to the BD PureHub™ Disinfecting Caps IFU. A warning statement "Keep out of reach of children. In case of accidental ingestion, seek medical help or consult a poison control center immediately", is included in the BD PureHub™ Disinfecting Caps IFU.
Potential choking hazard for the pediatric population	The literature also identified disinfectant caps as esophageal foreign bodies in pediatric patients, suggesting that they should be used with caution in this patient population given their potential to become ingested. One event like this was also identified in the database analysis of Clinical Experience. A potential for a choking hazard exists with a pediatric patient if the user does not apply the cap properly and the cap inadvertently falls off during unsupervised use or is not disposed of properly. Choking hazards are prevalent and always a risk with pediatric patients. The benefits of the disinfecting cap currently outweigh the risk of potential for choking. The risk has been assessed as mitigated and has been determined to be acceptable.	The IFU instructs the user of proper application of the disinfecting cap, and to discard after use. A warning statement, "Potential choking hazard", is included in the BD PureHub™ Disinfecting Cap IFU.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention (s)		
Process considerations that could lead to particulate within sponge assembly	These are identified potential process considerations	The IFU instructs clinicians that: "After removing the foil film, visually inspect the contents of the cap and do not use if it appears dry or contains particulate matter."
Process considerations that could lead to a dry sponge or insufficient IPA amount that may lead to ineffective disinfection.	These are identified potential process considerations	The IFU instructs clinicians that: "After removing the foil film, visually inspect the contents of the cap and do not use if it appears dry or contains particulate matter."
Study Procedures		
No study-specific risks identified		
Other		
Not applicable		

2.3.2 Benefit Assessment

There is no direct benefit for study participation for an individual patient, however the clinical benefits for the BD PureHub™ Disinfecting Cap are as follows:

a. Easy to use disinfecting device for needle-free connectors.
b. Easy to use device to act as a physical barrier on needle-free connectors between line accesses.
c. Demonstrated in a laboratory a >4 log (99.99%) reduction on common causative agents in CRBSI including: *Staphylococcus aureus, Staphylococcus epidermidis, Pseudomonas aeruginosa, Escherichia coli, Candida glabrata, Candida albicans, Acinetobacter baumannii.*
d. The BD PureHub™ Disinfecting Cap complies with the Infusion Nursing Society (2021) recommendation to perform passive disinfection on needle-free connectors by applying a cap or covering containing a disinfectant agent (e.g., 70% isopropyl alcohol, iodinated alcohol) to create a physical barrier to contamination between use.

2.3.3 Overall Benefit: Risk Conclusion

The BD PureHub™ Disinfecting Cap will be used by trained individuals as intended as part of this study on any patient population with consideration given to the procedure being performed and the disease state of the patient. There is no anticipated additional risk associated with the device use or any study procedure due to participation in this study compared to any BD PureHub™ Disinfecting Cap use as part of standard medical care.

3 OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary Performance 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
Informational Objective	
To assess the frequency of BD PureHub™ Disinfecting Cap use	• The number of BD PureHub™ Disinfecting Caps used per day/per study participant
To summarize the purposes for removal of the BD PureHub™ Disinfecting Cap from the needle-free connector	• The purpose for each intended removal of the BD PureHub™ Disinfecting Cap from the needle-free connector
To summarize the incidence of blood stream infection	• Incidence of central line associated bloodstream infection (CLABSI) • Incidence of bloodstream infections

4 STUDY DESIGN

4.1 Overall 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.

4.2 Scientific Rationale for Study Design

This study is designed to collect clinical data on the performance of the BD PureHub™ Disinfecting Cap. The usage of the BD PureHub™ Disinfecting Cap according to its intended use will ensure that study activities have no direct impact on the endpoints being assessed and that they represent outcomes typically associated with intended medical use of the study device in clinical practice.

4.2.1 Participant Input into Design

Not applicable.

4.3 End of Study Definition

A participant is considered to have completed the study when one of the following conditions are met, whichever is the earliest.:

- upon one week post VAD therapy (after the last VAD is removed),
- at department discharge provided the clinical investigation team cannot follow-up the participant on another ward for study purposes,
- at hospital discharge provided participant, if VAD is still placed, will not return for catheter access to the site or,
- 45 days from enrollment

If a participant has more than one (1) VAD with eligible needle-free connectors at study start, data will be collected on each VAD and the end of study time point occurs when the last VAD is removed. If an additional VAD is placed at a later time point, or if one of these VADs is replaced, then the new VAD is excluded from the study.

The end of the study is defined as the date of the last study assessment of the last participant in the study.

5 STUDY POPULATION

5.1 Inclusion Criteria

In order to be eligible to participate in this study, an individual of any age or gender, must meet all of the following criteria:

1. Has an eligible vascular access device in situ or will have one placed with needle-free connectors
   Note: This covers all needle-free devices, including central venous catheters, peripheral IV catheters and arterial VADs
2. Is expected to receive VAD therapy for a minimum of 3 days
3. Is expected to be available for regular observation from consent until end of study.
4. Able and willing to provide informed consent or legal authorized representative (LAR)* authorized to give consent on behalf of the participant.

*LAR not applicable for AT01

5.2 Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

1. BD PureHub™ Disinfecting Cap or any other disinfecting cap in place for more than twelve (12) hours (>12 hours) prior to study participation
2. Presence of any infection, bacteremia, or septicemia is known or suspected
3. Any condition which, in the opinion of the Investigator, precludes the participant from participation in this study

5.3 Lifestyle Considerations

Not applicable.

5.4 Screen Failures

Screen failures are not anticipated due to the non-investigational nature of the study.

5.5 Vulnerable Population

As the instruction for use of the BD PureHub™ Disinfecting Caps does not foresee any limitations in terms of subject age or status and the study aims to collect data on clinical use, the study will also consider participants under 18 years of age, or participants requiring a LAR. In addition, pregnant and breastfeeding subjects are not excluded from study participation. As the study device will be used as intended, this population is considered to be not exposed to any additional risk due to study participation.

Some participating clinical sites may decide to not include vulnerable subjects as per their hospital policy or may not include minors as the participating department treats only adults.

6 STUDY INTERVENTION

6.1 Investigational/Test Device

BD PureHub™ Disinfecting Caps are intended to be used as a disinfecting device for swabbable needle-free luer connectors prior to access and to act as a physical barrier between line accesses. It is comprised of a threaded plastic cap containing a porous pad pre-saturated with 70% IPA, and sealed with a multilayer foil film. The BD PureHub™ Disinfecting Cap will disinfect the needle-free luer connector one (1) minute after application and act as a physical barrier for up to seven (7) days, if not removed. Proper application and removal of the device is detailed in the IFU. This product is not made with natural rubber latex or plasticizer Diethylhexyl Phthalate (DEHP). A picture of the device is provided below.

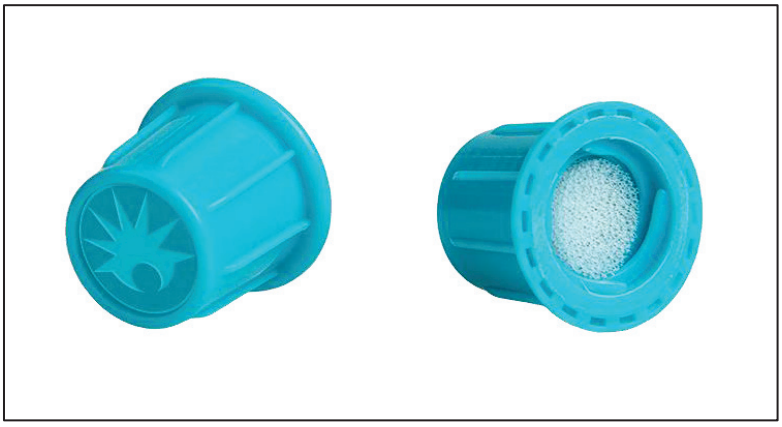

Figure 1 Example of disinfecting cap (BD PureHub™ disinfecting cap)

6.2 Control Device/Standard of Care

Not applicable; this is a single-arm study.

6.3 Ancillary Devices/Products

Ancillary devices will include the participant's VAD, eligible needle-free luer connectors, intravenous tubing, and dressings, or any other material associated with the participant venous access. These products will be used as part of the standard of care of each site. Selected information regarding these devices will be collected (See Section 7.7). The use of other disinfecting caps than the PureHub™ disinfecting cap is not allowed.

6.4 Device Labeling

This study will utilize marketed product. As such, no special labelling is required. However, to ensure that the BD PureHub™ disinfecting cap will be used at the study sites only on behalf of the study, the device packaging will be labeled as "For clinical trial use only".

6.5 Treatment Allocation and Measures to Minimize Bias

This is a post-market clinical follow up study in which the BD PureHub™ disinfecting cap is used as intended. The choice of using the cap is left to the discretion of the clinician.

7 STUDY PROCEDURES AND ASSESSMENTS

- Study activities and their timing are summarized in the Schedule of Activities (Table 1)
- Adherence to the study design requirements, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

7.1 Study duration

The study participation per participant will last 45 days at maximum, the overall conduct of the study is expected to last approximately 14-15 months from first participant enrolled up to last participant having last visit, which is projected for ~ Q2 2023. The anticipated enrollment period is 13 months.

7.2 Screening and Enrollment

After screening against inclusion/exclusion criteria, potential participants will be provided with detailed information about the study. For details on the Informed Consent process, please refer to section 14.2. A participant will be considered enrolled once informed consent (or assent as applicable) is signed. Enrolled patients will be assigned a unique participant number.

7.3 Medical History / Baseline Assessments

Participant baseline and demographic information will be documented, including, but not limited to age, sex assigned at birth, primary diagnosis, and medical history. Information on the participants vascular access device, including but not limited to:

- Type of VADs to be assessed per study participant
- Per VAD the following information will also be collected:
  - Date of insertion
  - Date of removal
  - 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

7.4 Device Use

Each study participant will have a BD PureHub™ Disinfecting Cap attached to each eligible needle-free connector by a clinician. "Eligible" needle-free connector will be defined as a swabbable needle-free connector not already in use and is reasonably able to be accessed by a clinician.

Clinicians should place subsequent BD PureHub™ Disinfecting Caps as per the Instructions for Use. Lot numbers of the PureHub™ devices will be documented in the eCRF.

Clinicians will be advised to follow the respective unit protocol for disinfection of needle-free luer connectors prior to initial access.

7.5 Efficacy (Performance) Assessment

Clinicians will be requested to document the following with each use of the BD PureHub™ Disinfecting Cap:

- Attachment success: The clinician will document if able to successfully attach the BD PureHub™ Disinfecting Cap to each of the applicable needle-free connectors securely. (Documenting either "Yes" or "No").
  - An *attachment* is defined as the process of placing a PureHub™ Disinfecting Cap on an eligible needle-free connector.
  - If the clinician can successfully attach the first BD PureHub™ Disinfecting Cap, they should document "Yes" as this would be an attachment success. Attachment success means the cap is securely attached to the needle-free connector and that the needle-free luer is connected.
  - If the clinician is unable to successfully attach the cap to the needle-free connector, they should use a new subsequent BD PureHub™ Disinfecting Cap. The answer to attachment success would be "No" as more than one cap was needed to reach attachment success. The number of subsequent caps needed to achieve a successful attachment during this procedure need to be documented.

If the clinician is unable to attach the cap to the needle-free connector with any subsequent caps, they should document the number of subsequent caps used and document "Unable to attach."

- Removal success: The clinician will document if able to successfully remove the BD PureHub™ Disinfecting Cap from the needle-free connector (Yes/No).
  - An *intended removal* is defined as the process of removing a successfully attached PureHub™ Disinfecting Cap from an eligible needle-free connector for the purpose of access to the needle-free connector or to replace with a new PureHub™ Disinfecting Cap.

If the clinician can remove the PureHub™ Disinfecting Cap from the needle-free connector, they should document "Yes" as this would be a removal success.
If the clinician cannot remove the PureHub™ Disinfecting Cap from the needle-free connector, they should document "No".

7.6 Safety Assessments

Device-related AEs and device deficiencies will be captured as they occur until the participant concluded his/her participation to the study. Details about AEs are provided in Section 9.

7.7 Informational Assessments

The following data may also be collected for informational purposes only:

- Participant in-hospital location: Main department/ward, date of hospitalization, if applicable: any participant transfer in the hospital provided participant is still followed up by the clinical investigation team: date of move to another department/ward, name of new department/ward
- Vascular access device details used in conjunction with the BD PureHub™ Disinfecting Cap. In addition to the VAD information to be collected as referenced in section 7.3 , the following information will be documented throughout the study:
  - Per catheter:
    - Type of dressing
    - Dressing changes
    - Needle-free connecter changes
    - Daily assessment of any change to type and number of intravenous tubing/ extension set(s)
    - Daily assessment of any change to type and number of other add-on devices i.e. valves, stop cocks
  - Current catheter care practice
- The number of BD PureHub™ Disinfecting Caps used per day/per study participant
- The primary reason for each intended removal of the BD PureHub™ Disinfecting Cap removal.
- Incidence of bloodstream infection, including CLABSIs will be documented.

8 PARTICIPANT DISCONTINUATION/WITHDRAWAL

8.1 Discontinuation/Withdrawal

- A participant may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the investigator or sponsor for safety, behavioral, compliance, or administrative reasons. This is expected to be uncommon.
- At the time of discontinuing from the study, no further data will be collected for the participant.

- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- Participants who withdraw or discontinue the study early may be replaced.

8.2 Lost to Follow-Up

Not applicable; these participants will be in the department/hospital for the duration of the study.

9 ADVERSE EVENTS AND DEVICE DEFICIENCIES

9.1 Definitions of Events

9.1.1 Adverse Events (AEs)

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 or procedure and whether anticipated or unanticipated [ISO14155:2020].

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 CLABSIs (as defined in the List of Abbreviations).

Pre-existing conditions should be considered as part of the participant's medical history and should not be reported as an AE unless there is a substantial increase in severity or frequency of the condition, which has not been attributed to natural history. Likewise, planned hospital visits and/or hospital stays should not be considered as adverse events. Exacerbation of an existing condition should be reported as an AE if the event meets the protocol definition of an AE.

The clinical course of the event will be followed according to accepted standards of medical practice until the event resolves, stabilizes, or in the opinion of the Investigator, is no longer considered clinically significant. The Investigator must supply the Sponsor with information concerning the follow up and/or resolution of the AE.

9.1.2 Serious Adverse Events (SAEs)

A serious adverse event is defined by ISO14155:2020 as an adverse event that led to:

a. death,
b. serious deterioration in the health of the participant, users, or other persons as defined by one or more of the following:
    a. a life-threatening illness or injury, or
    b. a permanent impairment of a body structure or a body function including chronic diseases, or
    c. in-patient or prolonged hospitalization, or
    d. medical or surgical intervention to prevent life-threatening illness or injury, or permanent impairment to a body structure or a body function,

e. fetal distress, fetal death, a congenital abnormality, or birth defect including physical or mental impairment

9.1.3 Adverse Device Effect (ADE) / Serious Adverse Device Effect (SADE)

An adverse device effect is defined as any adverse event that is considered to be related to the use of an investigational medical device. This definition includes any event resulting from insufficiencies or inadequacies in the instructions for use, deployment, implantation, installation or operation or any malfunction of the investigational device (study device) and includes any event that is a result of a user error.

A serious adverse device effect (SADE) is defined as an ADE that has resulted in any of the consequences characteristic of an SAE.

9.1.4 Unanticipated (Serious) Adverse Device Effect (UADE/USADE)

An unanticipated (serious) adverse device effect (UADE/USADE) is any (serious) adverse device effect on health or safety or any life-threatening problem or death caused by, or associated with, a study device, which by its nature, incidence, severity, or outcome has not been identified in the current instructions for use and/or current version of the risk analysis report, or any other unanticipated serious problem associated with a device that relates to the rights, safety or welfare of participants.

UADEs/USADEs will be reported to the appropriate governing body per ISO 14155:2020.

9.2 Severity of Adverse Events

Each AE shall be assessed for its severity, or the intensity of an event, experienced by the participant according to the criteria below.

Severity Rating	Description
Mild	Event, signs, or symptoms that do not interfere with the participant's daily activity, are usually considered self-limiting, can be treated with non-prescription type medications, and do not require medical intervention
Moderate	Event may interfere or cause low level inconvenience with the participant's daily activity. Requires medical intervention and/or treatment; however, unlikely to require hospitalization or be considered potentially life-threatening in nature
Severe	Event may cause significant discomfort to the participant and/or interferes with the participant's daily activity. Requires medical intervention and/or treatment to preclude a permanent impairment; may be life threatening and/or require hospitalization

9.3 Relationship of Adverse Event to Device(s)/Procedure

Each AE will be assessed for its relationship to the study device or procedure according to the following guidelines.

A. Assess each AE for its relationship to the device, that is, AEs directly attributable to the study device (BD PureHub™ Disinfecting Cap) used.

B. The following categories shall be used for assigning the certainty of the relatedness.

Relatedness	Description
Not Related	Event is independent of study intervention and/or evidence exists that the event is related to another etiology. There must be an alternative etiology documented by the clinician.
Unlikely Related	Event in which the temporal relationship to study intervention makes a causal relationship improbable (e.g., the event did not occur within a reasonable time of the study device use) and in which underlying disease provides plausible explanations (e.g., the participant's clinical condition other concomitant treatments).
Likely Related	Event in which there is evidence to suggest a causal relationship and the influence of other factors is less likely. The event occurs within a reasonable time after use of the study device and is less likely to be attributed to concurrent disease.
Related	Event in which there is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out. The event occurs in a plausible time relationship to use of the study device and cannot be explained by concurrent disease.

9.4 Reporting of Events

For all adverse events, all sections of the appropriate electronic Case Report Form (eCRF) must be completed.

- All SAEs, SADEs, and/or UADEs/USADEs must be reported to the Sponsor via the eCRF without unjustified delay and within three (3) working days of the site/investigator becoming aware of the event.

- De-identified copies of all requested relevant documentation should be submitted to the Sponsor within 72 hours of knowledge, as appropriate.

- Safety related correspondence or questions can be addressed to following contact:
  CROMSOURCE Safety Unit:
  Email: pharmacovigilance@cromsource.com
  Fax: +39 045 825 0574

It is the responsibility of the Investigator or their designee to report adverse events to individual Institutional Review Boards (IRBs)/Ethics Committees (ECs). The Sponsor or their designee is responsible for reporting AEs to regulatory authorities according to the local regulations in each participating country.

9.5 Safety Committees

A safety committee will not be used for this study.

9.6 Device Deficiencies

The Investigator will record a device deficiency if a device used in the study, which appeared to be inadequate with respect to its identity, quality, durability, reliability, usability, safety or performance, whether due to mechanical failure, malfunction, or defect. Device deficiencies also include use errors and inadequate labeling. This applies to: devices used to treat the participant, or devices in which the package was opened, but the device was not used for treatment, or devices with which treatment was attempted, but the device did not remain through the entire study procedure/period.

All mechanical failures, malfunctions, missing components, and defects of the study devices will be recorded on the appropriate Case Report Form and will be promptly reported to the Sponsor. The device(s) should be returned to the Sponsor if requested.

If the device deficiency was associated with an AE, the reporting provisions for AEs, ADEs, SAEs, SADEs and UADEs/USADEs apply.

Reported deficiencies will be investigated and reported by the Sponsor under 21 CFR part 803 Medical Device Reporting if necessary, or as required by appropriate national laws and regulations. The site may be contacted to provide additional information to allow the Sponsor to conduct a thorough investigation.

It is the responsibility of the Investigator to notify the IRB/EC of such device deficiencies in accordance with the IRB/EC and/or local regulations.

9.7 Serious Health Threat

During the course of the study, device deficiencies or adverse events will be assessed if they constitute a serious health threat. The serious health threat is a signal from any adverse event or device deficiency that indicates an imminent risk of death or a serious deterioration in the health in subjects, users or other persons, and that requires prompt remedial action for other subjects, users or other persons. Serious health threat includes the possibility of multiple deaths occurring at short intervals, or other significant and unexpected serious adverse events that can be regarded as a potential serious health hazard in subjects, users or other persons and which are possibly related to the investigation device use.

10 STATISTICAL METHODS

The statistical analysis plan will be finalized prior to the database lock and will include a more technical and detailed description of the statistical analyses described in the following sections. This section includes a summary of the planned statistical analyses of the most important endpoints including primary and exploratory endpoints.

10.1 Overview of Study Design

This is a multi-center, single-arm, prospective study to assess the overall safety and performance of the BD PureHub™ Disinfecting Cap.

10.2 Sample Size Considerations

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 (CI) is the point estimate ±4.8%, using a simple asymptotic approach for CI 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%.

10.3 Analysis Population

The following populations are defined:

Population	Description
Enrolled	All participants who sign the ICF
Evaluable	All enrolled participants who have at least 1 BD PureHub™ Disinfecting Cap applied.

10.4 Primary Performance Endpoints

The attachment (removal) success rate will be calculated by dividing the number of successful attachment (removal) by the total number of attachments (removals); 95% CI will be calculated using a score method.

10.5 Primary Safety Endpoint

The rate of device-related adverse events will be calculated as the number of participants with adverse events related to device divided by the total number of participants; 95% CI will be calculated using a score method.

10.6 Informational Endpoint(s)

Descriptive statistics for the informational endpoints defined in Section 3 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.

10.7 Other Analyses

Not applicable.

10.8 Interim Analysis

No interim analysis is planned for this study.

11 DATA COLLECTION AND RECORD MAINTENANCE

11.1 Electronic Case Report Forms

The Investigator is responsible for ensuring the completeness and accuracy of all study documentation.

All required clinical data will be collected/documented in sponsor-provided electronic Case Report Forms (eCRFs). Applicable national and local regulations are followed on the handling of electronic data. Modification of the eCRFs will only be made if deemed necessary by the Sponsor and/or the appropriate regulatory body.

Site numbers and participant numbers will be used to track participant information throughout the study. Participant personal information will be pseudonymized/de-identified.

11.2 Source Documentation

Original or certified copies of all relevant clinical findings, observations, and other activities throughout the clinical investigation must be recorded and maintained in the medical file of each enrolled participant.

11.3 Data Management

Data management is the responsibility of the Sponsor or their designee. Data from completed eCRFs will be managed in a secured, controlled database. A Data Management Plan (DMP) will be developed that outlines the procedures used for recording, data tracking, data review, database cleaning, issuing/resolving data queries and database lock. Procedures for rectifying errors and omissions, verification, validations and securing of the electronic data system as well as data storage will also be contained within the DMP. The procedure to maintain and protect the participants data privacy and information on data storage upon completion of the study will be detailed in the DMP too.
A data snapshot is planned to be performed after 50% of the participants have completed the study. The data will be used for monitoring purposes only and will not impact the design or conduct of the study. Further details on the data snapshot process will be addressed in the DMP.

11.4 Record Retention

The Investigator shall retain all study records for a minimum of ten (10) years after the study has ended. Study records may be stored longer if required by national law or other local rules. The data for some of these records may be available in computerized form but the final responsibility for maintaining study records remains with the Investigator.

The Investigator may withdraw from the responsibility to maintain records for the period required by transferring custody of the records to any other person who will accept responsibility for retaining them. Notice of a transfer shall be given to the Sponsor not later than ten (10) working days after the transfer occurs.

11.5 Device accountability

If a study site is provided with PureHub™ Disinfecting Caps by the Sponsor, device accountability between Sponsor and the site will be performed (Number of devices shipped, number of devices used at trial site, number of devices shipped back/discarded at end of study). In this case, Principal Investigator needs to ensure that the caps are only used for study purposes.

12 QUALITY CONTROL AND ASSURANCE

12.1 Control of Study Products

In this post-market study, marketed devices will be used, provided by the Sponsor. No special controls are required in this study.

12.2 Monitoring

The Sponsor will designate trained and qualified personnel to monitor the progress of this clinical study in accordance with established standard operating procedures and the study-specific Monitoring Plan.

Prior to study start, a study initiation visit (SIV) will be conducted to review with the Investigator(s) and staff the provisions and proper conduct of this study. This visit will include a detailed review of this protocol, verification that all necessary documents are on file at the investigational site and confirmation of IRB/EC approvals.

During the study, routine monitoring visits (RMVs) will be conducted to assure the site continues to adhere to the protocol, the investigator agreement, and regulations regarding conduct of clinical studies. The Sponsor-Monitor will confirm that the ICF to be used is the version approved by the IRB/EC, confirm the applicable national privacy laws have been followed, verify that all necessary documents are on file at the investigational site and confirm that there are provisions to continue and maintain all documents and records throughout the study as required by applicable regulations. These monitoring visits will assess continued protocol compliance, adequate participant enrollment, accurate data reporting, monitoring of participant safety through identification and/or review of any device-related AEs, UADEs, or SAEs, device accountability between Sponsor and the site,

continued maintenance and calibration of study-specific equipment (if applicable), and continued IRB/EC acceptance of the study.

At the completion of the study, the Sponsor-Monitor will conduct a final close-out visit (COV). The purpose of this visit may include but is not limited to collecting all outstanding study data documents, confirming that the Investigator's files are accurate and complete, reviewing the record retention requirements with the Investigator, and ensuring that all applicable requirements for closure of the study are met.

12.3 Audits and Inspections

If the study is selected for audit by the Sponsor or if there is an inspection by the appropriate Health Authorities, the Investigator and his team will make themselves available during the visit. The Investigator must agree to the inspection of all study related records and give the auditor/inspector direct access to source documents for verification of data on eCRFs. The participant's anonymity must be ensured, and data checked during the audit must remain confidential.

As soon as the Investigator is aware of an upcoming inspection/audit by the Health Authorities, he/she will promptly inform the Sponsor. As agreed with the Investigator, Sponsor personnel may be present at the site during the inspection.

12.4 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.

Except when necessary to protect the life or physical well-being of a participant, protocol deviations are not permitted. The Sponsor and the investigational site's IRB/EC must be notified immediately if an emergency situation arises in which the safety of a participant may require immediate intervention different than that defined in the protocol. This must be followed by written confirmation that describes the emergency action and outcomes, within five (5) working days from the date of the emergency action in accordance with the governing IRB/EC's requirement.

It is the Investigator's responsibility to ensure that there are no deviations from the Protocol. Except in an emergency, when a protocol deviation is planned or anticipated, the Sponsor should be contacted for approval. All deviations must be recorded on the appropriate eCRF regardless of whether medically justifiable or sponsor approved. Upon evaluation by the Sponsor, actions may be required to prevent additional deviations, such as retraining of the site, implementation of additional site procedures, and more frequent monitoring. If these steps fail, more serious measures, up to and including termination of enrollment at the site.

13 ADMINISTRATIVE REQUIREMENTS

13.1 Investigator and Site Selection

The Investigator must be of good standing as an Investigator and knowledgeable in relevant areas of clinical research to ensure adherence to the requirements of this protocol, including the protection of human participants. Other site personnel must have appropriate research experience and infrastructure to ensure adherence to this protocol and enrollment of sufficient numbers of evaluable participants. The curriculum vitae (CV) of the Investigator(s), Sub-Investigator(s) and Study Coordinator(s) will be maintained in the Sponsor's files as documentation of qualification by training and experience.

The Principal Investigator will sign the Investigator Agreement page of this protocol, agreeing to comply with all applicable regulations and the requirements of this study as per the CSA.

Any site that is deactivated prior to initial enrollment, either by the Sponsor or by the individual site itself, may be replaced.

13.2 Training

Each Investigator and appropriate site personnel will be trained on this protocol and study requirements during the SIV and on the study device, if needed. All training will be documented and filed at the investigational site and with the Sponsor.

13.3 Required Documents

An Investigator may not screen or enroll participants until authorized to do so by the Sponsor. At a minimum, the following documentation should be received by the Sponsor prior to the commencement of study activities:

- Fully executed Non-disclosure Agreement (NDA) between PI/site and Sponsor;
- CVs, signed and dated within 2 years of study start for the PI and Sub-Investigator(s);
- CVs for Study Coordinator(s);
- Signed CSA by PI/site (or designee);
- Signed Investigator Agreement Page by PI and Sub-Investigator(s);
- Signed Financial Disclosure Statement by PI and Sub-Investigator(s);
- Completed and Signed Training Log by PI and Sub-Investigator(s);
- Study Personnel Identification list;
- Written approval from the IRB/EC of both the protocol and ICF, and any other applicable protocol specific material; and
- IRB/EC Membership List, Assurance of Compliance Form, or equivalent.

13.4 Insurance

Where required by local regulation, insurance coverage will be provided by BD for study participants.

13.5 Publication Policy

The sponsor believes that results of applicable clinical studies should be published in peer-reviewed literature in a timely, accurate, complete and balanced manner, regardless of study outcomes, whenever possible. As such, at the conclusion of this study, an article may be prepared for publication in a reputable scientific journal. Formal presentation(s) or publication(s) of data collected from this study will be considered as a joint publication by the investigator(s) and the appropriate personnel of the Sponsor. Authorship will be based on generally accepted criteria of the ICMJE (International Committee of Medical Journal Editors) and determined by mutual agreement.

The publication of the principal results from any single-center experience within the study is not allowed until the preparation and publication of the multicenter results. Exceptions to this rule require the prior approval of the Sponsor. The analysis of other pre-specified and non-pre-specified endpoints will be performed by the Sponsor or its designee. Such analyses, as well as other proposed investigations or manuscripts will require the approval of the Sponsor.

13.6 Study Registration

While this is a not an Applicable Clinical Trial and does not meet the FDA Amendments Act of 2007 (FDAAA) criteria for clinical study registration, the study will be registered on www.clinicaltrials.gov to ensure transparency. The study will also be registered on additional local registries, if applicable. The content of the publicly accessible database(s) will be updated throughout the conduct of the clinical study and the results will be entered after study completion.

13.7 Termination of Study

The Sponsor reserves the right to suspend enrollment or terminate the study at any time for any reason. If suspicion of an unacceptable risk, including serious health threat to subjects, arises during the study, the Sponsor may suspend the study while the risk is assessed. The sponsor shall terminate the clinical investigation if an unacceptable risk which cannot be controlled is confirmed.

Additionally, the Sponsor may suspend enrollment or terminate the study at a specific investigational site for reasons including, but not limited to, inadequate data collection, low participant enrollment rate, achievement of the total enrollment, conditions imposed by the reviewing IRB/EC and/or non-compliance with this protocol or other clinical research requirements. Written notice will be submitted to the Investigator in advance of such termination.

In the event of study suspension or termination, the Sponsor will send a report outlining the circumstances to the IRB/EC, and all Investigators and Regulatory Authorities as required by regulation.

14 ETHICAL AND REGULATORY CONSIDERATIONS

14.1 IRB/EC Approval

Investigators or designees must submit the study protocol, Informed Consent Forms (if applicable), and all other locally required documentation to an appropriate IRB/EC and obtain study-specific written approval (favorable opinion) before being allowed to participate in the study. Before commencement of the study, the Investigator or designee must provide the Sponsor with written documentation of such approval. The IRB/EC must give written renewal of the original approval at least annually to continue the study, if applicable per local regulation. In this case, a copy of the written renewal must be provided to the Sponsor.

The IRB/EC will be notified of any amendments to the protocol, as well as possible associated information and consent form changes, where applicable, and written approval (favorable opinion) will be obtained prior to implementation, as applicable.

The Investigator or designee is responsible for fulfilling any conditions of approval imposed by the IRB/EC, such as regular safety reporting, study timing, etc. The Investigator or designee will provide the Sponsor with copies of such reports.

14.2 Informed Consent and Confidentiality

Prior to any study procedure, the Investigator (or designee) must explain to each participant in layman's terms, the nature of the study, its purpose, expected duration, and the risks and benefits of study participation. For participants under the age of 18, participants' parent(s)/guardian must provide their informed consent and the child must provide assent, depending on local EC requirements, by personally signing and dating the respective consent form prior to begin of this study. For adult participants, where the participant is not able to or not capable to give informed consent, the legal representative will be asked to give consent on behalf of the participant. However, the participant will also be informed about the study within his/her ability to understand.

The Informed Consent process has to be documented in the participant's medical records. Also, participant will be informed of uses and disclosures of their medical information for research purposes, and their rights to access information about them. All applicable national privacy laws (e.g., General Data Protection Regulation [GDPR] requirements in the EU) will be followed in this study. The participants must be informed of their right to withdraw from the study at any time and for any reason without sanction, penalty, or loss of benefits to which they are otherwise entitled, and that withdrawal from the study will not jeopardize their future medical care. Participants will be informed of their right to new information and/or findings relating to the clinical study, and the process by which this information is made available. After this explanation, given sufficient time to decide whether to participate, before any study procedure is conducted, and before entering the study, the participant must voluntarily provide consent by signing and dating the form personally in accordance with ISO 14155: 2020(E). The participant will receive a copy of

his/her signed ICF. If new information becomes available that may significantly affect the subject's health status, then this information will be provided in written form. Re-consent will be obtained if this is considered as necessary.

The above requirements also apply with respect to informed consent obtained from participant's legally designated representative.

14.2.1 Confidentiality

Participant confidentiality must be strictly held in trust by the Investigator, study staff, and the Sponsor. Participant confidentiality and anonymity will be maintained by removal of identifiers from any data, documentation, or clinical samples submitted to the Sponsor.

Any data collected meeting the definition of protected/confidential health information or personal identifying information will be collected and maintained using the designated authorizations and following privacy procedures as specified in the applicable regulatory authority regulations including the EU GDPR.

The Sponsor-Monitor, authorized representatives of the sponsor, and/or applicable Health Authorities may inspect all documents and records required to be maintained by the Investigator. The Investigator/Site will permit access to such records.

14.3 Regulatory Status

The study device is CE marked and will be studied in a post-market fashion in Europe.

14.4 Statement of Compliance

This clinical investigation will be conducted in compliance with the protocol and following regulatory requirements:

- ISO14155:2020 (Good Clinical Practice);
- EU MDR (Council Regulation 2017/745 of 5 April 2017);
- Ethical principles of the Declaration of Helsinki, in its current revision; and
- Applicable sections of the national laws and regulations.

The clinical investigation will not commence at a clinical site until approval (favorable opinion) from the respective IRB/EC has been received. All additional requirements imposed by the IRB/EC(s) will be followed. Involvement of the national competent authorities (e.g. by notification, seeking authorization) will be accomplished as required by national laws and regulations.

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