Clinical Investigation Plan

Safe and Timely Antithrombotic Removal - Ticagrelor (STAR-T): A Prospective, Multi-center, Double-blind, Randomized, Study to Evaluate Reduction in Postoperative Bleeding by Removal of Ticagrelor with the Intraoperative use of the DrugSorb™-ATR Device in Patients Undergoing on-pump Cardiothoracic Surgery within Two Days of Ticagrelor Discontinuation.

Clinical Investigation Plan Status: Final
Clinical Investigation Plan Version 5.1 Date: 26-May 2023
Investigational Medical Device: DrugSorb™-ATR
Global Trade Item Number: 01230000006002

CytoSorbents Clinical Investigation Plan Reference Number: 2021-01

Sponsor:
CytoSorbents, Inc.
305 College Road East
Princeton, New Jersey 08540

Sponsor Signatory:
Efthymios Deliargyris, MD, FACC, FESC, FSCAI
Chief Medical Officer

SIGNATURE PAGE – SPONSOR APPROVAL

This Clinical Investigation Plan is in accordance with the clinical research guidelines established by the US Code of Federal Regulations (Title 21, Parts 50, 54, 56, and 812), the regulations and guidelines of International Council for Harmonisation for Good Clinical Practice, and International Organization for Standardization 14155 (Clinical Investigation of Medical Devices for Human Subjects - Good Clinical Practice). Study documents will be maintained in accordance with applicable regulations.

SPONSOR APPROVAL

I have read the Clinical Investigation Plan and approve it:

Efthymios Deliargyris, MD, FACC, FESC, FSCAI
Chief Medical Officer

May 26, 2023
Date

BRIEF PROTOCOL REVISION HISTORY

Version	Date	Brief Description of Changes
Final	3-15-2021	Original Submission
1.1	4-12-2021	The following sections were updated to address requests by the agency: • Inclusion/Exclusion Criteria • Potential Investigational Device Risks • Addition of a Secondary Endpoint: Re-exploration for excessive bleeding • Maintaining the Study Blind • Schedule of Events
1.2	4-15-2021	Revised wording in 9.2.6 and Table 6
1.3	5-19-2021	Labeling for the DrugSorb device has been updated to reflect current trademark status more accurately (DrugSorb® to DrugSorb™) The following sections and subsections were updated to address suggestions by the agency: • Study Design • Primary Effectiveness Endpoint • Addition of an exploratory endpoint: AUC for intraoperative ticagrelor PK analysis • Blood Sampling for Drug Removal • Data Safety and Monitoring Board (DSMB) • Statistical Considerations The following sections were updated to provide additional guidance for investigators: • Study Justification • Subject Randomization

		• Field Clinical Engineers • Unblinding Procedure • Bleeding Event AEs • Unanticipated Adverse Device Events
1.3	7-6-2021	Update on the timing of blood sampling for the drug removal endpoint: *the post-CPB sample should be collected as soon as possible following the end of CPB, and no later than 30min after the subject has been disconnected from the CPB circuit*
2.0	12-12-2021	Updates have been made to the protocol wording and details to ensure clarity and consistency in the following sections: • Synopsis • Sections: 1, 4, 6, 7, 9, 11 • Table 6 • Figures 3 and 5 • Appendix 2 Number of allowed study sites increased from 20 to 30. Statistical Considerations (Section 11) has been adjusted to correct typographical errors, better match sister study (STAR-D, G210263), describe stratified Win Ratio analysis, and add more conservative stopping boundaries for the pre-specified interim analysis.
3.0	01-21-2022	• Language around inclusion criteria #3 has been updated to allow enrollment of patients undergoing CT surgery with CPB "***within two days following ticagrelor discontinuation (date of last dose = day 0)***." The change to the inclusion criteria itself is reflected in the protocol **Synopsis** and **Section 4.4.1** *Inclusion Criteria.* References to this time-point have been updated through-out the remainder of the text where relevant • All references to prior eligibility timeframe of "***48hrs since last ticagrelor dose***" have been updated to "***within two days of ticagrelor discontinuation***" through-out the protocol to ensure consistency with the above • Language around exclusion criteria #1 has been revised to exclude those patients who are undergoing "***cardiothoracic surgery occurring 3 or greater following ticagrelor discontinuation***." This update has been made within the protocol **Synopsis** and **Section 4.4.2** *Exclusion Criteria* • The screening period described in **Table 6** (*Schedule of Assessments*) has been updated to "*Up to two days prior to the day of operation*," to maintain consistency with the revised Inclusion Criteria #3 • The primary analyses of the trial will be performed on the modified intent-to-treat (mITT) population rather than the intent-to-treat (ITT) population, with supplemental analysis to be performed on the ITT population. This language has been updated in the protocol **Synopsis** and **Section 11.2** *Analysis Populations* accordingly
4.0	08-10-2022	• Geographic location of study sites has been updated to include both the US and Canada (**Synopsis** and **Section 1.1**) • The term "response rate" has been revised to "effect size" in **Section 11.1** *Statistical Power and Sample Size Determination* • Additional clarifying language added around the ITT,

		mITT, PP, and Safety Populations, and their planned analysis (**Synopsis** and **Section 11.2**) • Language around stratification of the Win Ratio analysis by study site and surgery type has been removed from **Section 11.3** *Effectiveness Analysis* • Language around planned subgroup analyses has been moved to a separate section (**Section 11.4** *Subgroup Analysis*) • Typographic error has been corrected in **Section 11.6** *Treatment of Missing Data* • Language incorrectly referring to subgroup analysis of safety results in **Section 11.7** *Safety Analysis* has been removed
4.1	09-16-2022	• The following sections/subsections were updated to clarify safety analysis as proposed by the Agency in their response to the STAR-T IDE: **Synopsis** and **Section 11.7** • The following sections/subsections were updated to address primary hypothesis proposed by the Agency in their response to the STAR-T IDE: **Section 11** • Updates were made to Executive Committee membership (**Study Organization**) • Updates were made to include abbreviations for per population and safety analysis **(List of Abbreviations)**
5.0	04-02-2023	• The interim analysis will not be performed. Mention of the interim analysis has been removed from the synopsis, from the DSMB oversight duties, and **Section 11.5,** *Interim Analysis* has been deleted. • The planned enrollment is increased to up to 140 subjects. • **Table 6** (*Schedule of Assessments*) in **Appendix 4** has been modified to specify that certain assessments (vital signs), laboratory testing (hematology, clinical chemistry and coagulation panel), and other assessments related to mechanical ventilation, FiO2 and vasopressor requirements will only be scheduled as part of the trial through postoperative day 2. These tests are optional beyond post-operative day 2, and may be recorded if they are performed in accordance with SOC at the particular institution. • Clarifications have been added and typographical errors have been fixed.
5.1	05-26-2023	• Updates were made to Executive Committee membership (**Study Organization**) • Addition of Exclusion Criterion #15 for performance of Acute Normovolemic Hemodilution (ANH) (**Synopsis** and **Section 4.4.2 *Exclusion Criteria)*** • The actual number of patients reflecting the 15% site enrollment cap (i.e., 18 subjects) has been removed (**Sections 6.2 and 11.1**)

SIGNATURE PAGE – INVESTIGATOR AGREEMENT

This Clinical Investigation Plan is in accordance with the clinical research guidelines established by the US Code of Federal Regulations (Title 21, Parts 50, 54, 56, and 812), the regulations and guidelines of International Council for Harmonisation for Good Clinical Practice, and International Organization for Standardization 14155 (Clinical Investigation of Medical Devices for Human Subjects - Good Clinical Practice). Study documents will be maintained in accordance with applicable regulations.

INVESTIGATOR AGREEMENT

I have read the Clinical Investigation Plan and agree to conduct the investigation as described herein.

_____
Principal Investigator (Printed)

_____ _____
Principal Investigator (Signature) Date

_____
Clinical Site

SYNOPSIS

Title of investigation: Safe and Timely Antithrombotic Removal - Ticagrelor (STAR-T): A Prospective, Multicenter, Double-blind, Randomized, Study to Evaluate Reduction in Postoperative Bleeding by Removal of Ticagrelor with the Intraoperative use of the DrugSorb™-ATR Device in Patients Undergoing on-pump Cardiothoracic Surgery within Two Days of Ticagrelor Discontinuation.

Objectives:

- To demonstrate reductions in postoperative bleeding complications with the intraoperative use of DrugSorb™-ATR in patients undergoing cardiothoracic surgery within two days of ticagrelor discontinuation.
- To demonstrate reductions in ticagrelor blood levels (Δ[ticagrelor]) with the intraoperative use of DrugSorb™-ATR.
- To establish the safety of the intraoperative use of DrugSorb™-ATR in the intended population.

Background and rationale:

Ticagrelor is a reversibly-binding inhibitor of the platelet $P2Y_{12}$ receptor, antagonizing the activation of $P2Y_{12}$ by ADP. [1] Ticagrelor is indicated to reduce thrombotic cardiovascular events in patients with acute coronary syndrome (ACS). [1] As with all antithrombotics, the predominant safety concern with ticagrelor is the risk of bleeding. For patients on ticagrelor requiring cardiothoracic surgery, the 2011 ACCF/AHA guidelines for CABG recommend discontinuing ticagrelor at least 5 days before elective surgery, and at least 24 hours prior to urgent surgery. [2] [3] Nonetheless, the PLATO study showed that up to 5% of patients on ticagrelor may require cardiac surgery before the recommended washout period. [4] In those patients, very high rates of major bleeding were observed especially if the surgery occurred within two days of ticagrelor discontinuation.[5, 6] Likewise, patients on ticagrelor initially deemed stable enough to attempt washout before cardiothoracic surgery may still experience clinical deterioration and therefore benefit from urgent surgery before complete washout. Currently, there is no intervention available to address this significant unmet medical need from ticagrelor-induced surgical bleeding in the patients who proceed to surgery before complete washout.

The DrugSorb™-Anti Thrombotic Removal (ATR) device has high affinity for binding hydrophobic small molecules and drugs (~5-kDa to 60-kDa). Data on drug removal capabilities of the device have previously been published in Europe under the name CytoSorb®. However, DrugSorb™-ATR is the appropriate name whenever reference is being made to the device's specific use in the indication of antithrombotic drug removal (ATR), unless citing previously published data. In such cases the name CytoSorb® will be used to remain consistent with the literature.

Ticagrelor is rapidly and efficiently removed from whole blood by DrugSorb™ hemoadsorption. An early benchtop experiment published by Angheliou et. al. demonstrated peak ticagrelor removal rate of 94-99% during 3-10hr recirculating experiments. [7] Additional preclinical studies have demonstrated that the bulk of ticagrelor removal from blood happens early with >60% removal in the first 60 minutes and approximately 80% removal by 90 minutes of DrugSorb™-ATR hemoadsorption (unpublished data).

A retrospective case-series study from Asklepios Klinik St. Georg (Hamburg, Germany) evaluated the use of the CytoSorb® device in (primarily ACS) patients on ticagrelor undergoing emergent cardiothoracic surgery with cardiopulmonary bypass (CPB). Patients on ticagrelor operated on CPB alone (control) were compared to patients operated on CPB with CytoSorb® (treatment). Results showed significant reductions in multiple measures of postoperative bleeding in patients managed with CytoSorb® compared with the control cohort.[8] No device-related adverse events (AEs) or device malfunctions/deficiencies were reported. Since January 2020, the CytoSorb® device has CE mark approval for the removal of ticagrelor during surgery requiring cardiopulmonary bypass (CPB).

Thus, as a result of these preclinical and clinical findings, the Sponsor proposes to conduct a prospective, multi-center, double-blind, randomized, clinical trial to demonstrate that DrugSorb™-ATR use during CPB significantly reduces postoperative bleeding complications and efficiently removes ticagrelor in patients undergoing cardiothoracic surgery within two days of ticagrelor discontinuation, while demonstrating a

favorable safety profile.

Hypothesis:
In patients undergoing cardiothoracic surgery on CPB within two days of ticagrelor discontinuation, intraoperative ticagrelor removal with DrugSorb™-ATR will significantly reduce postoperative bleeding complications.

Endpoints:
Primary Effectiveness Endpoint:

- Perioperative bleeding complications, assessed by the ranked composite of:
  1) Fatal perioperative bleeding (occurring within 48hrs post-index operation),
  2) Moderate, severe, or massive bleeding events based on the Universal Definition of Perioperative Bleeding in Cardiac Surgery (UDPB) ≥2 classification, and
  3) 24-hour chest tube drainage.

Key Secondary Effectiveness Endpoint:

Change in blood ticagrelor levels (Δ[ticagrelor]) pre- vs. post-CPB measured by liquid chromatography/tandem mass spectrometry (LC/MS-MS)

Additional Secondary Effectiveness Endpoints:

- 24-hour chest tube drainage (volume);
- Total platelet transfusions during hospitalization (volume and units);
- Total PRBC transfusions during hospitalization (volume and units);
- Total UDPB events (by class);
- All surgical re-exploration for excessive bleeding
- Total fatal perioperative bleeding events

Exploratory Endpoints:

- Area under the concentration time curve (AUC), for intraoperative ticagrelor pharmacokinetic (PK) concentration
- Duration of index operation (minutes);
- Length of ICU stay;
- Length of hospital stay;
- 30-day hospital readmissions.

Primary Safety Endpoint:

- GCP-level assessment of all AEs during the study period

Additional Safety Endpoints:

- 30-day cardiac mortality
- 30-day all-cause mortality;
- Postoperative stroke during index hospitalization
- Postoperative myocardial infarction (MI) during index hospitalization
- Urgent postoperative coronary revascularization during the index hospitalization
- Serious device-related adverse events

Investigational design:
This study is a prospective, multi-center, double-blind, randomized pivotal trial to evaluate the safety and effectiveness of the DrugSorb™-ATR device to reduce postoperative bleeding as measured by a composite endpoint of: fatal perioperative bleeding (occurring within 48hrs of the index operation), moderate, severe, or massive bleeding (UDPB ≥2), and 24-hour chest tube drainage in patients undergoing cardiothoracic surgery requiring CPB within two days of ticagrelor discontinuation. Subjects will be randomized in a 1:1 ratio to either standard of care (SOC) alone (control arm) or standard of care plus intraoperative ticagrelor removal with DrugSorb™-ATR integration in the CPB circuit (investigational arm). In the control arm a sham device that is not actively connected to the CPB circuit will be placed in the identical location as the DrugSorb™-ATR device in the investigational arm, with the entire set-up covered by a drape to maintain the

blind. Subjects will be followed out to 30 days after the surgical procedure for assessments of adverse events (AE) and survival.

Prior to randomization, subjects will be stratified based on a) site, and b) type of planned cardiothoracic surgery [either CABG alone, or all other surgeries (including but not limited to combination cardiac procedures, and aortic interventions)]. Stratification is intended to control for confounding effects arising from differing institutional practices and from procedure-specific CPB duration (i.e., device exposure – treatment duration) and bleeding risk.

Number of subjects:
Up to 140 subjects will be randomized into the study (70 into each arm).

Number of sites:
Approximately 30 investigational sites in the US and Canada will participate in the study.

Subjects must meet all inclusion criteria to be eligible to participate in the study. Subjects meeting any of the exclusion criteria are not eligible to participate in the study.

Inclusion criteria:

1. Males and females aged ≥18
2. Written full informed consent
3. Cardiothoracic surgery requiring CPB within two days of ticagrelor discontinuation (last day of completed ticagrelor treatment = day 0):
    - CABG alone
    - Valve repair or replacement
    - Combination surgery (i.e., CABG + valve operation)
    - Aortic surgery

Exclusion criteria:

1. Cardiothoracic surgery occurring 3 days or greater following ticagrelor discontinuation
2. Heart-lung transplant procedures
3. Procedures for ventricular assist device (i.e., implant or revision of LVAD or RVAD)
4. Any of the below conditions that pose a known risk for bleeding:
    - Heparin induced thrombocytopenia
    - Peri-operative platelet count < 50,000 μ/L
    - Hemophilia
    - INR > 1.5
5. Prohibited concomitant antithrombotic medications (reference Appendix 5 of study protocol);
6. Acute sickle cell crisis
7. Known allergy to any of the device components
8. Subjects with active (untreated) systemic infection
9. Subjects with a history of major organ transplantation and those currently receiving immunosuppressive medication (corticosteroids excluded) or who are profoundly immune suppressed
10. Women of childbearing potential with a positive pregnancy test performed during the current admission or who are breast-feeding
11. Subjects with life expectancy of <30 days (not inclusive of the critical condition that is requiring the cardiac operation under study)
12. Inability to comply with the requirements of the study protocol
13. Treatment with an investigational drug or device within 30 days prior to surgery
14. Subjects with previous enrollment in this trial
15. Subjects in whom acute normovolemic hemodilution (ANH) is used perioperatively

Duration of subject participation in the investigation:
Duration of treatment with the DrugSorb™-ATR device is limited to the CPB duration. Subjects will undergo scheduled study procedures until hospital discharge. Hospital discharge means the date of initial discharge from the hospital after the index procedure, irrespective of whether the subject is discharged to home care, secondary care or other rehabilitation unit.

Study follow-up will continue out to 30-days after the index operation to monitor occurrence of adverse events and vital status of study participants.

Test device and subject treatment:
The DrugSorb™-ATR device is a sorbent-filled hemoperfusion cartridge that is able to efficiently adsorb ticagrelor and thereby reduce circulating drug levels in blood. The device is placed into a parallel bypass circuit (between the oxygenator and the venous reservoir) to the main blood flow in a standard CPB circuit. Standard CPB anticoagulation protocols will be followed, since Heparin is not adsorbed by the DrugSorb™-ATR device.

Statistical methods:
Effectiveness Analysis
The primary effectiveness endpoint will be evaluated using the Win Ratio method of analysis for a hierarchical composite endpoint based on the Finkelstein-Schoenfeld test (Finkelstein and Schoenfeld, 1999; Pocock, et al., 2012) with three components: a) fatal perioperative bleeding events (within 48hrs of the index procedure), b) moderate, severe, or massive bleeding based on the Universal Definition of Perioperative Bleeding in Cardiac Surgery (UDPB) ≥2 classification, and c) 24-hour chest tube drainage (volume, mL). The Win Ratio assigns "wins", "losses", or "ties" between randomized groups in a serial fashion across all components of the composite endpoint adhering to the declared hierarchical order from higher to lower clinical importance.[9] [10] A ratio of "wins" greater than 1.0 favors the treatment arm; when the lower bound of a 95% confidence interval (CI) around the ratio exceeds 1.0, the treatment is shown to be statistically superior to control at alpha = 0.05.

The key secondary effectiveness endpoint is the pre-CBP vs. post-CPB change in ticagrelor blood levels as measured by liquid chromatography/tandem mass spectrometry [drug removal endpoint]. Change in each subject's blood concentration of ticagrelor (Δ[ticagrelor]) from immediately before to immediately after CPB will be collected and analyzed by a central core laboratory.

Change from baseline in blood concentration of ticagrelor is defined as:

$$\frac{\text{pre-CPB } [\text{ticagrelor}]_{\text{blood}} - \text{post-CPB } [\text{ticagrelor}]_{\text{blood}}}{\text{pre-CPB } [\text{ticagrelor}]_{\text{blood}}} * 100\%$$

Based on existing benchtop evidence, a conservative estimate of 40% reduction in blood concentration of ticagrelor between pre- and post- DrugSorb™-ATR removal is expected, with a standard deviation of 40%, in the treatment arm. Minimal change is expected in the control arm. A two-sample t-test will be used to evaluate the difference between treatment arms. We anticipate that drug removal data from clinical use in this application will become available during the course of the study and we plan to validate the above assumption based on the *in vivo* data.

Additional powered secondary endpoints include 24-hour CTD (volume [mL]), total platelet transfusions (volume [mL] and units), and total PRBC transfusions (volume [mL] and units) during the index hospitalization. Twenty-four-hour CTD (mL) will be assessed via two-sample t-test for mean difference. The transfusion endpoints will all be analyzed using two-sample t-tests for mean differences, and Fisher-Freeman-Halton exact tests for units. In the event the assumptions for a two-sample t-test are not met in any of the above, a nonparametric test such as a Mann-Whitney test will be employed, with median and range values provided in the output. Other secondary endpoints include the remaining Win Ratio component parts: proportions of fatal perioperative bleeding events will be assessed via Fisher's exact test; and proportions of UDPB events (by category) will be assessed via a Fisher-Freeman-Halton exact test. The secondary endpoint of surgical re-exploration for bleeding will take into account time to re-exploration.

Sample Size

Up to 140 subjects will be randomized in a 1:1 ratio to the treatment and control arms. Sample size is based on assumed response rates for the primary effectiveness Win Ratio sub-components, and can be calculated via an iterative simulation process with programming code available in an appendix to Redfors et al. (2019).[11] With a Finkelstein-Schoenfeld test, total of 57 subjects per arm ensures power of ≥99.7%, using a two-sided alpha (α) of 0.05. With this same per arm sample size, power for the key secondary endpoint is estimated at >99.9%, and for 24-hour chest tube drainage (mL), >99.9%, based on a two-sample t-test assuming equal variance and a two-sided alpha of 0.05. Similarly, although assuming unequal variances, power for comparisons of platelet transfusions (volume [mL]) and PRBC transfusions (volume [mL]), is estimated at 98.0% and 96.7%, respectively.

Analysis Populations

Enrolled subjects include all subjects who provide informed assent/consent. Enrolled subjects who do not meet criteria for study eligibility are screening failures and will exit the study.

The Intent-to-Treat (ITT) Population will include all subjects who are randomized. The modified Intent-to-Treat (mITT) Population will include all randomized subjects who undergo the index surgical procedure **and** receive a study device (whether DrugSorb™-ATR or *sham*). The primary analyses of the trial will be performed on the mITT Population. Baseline demographic and clinical variables will be summarized for each of the treatment groups in the mITT population. So long as the ITT and mITT populations are not identical, the ITT patients who do not fall within the mITT population will be presented in a listing, including the reasons for why they did not receive a study device. The Per Protocol (PP) Population will include all mITT subjects who have no major protocol violations. Analysis of the primary efficacy endpoint will be performed in the PP population as a supplemental analysis.

The Safety Analysis (SA) Population will include all enrolled subjects who are treated with a study device.

Safety Analysis

All the safety endpoints will be analyzed in the SA population. Additional safety analyses will be conducted on the mITT and PP Population if they are different from the SA population.

All AEs occurring after the start of the CPB procedure will be listed and summarized using descriptive methodology. The incidence of AEs will be presented by severity and by relationship to the investigational device (DrugSorb™-ATR or sham) as determined by the Investigator (or designee). Each AE will be coded using the Medical Dictionary for Regulatory Activities®. Observed values for clinical laboratory test data and vital signs, along with change from baseline results, will be summarized by collection time point. A summary of clinically notable values will be provided.

Safety oversight committees:

DSMB:

Three physicians with relevant clinical/medical and investigational expertise together with an independent statistician will form the Data Safety Monitoring Board (DSMB). The primary role of the DSMB is to oversee the safety of subjects enrolled in the study. All DSMB members will be independent from the investigative sites and the study sponsor. The schedule and process associated with DSMB activities will be outlined in the DSMB charter.

CEC:

An independent group of physicians who are not involved in the clinical investigation will act as the Clinical Events Committee (CEC) under the direction of an academic research organization. The CEC will be responsible for the review and adjudication of effectiveness endpoints and safety events that occur during study duration (i.e., within 30 days post-operation) according to standardized definitions as outlined in the CEC charter.

STUDY ORGANIZATION

Sponsor:
CytoSorbents, Inc.

Executive Committee:

- **U.S. Principal Investigators:**
  - Michael Mack, MD (Baylor Scott & White Health)
  - C. Michael Gibson, MD (Beth Israel Deaconess Medical Center)
- **Canada Principal Investigator:**
  - Richard Whitlock, MD (McMaster University)
- **Members:**
  - David Schneider, MD (University of Vermont Medical Center)
  - Frank Sellke, MD (Brown University; Rhode Island Hospital and The Miriam Hospital)
  - Vinod Thourani, MD (Piedmont Heart Institute)
  - C. David Mazer, MD (St. Michael's Hospital- Toronto)
  - James Demetrios Douketis, MD (McMaster University; St. Joseph's Healthcare Hamilton)
  - Efthymios Deliargyris, MD (CytoSorbents, Inc.)

Clinical Events Committee (CEC):
Baim Institute for Clinical Research (previously known as the Harvard Clinical Research Institute)

Data Safety and Monitoring Board (DSMB):
Center for Interventional Cardiovascular Research and Clinical Trials, Icahn School of Medicine at Mount Sinai

Independent Statistician for the DSMB:
Stuart J. Pocock, PhD (London School of Hygiene & Tropical Medicine)

Contracted Research Organization (CRO):
Medpace

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LIST OF TABLES AND FIGURES

LIST OF ABBREVIATIONS

Abbreviation	Definition
ACS	Acute coronary syndrome
ADE	Adverse device effect
ADP	Adenosine diphosphate
AE	Adverse event
ANH	Acute normovolemic hemodilution
ATR	Anti-Thrombotic Removal
AUC	Area under the concentration time curve
CABG	Coronary artery bypass grafting
CEC	Clinical Events Committee
CFR	Code of Federal Regulations
CPB	Cardiopulmonary bypass
CIP	Clinical investigation plan
CRO	Contract Research Organization
Cryoppt	Cryoprecipitate
DSMB	Data Safety Monitoring Board
eCRF	Electronic case report form
EC	Ethics committee
ECG	Electrocardiogram
FDA	US Food and Drug Administration
FFP	Fresh frozen plasma
GCP	Good Clinical Practice
ICF	Informed consent form
ICH	International Council for Harmonisation
ICU	Intensive care unit
IFU	Instructions for use
ISO	International Organization for Standardization
ITT	Intent-to-Treat
IxRS	Interactive Voice/Web response
mITT	Modified Intent-to-Treat
MedDRA	Medical Dictionary for Regulatory Activities
NSTEMI	Non-ST segment elevation myocardial infarction
PCC	Prothrombin complex concentrates
PK	Pharmacokinetic
PLATO	Platelet Inhibition and Patient Outcomes
PLT	Platelet concentrates
PP	Per Protocol
PRBC	Packed red blood cells
RCT	Randomized controlled trial
rFVIIa	Recombinant activated factor VII

SA	Safety Analysis
SADE	Serious adverse device effect
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SOC	Standard of care
UADE	Unanticipated adverse device effect
UDPB	Universal definition of perioperative bleeding in cardiac surgery
WBC	White blood cell
WHO	World Health Organization

1. INTRODUCTION

1.1. Background and Clinical Need

Ticagrelor is a reversibly binding inhibitor of the platelet $P2Y_{12}$ receptor, antagonizing the activation of $P2Y_{12}$ by adenosine diphosphate (ADP). Ticagrelor is indicated to reduce thrombotic cardiovascular events in patients with acute coronary syndrome (ACS). [1] As with any drug that inhibits platelet function, the predominant safety concern with ticagrelor is the heightened risk of bleeding. For patients on ticagrelor requiring cardiac or cardiothoracic surgery, the 2011 ACCF/AHA guidelines recommend discontinuing ticagrelor at least 5 days before elective CABG, and at least 24 hours before urgent CABG. [2]

The pivotal study of Platelet Inhibition and Patient Outcomes (PLATO) study compared ticagrelor to another $P2Y_{12}$ receptor antagonist, clopidogrel, administered with aspirin and other standard therapy in patients with ACS for the prevention of major adverse cardiovascular events. [4] In the PLATO study approximately 10% of the study population required coronary artery bypass grafting (CABG) surgery and approximately half of those patients had CABG before the recommended washout period. These patients experienced very high rates of serious postoperative bleeding, especially if the operation was within two days of ticagrelor discontinuation. [4] Importantly, studies in this setting have shown that platelet transfusions are inefficient in reversing the antiplatelet action of ticagrelor and limiting the excess bleeding risk, which is consistent with the drug labeling. [3] [12]

In contrast to ticagrelor that requires washout before surgery, aspirin is continued during coronary artery bypass grafting (CABG) in standard-of-care practices at United States (US) and Canadian centers. The rationale is that although there is some evidence that aspirin increases the risk of bleeding in CABG patients, on balance the protective benefits are generally thought to outweigh the bleeding risk. Practice guidelines from the ACCF and AHA in 2011 therefore recommend not discontinuing aspirin in patients undergoing CABG. [2] Indeed, the above guidelines recommend that if aspirin was not initiated pre-operatively, it should be initiated (100mg-325mg) within six hours postoperatively and continued indefinitely to improve graft patency and reduce risk of adverse cardiovascular events.

The effects of ticagrelor in combination with aspirin versus aspirin alone on bleeding in CABG patients can be estimated from observational studies that investigated the timing of ticagrelor discontinuation and bleeding in CABG patients. In the SWEDEHEART registry, patients who underwent CABG $\leq$24 hours following ticagrelor discontinuation (with aspirin continued) had an incidence of major bleeding [Bleeding Academic Research Consortium-CABG (BARC-4) definition] of approximately 38%.[13] This incidence was reduced to <10% in those undergoing surgery 4-5 days after ticagrelor discontinuation. Data from PLATO showed that >65% of patients who underwent CABG within 24 hours of ticagrelor discontinuation experienced major, life-threatening, or fatal CABG-related bleeding (PLATO definition). In contrast, patients who underwent CABG 4-5 days after discontinuation of ticagrelor had an incidence of major/life-threatening/fatal bleeding of 27.8%.[5] It can be inferred from this that dual antiplatelet therapy with ticagrelor and aspirin has a large impact on bleeding that is greatly reduced if standard recommended wash-out durations are followed (time taken for offset of action of ticagrelor). Similar results from review of the European Multicenter Registry on Coronary Artery Bypass Grafting (E-CABG) are detailed in **Section 3**.

Currently, there are no available interventions to address the significant unmet medical need in patients whose clinical condition necessitates cardiothoracic surgery before adequate washout of ticagrelor can occur. It is for this reason, DrugSorb™- ATR has been designated a Breakthrough Device by the FDA.

1.2. Preclinical Data Informing Study Design

Preclinical studies have shown that ticagrelor is rapidly and efficiently removed from whole blood by CytoSorb® hemoadsorption. Of note, DrugSorb™-ATR is identical to the CytoSorb® device but with an updated name (refer to **Section 1.4** for details). To maintain consistent nomenclature with that used in published data, the device will be referred to by its historic name CytoSorb® in the discussions of preclinical and clinical data informing study design.

Human Whole Blood Experiments

Removal of ticagrelor from human whole blood ex vivo by CytoSorb® hemoadsorption has been shown in a model using approximately 500 mL of blood obtained from healthy volunteers. [7] The blood was placed in a one-liter perfusion bag and was anticoagulated with heparin and mixed with 18.1 mg of ticagrelor. The blood-drug mix was then allowed to equilibrate for 30 minutes at room temperature under gentle agitation of the bag to achieve a starting drug concentration of 70 μmol/L (36.2 μg/mL). This high drug concentration was reportedly chosen to provide a large dynamic range to study changes in drug concentration over the time course of the experiment. Using a standard infusion pump, blood was then circulated from the bag through the CytoSorb® device at a flow rate of 17 mL/min, a rate that circulates 500 mL every 29 minutes, and then back to the bag. (Note: for comparison, a 60 kg human with an estimated total blood volume of 4.7 L will circulate this total blood volume through the CytoSorb® device every 16 minutes at a flow rate of 300 mL/min). The reservoir bag underwent continual gentle agitation to mix reservoir blood with returned blood. Blood samples to assay for the concentration of ticagrelor were drawn from the reservoir bag every hour after start of flow through the CytoSorb® device, up to 10 hours. Concentrations of ticagrelor were determined using tandem liquid chromatography mass spectrometry. The results showed that >99% of the ticagrelor was removed from human whole blood ex vivo within the first 3 hours of CytoSorb® hemoadsorption.

Bovine Whole Blood Experiments

Studies were conducted to evaluate the removal of ticagrelor from bovine whole blood ex vivo by CytoSorb® and were similar in design to the human whole blood experiments described above. Approximately 800 mL of bovine whole blood was used for the study. The starting concentration of ticagrelor was 1.15 μg/mL, a concentration representative of plasma drug levels in humans following standard dosing of ticagrelor. The pump circulated blood through the CytoSorb® device at a rate similar to the rate used in humans. Blood samples to assay for the concentration of ticagrelor were drawn from the reservoir bag at specific intervals after start of flow through the CytoSorb® device. Concentrations of ticagrelor were determined using tandem liquid chromatography mass spectrometry. The results (**Figure 1**) showed that approximately 80% of the ticagrelor was removed from bovine whole blood ex vivo within 90 minutes of CytoSorb® hemoadsorption.

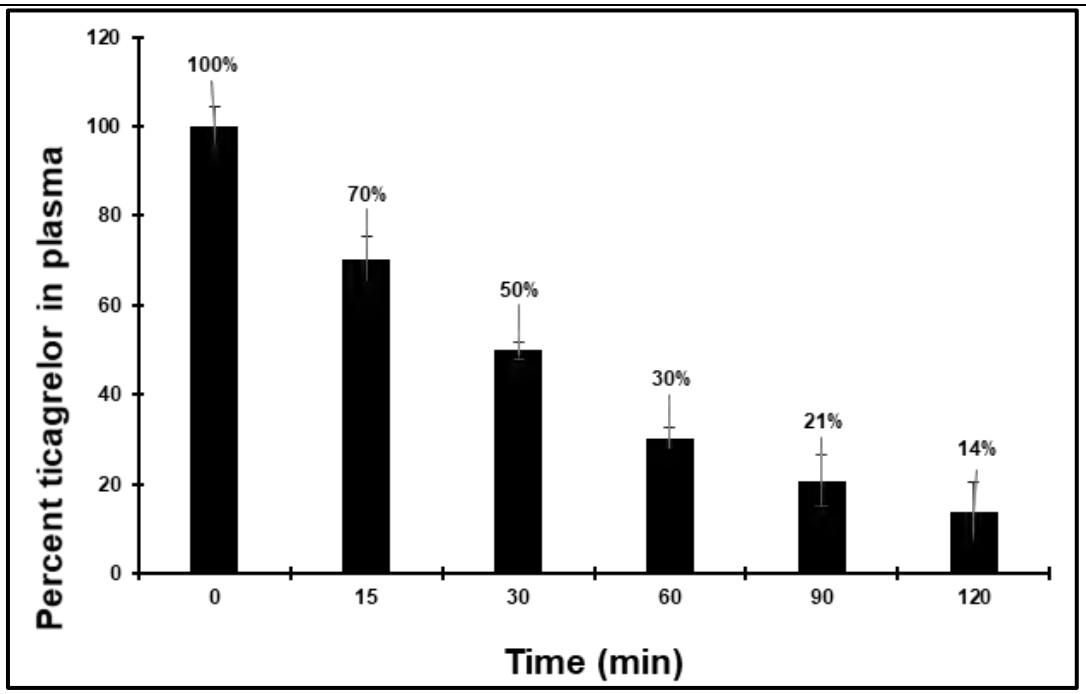

Figure 1: Removal of Ticagrelor From Whole Bovine Blood Ex Vivo

1.3. Clinical Data Informing Study Design

To date, over 120,000 CytoSorb® treatments have been performed globally. Approximately 10% of the treatments have been intra-operative on cardiopulmonary bypass (CPB) including a significant number for the removal of ticagrelor and rivaroxaban that are both CE mark approved. Overall, the device has a favorable safety profile.

A retrospective case-control series from Asklepios Klinik St. Georg (Hamburg, Germany) evaluated the use of the CytoSorb® device in patients on ticagrelor undergoing emergent cardiothoracic surgery with CPB. A historical cohort of patients who underwent standard surgery on CPB but without the use of CytoSorb® was compared to the cohort of patients who received CytoSorb® hemoadsorption during CPB. Results showed significant reductions in multiple measures of postoperative bleeding with the intra-operative use of CytoSorb® that included blood products transfused, 24-hr chest tube drainage volume, rate of surgical re-exploration, length of ICU and total hospital stay. [8] Importantly, no device-related adverse events (AEs), unanticipated adverse device events (UADEs) or device malfunctions were reported.

1.4. Device Background and Nomenclature

The DrugSorb™-ATR device is identical to the CytoSorb® device discussed in the above preclinical and clinical data. The only difference between the two devices is a name change which was implemented to more closely align the device name with its intended use. As such, for the purposes of this study, the device will hereafter be referred to as DrugSorb™-ATR whenever reference is being made to its use in the indication of antithrombotic drug removal.

1.5. Study Design

The STAR-T study is designed to demonstrate reductions in postoperative bleeding complications with the intraoperative use of DrugSorb™-ATR in patients undergoing cardiothoracic surgery within two days of ticagrelor discontinuation. These patients have been demonstrated in the literature to be at

greatest risk for bleeding complications (refer to **Section 3** for details). The study also aims to establish the safety of intraoperative DrugSorb™-ATR use in the target population.

The mechanism of action is removal of ticagrelor from active circulation through hemoadsorption while the patient is on cardiopulmonary bypass. Thus, the change in total blood concentration of ticagrelor following CPB will be measured as a key secondary endpoint. To do so, patient blood samples will be obtained during the pre-operative and immediate post-CPB time periods for ticagrelor concentration testing. This will allow comparison of clinical outcomes with presence or absence of reduction in circulating drug concentration. Serial sampling (every 30 min) for quantification of serial changes in blood ticagrelor levels will also be obtained through the first 2 hours of therapy on CPB. This supplemental drug removal data will be analyzed as an exploratory endpoint. Additional outcome measures to be evaluated include those that are documented as part of routine care, and are detailed in **Section 4.3**.
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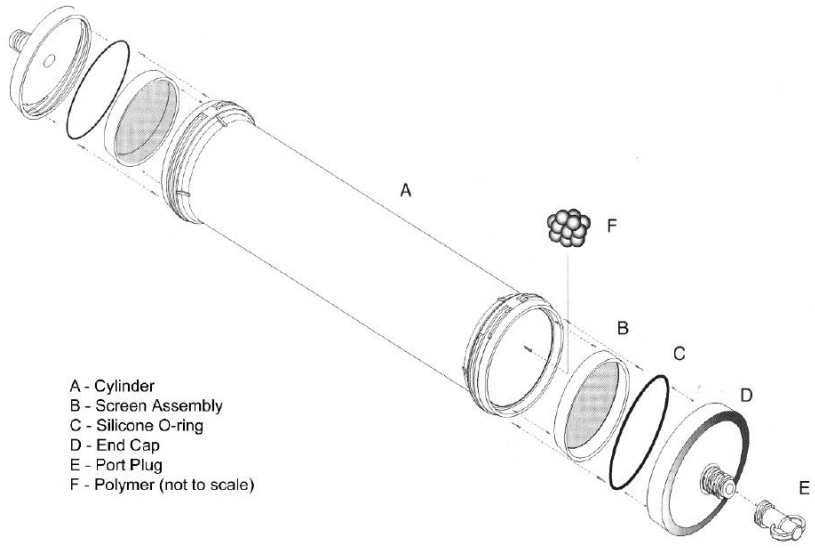
2. DRUGSORB™-ATR DESCRIPTION AND INTENDED USE

2.1. Description of the DrugSorb™-ATR Device and Principle of Operation

The DrugSorb™-ATR device is a sorbent-filled hemoperfusion cartridge (**Figure 2**). The cartridge consists of a cylinder and end-cap assembly filled with biocompatible porous polymer beads. At either end of the cylinder, a fine mesh screen is placed to retain the polymer beads within the device. Each end-cap has a standard blood tubing connector, which is compatible with standard CPB blood tubing lines.

The polymer beads are composed of a divinylbenzene/polyvinyl pyrrolidone co-polymer, where each bead has hundreds of thousands of tightly controlled pores and channels that are generated via suspension polymerization. These pores and channels, in turn, enable the porous polymer beads to remove middle molecular weight substances between ~5-kDa - 60-kDa, based on pore capture (size) and surface adsorption.

Figure 2. DrugSorb™-ATR Device



The polymer in the DrugSorb™-ATR device is effective at binding small molecules with molecular

moieties contained in ticagrelor. Ticagrelor easily passes into the pores of the polymer where it adsorbs onto the internal polymer surface. This surface adsorption is governed by the hydrophobic nature of the polymer, through a combination of non-polar interactions, hydrogen bonding, and Van der Waals forces. These drug-polymer interactions favor removal of hydrophobic molecules over hydrophilic ones.

The DrugSorb™-ATR device is designed for use in extracorporeal circuits. For this investigation, the device will be incorporated as a shunt in the standard CPB circuit (**Figure 3**), in accordance with the device Instructions For Use (IFU). The target flow rate through the device is to be 500 ± 100 mL/minute (approximately 15% to 20% of a typical flow rate in CPB). In patients on hypothermic circulatory arrest (HCA) where the clinical needs during CPB do not always allow the flow rate through the device to be maintained at 500 ± 100 mL/min, the flow rate through the device may range from 100 to 700 mL/min in accordance with the minimum/maximum parameters stated in the device IFU. Blood flow is controlled via an adjustable roller clamp distal to the cartridge and is monitored through ultrasonic flow detection (provided by Sponsor) to maintain a target blood flow consistent with protocol recommendations. Upon completion of the surgical procedure, the entire circuit containing the device is flushed with saline, which is consistent practice with all CPB circuits, and the blood in the circuit is delivered back to the patient.

For this investigation the duration of device exposure will be limited to the duration of CPB since the use of DrugSorb™-ATR will be initiated at the start of CPB and terminated at the end of CPB. Treatment is continuous and is expected to be of a shorter duration than the maximum treatment time provided in the IFU. Exceptions to continuous treatment could occur in the event of a device quality complaint (i.e., device deficiency/observation) in which case the flow through the device and therefore treatment may be terminated before the end of CPB.

The intraoperative use of anticoagulants (e.g., heparin) will be used in this investigation as per the standard procedures of each clinical institution and in accordance with the IFU.

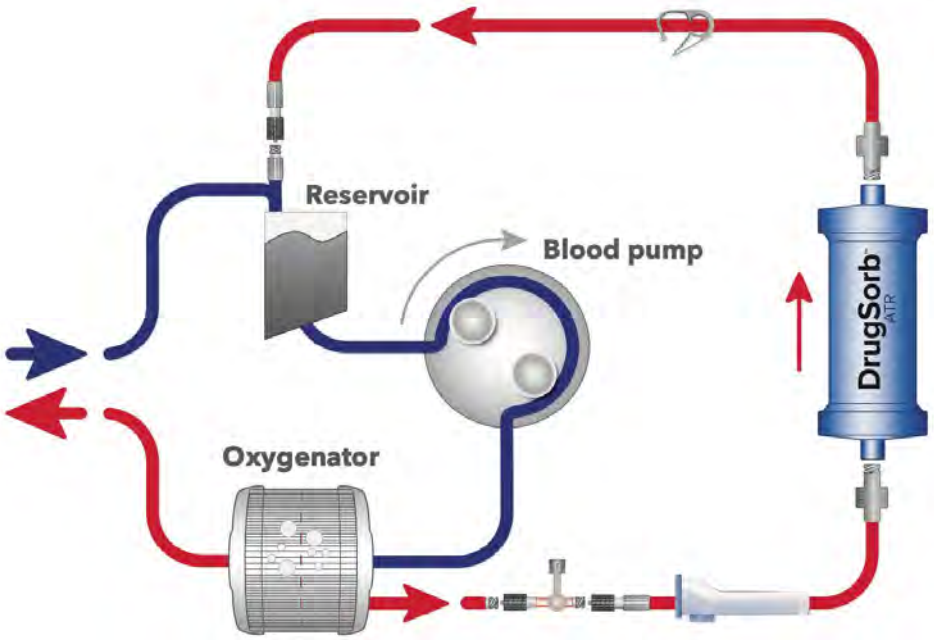


Figure 3. DrugSorb™-ATR Integration in the Cardiopulmonary Bypass Circuit

2.2. Treatment Conditions

In addition to the DrugSorb™-ATR device, the following will be provided by the Sponsor:

- IFU of the device
- Training from a Field Clinical Engineer to provide guidance on incorporating and using the device within a CPB circuit
- A transonic (or equivalent) flow detector
- Disposable connector and tubing sets to connect the investigational device to the CPB circuit
- Standard roller clamp
- Disposable hemostats

2.3. Device Accountability

The procedures for the accountability of investigational devices should follow the specifications below:

- Access to investigational devices shall be controlled and the investigational devices shall be used only in the clinical investigation and according to the Clinical Investigation Plan (CIP).
- The Sponsor or its designees shall keep records to document the physical location of all investigational devices from shipment of investigational devices to the investigation sites, use of the investigational devices, and either return or disposal.
- The Principal Investigator or an authorized designee shall keep records documenting the receipt, use, return, and disposal of the investigational devices, which shall include:
    - the date of receipt
    - identification of each investigational device (lot number and serial number)
    - the expiry date, if applicable
    - the date or dates of use
    - patient identification
    - the date of return of unused, expired, or malfunctioning investigational devices, if applicable

2.4. Use of the Investigational Device

The proposed investigative use of the DrugSorb™-ATR device is for the removal of ticagrelor as an adjunct to the standard of care in subjects undergoing cardiothoracic surgery requiring CPB within two days of ticagrelor discontinuation and will only be used as specified by this clinical protocol.

2.5. Investigational Device/Procedures Training

The DrugSorb™-ATR device is easily integrated in a standard heart-lung machine CPB circuit. In this study, as described in the Instructions for Use (IFU), one DrugSorb™-ATR cartridge will be placed in a bypass circuit connected between the oxygenator and cardiotomy reservoir as shown in **Figure 3**, and separate from the main blood flow to the subject. Blood flow through this circuit is controlled via an adjustable roller clamp distal to the cartridges and monitored via ultrasonic flow detection to maintain flow. In standard subjects, flow rates through the DrugSorb™-ATR device should be maintained at 500 ± 100mL/min. In subjects on HCA where CPB flow rates are diminished, flow through the device should be maintained ≥100mL/min. In accordance with the IFU, maximum blood flow through the device should not exceed 700mL/min at any point during the procedure.

The circuit containing the DrugSorb™-ATR device will be connected prior to the start of the procedure. Blood flow through the DrugSorb™-ATR device will commence when the subject goes on CPB. Use of the DrugSorb™-ATR device will stop at the end of CPB. Once the CPB procedure is

complete the hemoperfusion session will be ended, the circuit flushed with saline or drained by gravity, with the return of blood in the circuit back to the subject, per the hospital protocol.

DrugSorb™-ATR device training for the device users involved in this study will occur prior to DrugSorb™-ATR device use and will be documented in a training log.

3. STUDY JUSTIFICATION

Ticagrelor is the first FDA-approved, orally administered platelet inhibitor that reversibly antagonizes the $P2Y_{12}$ adenosine diphosphate (ADP) receptor on platelets. Ticagrelor is also recommended as part of dual anti-platelet therapy with aspirin, prior to percutaneous coronary intervention (PCI) and stent placement to reduce the risk of in-stent thrombosis. [1]

The most common adverse effect of ticagrelor is the increased risk of unwanted, serious, and potentially fatal bleeding from spontaneous events (e.g., gastrointestinal bleed, intracranial hemorrhagic stroke), major trauma, and/or unscheduled, emergent or urgent surgeries with high bleeding risk. Currently, there are no approved agents to either prevent or treat bleeding related to ticagrelor-induced platelet dysfunction. Held et. al. evaluated bleeding events in patients from the PLATO study who required CABG ≤7 days of last ticagrelor dose (nearly 50% of which underwent surgery ≤3 days since taking the drug). Within this population 81.3% experienced major bleeding events based on the PLATO study definitions; bleeding in accordance with the TIMI major criteria occurred in 59.3% of these patients, and 43.7% experienced CABG-related life threatening or fatal bleeding. [5] Most of the major bleeding events occurred within the first 24 hours after surgery. Data from the European Multicenter Registry on Coronary Artery Bypass Grafting (E-CABG) demonstrated that occurrence of major perioperative bleeding per Universal Definition of Perioperative Bleeding in Cardiac Surgery (UDPB) criteria was most significant in patients undergoing cardiac surgery ≤2 days after last ticagrelor dose. [6] These patients experienced a 17.7% incidence of severe or massive bleeding by UDPB criteria, as compared to just 7.7% in patients waiting 3 days after last ticagrelor dose before undergoing surgery. With a propensity-score matched cohort the difference was 16.0% vs 2.7%, respectively ($p = 0.003$). [6] Of note, incidence of even *moderate* bleeding events is strongly influenced by timing of last ticagrelor dose prior to surgery. As seen within the CAPITAL Registry dataset, patients had a 40.5% incidence of *at least moderate* bleeding (UDPB ≥2) when undergoing CABG <72hrs after last ticagrelor dose. This was compared to <20% incidence of such bleeding events in patients who were able to wait for longer wash-out periods. [14]

In patients with significant postoperative bleeding, current standards of care utilize blood product transfusions as part of the management strategy. However, blood products – including transfusion of platelets – have not been demonstrated to be particularly effective in addressing ticagrelor-induced bleeding. [15] Thus, the recommended strategy to reverse ticagrelor-induced platelet dysfunction and reduce the risk of bleeding is to discontinue ticagrelor therapy ≥5 days prior to elective cardiac surgery, to allow effective drug "wash out." [2] However, patients with emergent or urgent cardiovascular conditions (e.g., acute ascending aortic dissection, left main or multi-vessel coronary disease not amenable to PCI, or complications of PCI) cannot generally wait for this wash out period, and require emergent or urgent surgery, otherwise risking permanent injury, disability, or death. In such cases, the impaired platelet reactivity caused by ticagrelor is often associated with significant blood loss and associated morbidity, with no currently approved therapies to treat it.

Integration of a DrugSorb™-ATR device into the CPB circuit to remove ticagrelor from patients undergoing urgent surgery provides an option for clinicians to accelerate ticagrelor wash-out and reduce bleeding risk. **Figure 4** compares the natural washout of a single dose of ticagrelor, as measured in the ONSET-OFFSET trial (Husted et. al), to the accelerated removal with CytoSorb®

(i.e., DrugSorb™-ATR) using a simulated CPB circuit with bovine blood at comparable starting C_{max} values. [16] These *in vitro* data demonstrate that DrugSorb™-ATR removal of ticagrelor is substantially faster than natural washout. Levels of $P2Y_{12}$ receptor modification (and therefore platelet activity) closely follow plasma levels of ticagrelor due to the rapid on/off receptor kinetics of the drug. [1] Thus, it is hypothesized that ticagrelor removal by the DrugSorb™-ATR device will significantly reduce postoperative bleeding. As discussed above, this effect would be most meaningful in those patients undergoing cardiac surgery within two days of ticagrelor discontinuation, since those are the patients *at highest risk* of major bleeding complications.

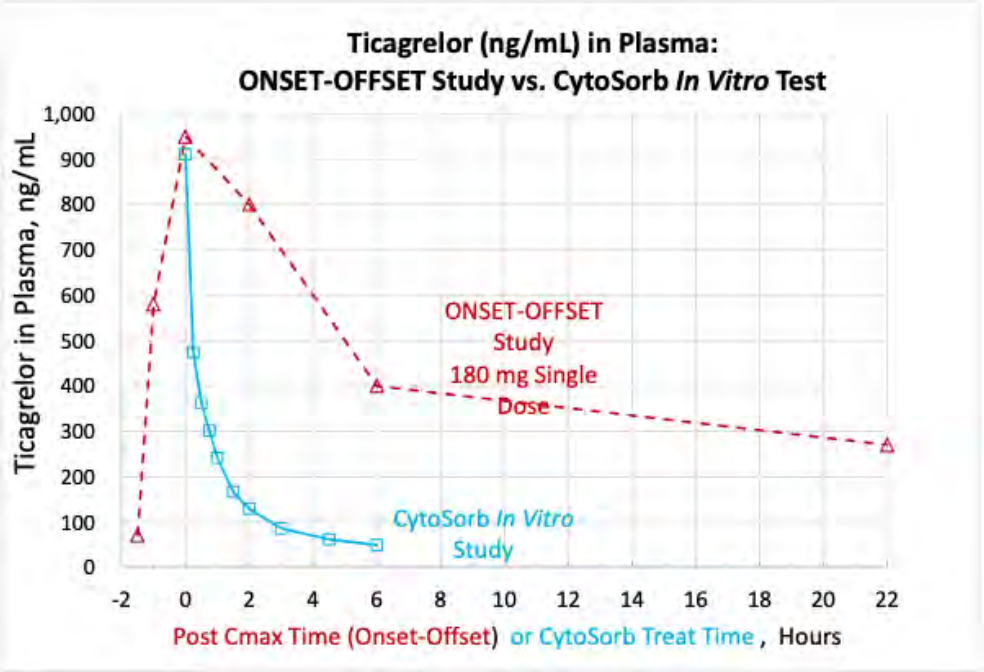


Figure 4. Comparison of Natural Washout (Onset-Offset Study) versus CytoSorb®/DrugSorb™-ATR Washout (In-vitro test) From C_{max}

Primary Effectiveness Endpoint: The composite primary endpoint of the trial was specifically constructed to assess the ability of the DrugSorb™-ATR device to reduce the full spectrum of postoperative bleeding in patients on ticagrelor undergoing cardiothoracic surgery with CPB within two days following the day of last dose. The primary effectiveness endpoint will be evaluated using the Win Ratio method of analysis for a hierarchical composite endpoint based on the Finkelstein-Schoenfeld test (Finkelstein and Schoenfeld, 1999; Pocock, et al., 2012) with three components ranked according to clinical importance. [9] [10] The three components are: a) fatal perioperative bleeding events, b) moderate, severe, or massive bleeding events based on the Universal Definition of Perioperative Bleeding in Cardiac Surgery (UDPB) ≥2 classification, and c) 24-hour chest tube drainage (mL). Accordingly, the composite primary endpoint will capture the full spectrum of postoperative bleeding ranging from catastrophic fatal bleeding to excess chest tube drainage.

The fatal perioperative bleeding events included in the primary effectiveness endpoint are those that occur within 48 hours of the index procedure. This window will focus on the fatal bleeding events that occur in temporal proximity to the index procedure and may therefore be modifiable by the intervention. In keeping with standard clinical practice, study subjects with ACS or recent coronary stent placement will be re-started on ticagrelor (or the treating physician's choice agent for DAPT) during postoperative day 1 if there is no concern for bleeding (**Section 9.1.3**). This increases the probability that fatal bleeding occurring >48 hours post-op is independent of DrugSorb™-ATR

effectiveness, and rather due to therapeutic drug levels from re-initiation of antithrombotic therapy.

The UDPB scale is a standardized bleeding definition that was specifically designed by experts to capture early bleeding after cardiac surgery and is based on the following 9 criteria occurring either in surgery or during the first postoperative day: (1) delayed sternal closure, (2) postoperative chest tube output, (3) packed red blood cell transfusion, (4) fresh frozen plasma transfusion, (5) platelet transfusion, (6) cryoprecipitate transfusion, (7) use of factor concentrates, (8) use of recombinant activated factor VII (rFVIIa), and (9) surgical re-exploration. [17] The UDPB scale defines 5 perioperative bleeding classes (0-4) as shown in **Table 1** (below). Importantly, it has been demonstrated that higher classification within the UDPB (starting from moderate, up through severe-massive) is correlated with higher 30-day mortality rate, thus making the standardized definition both a useful descriptive tool as well as a predictor of clinical outcome. [17]

Table 1. Bleeding Class According to the Universal Definition of Perioperative Bleeding in Adult Cardiac Surgery

Class	Sternal Closure delayed	Postoperative chest tube blood loss within 12 h (mL)	PRBC (units)	FFP (units)	PLT (units)	Cryoppt	PCCs	rFVIIa	Reexploration/ tamponade
0	No	< 600	0*	0	0	No	No	No	No
1	No	601-800	1	0	0	No	No	No	No
2	No	801-1000	2-4	2-4	Yes	Yes	Yes	No	No
3	Yes	1001-2000	5-10	5-10	N/A	N/A	N/A	No	Yes
4	N/A	>2000	>10	>10	N/A	N/A	N/A	Yes	N/A

Class 0 = Insignificant; Class 1 = Mild; Class 2 = Moderate; Class 3 = Severe; Class 4 = Massive
PRBC = packed red blood cells; FFP = fresh frozen plasma; PLT = platelet concentrates; Cryoppt = Cryoprecipitate; PCCs = prothrombin complex concentrates = rFVIIa, recombinant activated factor VII; N/A, not applicable
For purposes of UDPB, PRBC, PLT, FFP, and Cryoppt transfusions are counted beginning **at chest closure**. PCC and rFVIIa transfusions are counted beginning at the start of the procedure.
* Correction of preoperative anemia or hemodilution only; the number of PRBCs used should only be considered in the UDPB when accompanied by other signs of Perioperative bleeding. Prophylactic/preoperative transfusion of blood products and factor concentrates do not contribute to UDPB.

Exact measurements of postoperative blood loss are difficult, given that laboratory values such as hemoglobin and hematocrit are heavily influenced by intra- and postoperative fluid shifts, and transfusion protocols may vary by institution. However, chest tube drainage (CTD) in the early postoperative period (≤24 hours) is a metric that is easily quantifiable and routinely used in clinical practice. Enhanced Recovery After Surgery (ERAS) guidelines in cardiac surgery recommend chest tube placement and drainage to prevent accumulation of blood in the chest and mediastinum during the postoperative period, and their placement is standard of care following open cardiac surgery. [18]

The inclusion of CTD in the composite primary effectiveness endpoint is underscored by its clinical relevance evidenced by the use of CTD in everyday clinical practice protocols for postoperative decision-making (e.g., criteria for mediastinal re-exploration) that rely on rate and volume of chest tube drainage. [19] Postoperative CTD volume during the first 12 hours is included within the UDPB classification, however 24-hr CTD has also been identified as an important independent metric. Importantly, 24-hr CTD has been demonstrated to correlate with other clinical outcomes, including transfusion requirements and duration of hospital stay in linear regression models. [20, 21] Excessive 24-hr CTD as defined by >1000 mL has been shown to be an independent predictor of postoperative acute kidney injury (odds ratio 1.40, $p < 0.001$). [22] Most importantly, 24-hr CTD is an independent predictor of in-hospital mortality with a linear, ***dose-dependent*** relationship that is independent of blood transfusion requirement. [23]

Key Secondary Endpoint: Change in preoperative to postoperative ticagrelor concentration [drug removal] will be the key secondary endpoint that will investigate the ability of the DrugSorb™-ATR device to successfully remove ticagrelor. Furthermore, this information will be helpful for establishing a relationship between ticagrelor removal and decreased postoperative bleeding (i.e., less drug = less bleeding).

Pre-randomization stratification based on a) study site, and b) planned type of cardiothoracic operation will address potential confounding variables that may not be fully controlled in the randomization process. Stratification by site is intended to control for institutional differences in standard practices, such as transfusion and re-operation protocols. Stratification by the type of planned operation will separate subjects undergoing CABG-alone from those undergoing all other cardiothoracic surgeries. The category of "all other" cardiac surgeries includes combination cases (e.g., CABG + valve, double valve, etc.) and ascending aortic interventions. Compared to CABG-alone, these operations have a significantly different profile in regards to bleeding risk and procedure/CPB duration. This distinction is also important since device exposure is directly related to the amount of time spent on CPB. Details of the statistical considerations around the endpoints discussed above will be provided in **Section 11**.

In summary, the objective of the randomized, double-blind investigation outlined in this protocol will be to examine the ability of DrugSorb™-ATR (a non-pyrogenic, sterile, single-use device designed to remove the small hydrophobic drug, ticagrelor) to reduce postoperative bleeding compared to current standard of care. Measurements of drug removal will also be performed to establish that bleeding reductions are related to reductions in ticagrelor levels. The safety of the device in this setting will be assessed by systematic capture of all AEs at the CGP level.

4. INVESTIGATIONAL PLAN

4.1. Study Objective(s)

Patients undergoing cardiothoracic surgery within two days of ticagrelor discontinuation are at increased risk of bleeding complications due to platelet dysfunction. The DrugSorb™-ATR hemoadsorption device removes circulating ticagrelor at rates much higher than normal washout, thus reducing platelet dysfunction, improving hemostasis, and reducing postoperative blood loss.

The objectives of this study are as follows:

- To demonstrate reductions in postoperative bleeding with the intraoperative use of DrugSorb™-ATR in patients undergoing cardiothoracic surgery with CPB within two days of ticagrelor discontinuation;
- To demonstrate reductions in ticagrelor blood levels Δ[ticagrelor] with the intraoperative use of DrugSorb™-ATR;
- To establish the safety of the intraoperative use of DrugSorb™-ATR in the intended population.

The hypothesis is that, for patients undergoing cardiothoracic surgery with CPB within two days oϕ ticagrelor discontinuation, the intraoperative use of the DrugSorb™-ATR device will significantly reduce postoperative bleeding as measured by a ranked composite endpoint of clinically meaningful bleeding metrics: 1) fatal perioperative bleeding, 2) moderate, severe, or massive bleeding events based on the Universal Definition of Perioperative Bleeding in Cardiac Surgery (UDPB) ≥2 classification, and 3) 24-hour chest tube drainage (CTD).

4.2. Study Design

This will be a prospective, multi-center, randomized, double-blind clinical study. Subjects will be randomized in a 1:1 ratio to either standard of care (SOC) or standard of care plus intraoperative treatment with the DrugSorb™-ATR device.

4.3. Study Outcomes

4.3.1. Primary Effectiveness Endpoint:

- Ranked composite of perioperative bleeding events:
  1) Fatal perioperative bleeding (occurring within 48hrs post-index procedure),
  2) UDPB ≥2 perioperative bleeding, and
  3) 24-hour chest tube drainage volume (mL).

Refer to **Table 1** for details of the UDPB classification of bleeding events.

4.3.2. Key Secondary Effectiveness Endpoint:

- Percent difference in pre-CPB vs. post-CPB blood ticagrelor levels as measured by liquid chromatography/tandem mass spectrometry [LC/MS-MS] (i.e., Δ[ticagrelor]).

4.3.3. Additional Secondary Effectiveness Endpoints:

- 24-hour chest tube drainage volume
- Total platelet transfusions during the index hospitalization (volume and units)
- Total PRBC transfusions during the index hospitalization (volume and units)
- Total UDPB events (by class)
- All surgical re-exploration for excessive bleeding
- Total fatal perioperative bleeding events

4.3.4. Exploratory Endpoint(s):

- Area under the concentration time curve (AUC), for intraoperative ticagrelor pharmacokinetic (PK) concentration
- Operative time (measured from start of skin incision to completion of chest closure)
- Duration of ICU stay
- Duration of hospital stay
- 30-day hospital readmissions

4.3.5. Primary Safety Endpoint:

- The primary safety endpoint of this trial is to evaluate the product safety profile through the GCP-level assessment of AEs during the study period.

4.3.6. Additional Safety Endpoints:

- 30-day cardiac mortality
- 30-day all-cause mortality
- Postoperative stroke during the index hospitalization
- Postoperative myocardial infarction (MI) during the index hospitalization
- Urgent postoperative coronary revascularization during the index hospitalization
- Serious device-related adverse events

4.4. Subjects and Selection of Study Population

Subjects must meet all inclusion criteria to be eligible to participate in the study. Subjects meeting any of the exclusion criteria are not eligible to participate in the study.

4.4.1. Inclusion Criteria:

1. Males and females aged ≥18
2. Written full informed consent
3. Undergoing cardiothoracic surgery with CPB within two days of ticagrelor discontinuation (last day of completed ticagrelor treatment = day 0)

4.4.2. Exclusion Criteria:

1. Cardiothoracic surgery occurring 3 days or greater following ticagrelor discontinuation
2. Heart-lung transplant procedures
3. Procedures for ventricular assist device (i.e., implant or revision of LVAD or RVAD)
4. Any of the below conditions that pose a known risk for increased bleeding:
    a. Heparin induced thrombocytopenia
    b. Preoperative platelet count < 50,000 / μL
    c. Hemophilia
    d. INR > 1.5
5. Prohibited concomitant antithrombotic medications (reference Appendix 5)
6. Acute sickle cell crisis
7. Known allergy to any of the device components
8. Subjects with active (untreated) systemic infection
9. Subjects with a history of major organ transplantation and those currently receiving immunosuppressive medication (corticosteroids excluded) or who are profoundly immune suppressed
10. Women of childbearing potential with a positive pregnancy test performed during the current admission or who are breast-feeding
11. Subjects with life expectancy of <30 days (not inclusive of the critical condition that is requiring the cardiac operation under study)
12. Inability to comply with the requirements of the study protocol
13. Treatment with an investigational drug or device within 30 days prior to surgery
14. Subjects with previous enrollment in this trial
15. Subjects in whom acute normovolemic hemodilution (ANH) is used perioperatively

4.4.3. Informed Consent & Enrollment Procedures:

Informed consent shall be obtained in writing from the subject, or their legally authorized representative and the process shall be documented before any procedure specific to the clinical investigation is applied to the subject, except when special circumstances described in Appendix 3 apply. If during the course of the study assessments, a subject is found not to be eligible for inclusion in the study, the subject or their representative should be notified and the reason for ineligibility

documented on the screening log/form.

The general process for obtaining informed consent shall:

- Ensure that the principal investigator or his/her authorized designee conducts the informed consent process
- Include all aspects of the clinical investigation that are relevant to the subject's decision to participate throughout the clinical investigation
- Avoid any coercion or undue improper influence on, or inducement of, the subject to participate
- Not waive or appear to waive the subject's legal rights
- Use native non-technical language that is understandable to the subject
- Provide ample time for the subject to read and understand the informed consent form and to consider participation in the clinical investigation
- Include personally dated signatures of the subject and the principal investigator or an authorized designee responsible for conducting the informed consent process
- Provide the subject with a copy of the signed and dated informed consent form and any other written information
- Ensure important new information is provided to new and existing subjects throughout the clinical investigation

4.4.4. Subject Withdrawal/Discontinuation:

Investigation subjects may withdraw voluntarily from the research investigation for any reason and at any time during the course of the investigation. Subjects may also be discontinued from the investigation for the following medical or administrative reasons:

- At the request of the Investigator, if he/she feels that the subject can no longer fully comply with the requirements of the study or if any of the study procedures would not be in the best interest of the subject.
- Termination of the study by the Sponsor.
- Non-compliance with CIP procedures.
- The subject is lost to follow-up. A subject will be considered "lost to follow-up" when all the following criteria are met:
    - Failure to complete the 30-day follow up visit (can be performed via telephone contact, in person visit, or review of medical records) without due cause; and
    - Documentation of three unsuccessful attempts to contact the subject via telephone and/or by certified mail.

If a subject is withdrawn from treatment, the Sponsor will be notified and the date and reason(s) for the withdrawal will be documented in the subject's electronic Case Report Form (eCRF). For subjects who withdraw assent/consent and those withdrawn at the request of the Investigator, details of the reason for withdrawal will be captured to the extent possible. If a subject is withdrawn, efforts will be made to perform all follow-up assessments, if possible. Other procedures may be performed at the Investigator's (or designee's) and/or Sponsor's discretion. The Investigator (or designee) may also request that the subject return for an additional Follow-up Visit. All withdrawn subjects will be followed until resolution of all their AEs or until the unresolved AEs are judged by the Investigator (or designee) to have stabilized.

Subjects who are withdrawn for reasons not related to investigation treatment may be replaced following discussion between the Investigator and the Sponsor. For subjects who withdraw or discontinue at any point prior to completion of the required follow-up period, all available data will be

used in the analysis, following the intent-to-treat principle. In cases where particular analysis criteria are not met, for example for the per protocol (PP) Population, such subjects may not be included in the analysis. Subjects withdrawing or discontinuing early will be summarized as described in **Section 11.8**, and will be flagged in a listing of disposition information that includes reason for early withdrawal/discontinuation.

5. POTENTIAL RISK/BENEFIT

5.1. Potential Investigational Device Risks

DrugSorb™-ATR is a device that is incorporated into an extracorporeal CPB circuit. For the study described in this protocol, use of the DrugSorb™-ATR device will be limited to the duration of CPB. The risk profile associated with the DrugSorb™-ATR device is expected to be consistent with other extracorporeal treatments currently in clinical use. Potential risks associated with the use of the device are described below.

Risks Specific to DrugSorb™-ATR:

- Removal of therapeutic drugs <60kDa in size, that contain hydrophobic or aromatic moieties.
- Removal of endogenous, non-pathogenic, physiologic substances from the blood: A risk of removal of substances ≥900Da – 60kDa in size; this risk is greater the longer DrugSorb™-ATR hemoperfusion is performed on a subject.
- Hemolysis (if maximum recommended flow rate per the IFU is exceeded).
- Allergic response to device materials.
- Device leakage.
- Death.

Risks commonly associated with extracorporeal therapies will not be detailed here, however such risks would also apply to the DrugSorb™-ATR device, given its incorporation into these circuits.

5.2. Potential Benefits

The observed and potential benefits of using the DrugSorb™-ATR device intra-operatively during cardiothoracic surgery to remove ticagrelor include:

- Decrease in perioperative bleeding complications; including:
    - Decrease in perioperative blood loss, including that measured in chest/mediastinal drains
    - Decrease in blood product transfusions
    - Reduced risk of re-operation for bleeding
    - Reduced risk of fatal bleeding
- Improvement in hemodynamic stability and reduction in vasopressor requirements
- Decrease in mean operative time including time to hemostasis
- Decrease in the amount of time on a mechanical ventilator
- Decrease in hospital stay following surgery, including time in the ICU

5.3. Risk Mitigation

Mechanical and performance concerns have been reduced by extensive human, animal, and bench testing. The device materials have been shown to be biocompatible and acceptable for human use

through ISO10993 testing and prior human clinical studies of the device for removal of beta-2 microglobulin in subjects with end stage renal disease and removal of cytokines in the treatment of sepsis. The DrugSorb™-ATR Device has CE Mark approval under the name of CytoSorb® for removal of ticagrelor and/or rivaroxaban in subjects undergoing emergent cardiothoracic surgery with CPB and is believed to pose minimal additional risks compared to standard CPB circuits without DrugSorb™-ATR. Those risks and their mitigation strategies are presented in **Table 2** below.

DrugSorb™-ATR does not remove heparin or citrate, and therefore does not impact heparin- or citrate-mediated anticoagulation during CPB. Adherence to protocol will be stressed by CytoSorbents' personnel during in-service training. All subjects will be monitored per routine standard of care. Additionally, the Data and Safety Monitoring Board (DSMB) will be reviewing safety information on an ongoing basis, thus providing an additional level of risk mitigation.

Table 2. Risks and Mitigation Strategies

Potential Device/Intervention Risk	Action for Risk Mitigation
Risk of coagulation within the device or the CPB circuit, and associated thromboembolic events (e.g., stroke, peripheral embolus, etc.)	Visual inspection for signs of coagulation within the device or the circuit during CPB on a regular basis. Constant supervision during the CPB procedure.
Removal of drugs (such as antibiotics) and hormones	If a selective test is available, the treating physician is urged to check the concentration of applied drugs following CPB and adapt the dosages accordingly. This theoretical risk is greater, the longer DrugSorb™-ATR hemoperfusion is performed on a subject. Therefore, it would be anticipated that this risk would be acceptable when device exposure is limited to the brief intraoperative time period with CPB.
Allergic/ anaphylactic response to device materials	Subjects with known allergies against device materials (including but not limited to: polystyrene/divinylbenzene, polycarbonate, polypropylene, silicone and polyester) will be excluded from the study. If applicable, in subjects manifesting unexpected signs of allergic reaction during therapy with DrugSorb™-ATR, the exposure will be discontinued immediately. In addition, aggressive first-line therapy shall be applied to control the allergic or anaphylactic reaction.
Risks related to blood composition: • Reduction in platelet count • Reduction in white blood cell count • Reduction in proteins (albumin or total protein) • Hemolysis	Close monitoring of blood parameters prior, during, and after extracorporeal therapy according to the prescribed routine (reference the Schedule of Assessments in Table **6**) Flow through the device will be monitored closely through-out the procedure. The DrugSorb™-ATR device maximum flow rate has been validated for hemolysis, and there are no independent risks *associated with the maximum recommended flow rate* of the DrugSorb™-ATR device.
Impairment of device function (DrugSorb™-ATR and CPB) in combination with parenteral nutrition (most notably: lipid emulsions)	In case of need artificial nutrition, gastric application or other than parenteral application shall be preferred. In case of need for parenteral application of lipid-containing nutrition, it is recommended to postpone the application only after the procedure or to stop the application latest two hours prior to the CPB-procedure.

Bleeding events due to necessary anticoagulation with CPB and DrugSorb™-ATR device use	Constant supervision of coagulation parameters during the procedure, in accordance with standards of care.
Infection	DrugSorb™-ATR is sterile and is delivered in sterile packaging. The packaging will be checked for possible damage before use. Products with visible defects will not be used and will be reported to the Sponsor.
Blood loss	Return of the blood sucked from the surgical field to the CPB circuit for reduction of blood loss. Constant supervision of the extracorporeal circuit for blood loss through-out the procedure.
General complications within in context of extracorporeal therapies (including but not limited to): • Dyspnea • Hypoxia • Changes in body temperature • Muscle cramps • Headache • Nausea • Vomiting • Pruritus	Constant supervision of the subject during and after the CPB-procedure. Designation of personnel duly trained in the use of extracorporeal therapies.
Device or circuit leakage	Visual inspection for signs of leakage within the device, or the circuit during the CPB-procedure on a regular basis.
Unwanted penetration of air into the extracorporeal circuit, and risk of associated events such as pulmonary embolism and death due to pulmonary embolism	Checking of connections, lines, and circuit components for integrity of the system, and use of appropriate precautions to avoid introduction of air into the system when incorporating the device into the circuit. The device will be setup in a standardized configuration under positive pressure; the volume will be returned to the reservoir pre-pump and pre-oxygenator membrane, thus essentially eliminating risk for air introduction to the patient. Constant supervision of the subject during the CPB-procedure.

6. STUDY TREATMENT

All treatments will be provided by trained professionals. Use of the DrugSorb™-ATR Device will follow the instructions for use (IFU) under the guidance of a field clinical engineer.

6.1. Pre-randomization Stratification

Pre-randomization stratification will be performed on two levels, based on the rationale described below:

1. By study site in order to control for differences in institutional protocols that could impact outcomes. These may include but are not limited to different institutional practices for drug and transfusion administration intra-op and post-op. Institutions may also differ in metrics utilized for clinical decision-making (e.g., delaying sternal closure, or surgical reoperation).

2. By the intended surgical procedure in order to control for differing procedure-specific

bleeding risks, and duration of CPB (i.e., device exposure) as detailed below:

- CABG alone (irrespective of number of grafts); or
- All other cardiothoracic procedures (including but not limited to combination procedures (i.e., CABG + aortic/mitral valve procedures, double heart valve procedures, etc.), aortic intervention, and combination aortic + cardiac interventions.

Of note, during the pre-procedure and intraoperative periods, the intended procedure may change due to factors that could not be adequately determined or anticipated in advance of the procedures. These day-of-surgery changes to the planned operations may result in the completion of a procedure that a) does not align with eligibility criteria, or b) alters stratification. Any change to the intended procedure occurring on the day of surgery that is not updated in the final IxRS assignment will be considered a protocol deviation. These protocol deviations will be noted in a deviation log for data analysis considerations at the conclusion of the trial. Subjects who have changes to their intended procedures on the day of surgery should progress through the study as in the protocol.

6.2. Subject Randomization

All subjects will be prospectively randomized via an Interactive Voice/Web response (IxRS) system. Randomization must occur prior to the start of the cardiothoracic surgery procedure requiring CPB, but only after subject eligibility criteria is confirmed and written informed consent is provided by the subject or the subject's designated proxy. Subjects will be randomly assigned in a one to one (1:1) ratio to either the control arm (SOC) or the investigation arm (SOC + DrugSorb™-ATR device).

To ensure even distribution of subjects among the factors most likely to impact the primary and secondary outcomes they will undergo pre-randomization stratification based on study site (to account for different institutional protocols for bleeding and transfusion management), and type of surgery (isolated CABG – which generally has shorter CPB time, vs. all other cardiothoracic surgeries including combination cases – which generally require longer CPB times). Neither the investigator nor the subjects will be told their assignment prior to surgery. See below (**Section 6.3.1**) for details of the randomization assignment. A copy of the randomization assignment will be maintained in a confidential file maintained by the Randomization and Unblinding Administrator. If the subject withdraws consent following randomization but prior to surgery, the reason for failure to treat according to randomization will be recorded in the subject's study records.

To maintain the balance between sites in terms of numbers of subjects randomized, study sites will be capped at randomizing a maximum of 15% of the overall study sample. Sites may be allowed to randomize beyond the cap on a case-by-case basis in consultation with the sponsor, taking into account overall study goals, randomization balances between sites, and prior quality of data collected by the site.

6.3. Blinding

Blinding of the study subjects and site personnel (e.g., Surgeon, Anesthesiologist, operating room staff, study coordinator) to treatment assignment is implemented starting at the point of randomization and extending through the duration of the entire study. Accordingly, the blinding procedure will minimize any potential bias in both surgical and postoperative care decisions that may be introduced by knowledge of treatment assignment.

Each site will have an unblinded perfusionist to execute the necessary intraoperative study procedures. Extreme caution should be exercised by the perfusionist to prevent inadvertently

revealing treatment assignment to individuals making clinical decisions on subject care.

The unblinded perfusionist at the site will ensure the placement of a barrier that covers the device/sham set-up on CPB from view of the surgical staff. A Field Clinical Engineer (FCE), as designated by the Sponsor, may be present to assist with set up of the blind and provide guidance during the procedure. Details on the roles and responsibilities of the Sponsor FCE are provided in **Section 6.4**.

6.3.1. Maintaining the Study Blind

The following describes the measures being taken to maintain the study blind:

a) **Subjects:** Subjects will not be told their randomization assignment by any site study personnel involved in the trial and will receive the same care throughout the trial.

b) **Randomization Assignment:** Each site will randomize subjects using an Interactive Voice/Web response (IxRS) system. After the appropriate information is entered, an assignment is made (Standard of Care vs. Standard of Care + DrugSorb™-ATR device). This randomization process is performed by the unblinded team prior to the procedure.

c) **Site Study Personnel:** There are two designated teams at each site:

1. **Blinded**: These individuals remain blinded from the point of randomization through the duration of the study, inclusive of all subjects enrolled at the site.

    - Surgical team (including the surgeon, surgical assistant, circulating nurse, scrub tech, and other operating room staff);
    - Anesthesiologist and anesthesia team;
    - ICU staff;
    - Study coordinator.

2. **Unblinded**: These individuals will be aware of treatment assignment and will refrain from revealing it to any other study personnel for the duration of the study, inclusive of all subjects enrolled at the site.

    - Perfusionist;
    - Sponsor FCE.

The **Blinded Team** is responsible for administering all pre-, intra- and post-procedure subject testing and care as designated by the protocol. The blinded site study coordinator(s) will be responsible for data entry into the EDC, including input of follow-up visit data into the relevant eCRF. The blinded study coordinator will also be responsible for ensuring required follow-up care/visits for all study subjects are scheduled; The Sponsor will work with each individual site to determine the documentation needed in the subjects' medical records (e.g., procedure notes) to protect the study blind.

The **Unblinded Team** is responsible for activities related to the procedure, including set-up of the device according to randomization assignment (sham or DrugSorb™-ATR), oversight of the device during the procedure, and recording the device study data in the eCRFs and device accountability log. Other responsibilities include:

1. Obtaining a randomization code from the electronic system prior to the index procedure, including day of procedure;
2. Ensuring appropriate device cartridges are available and in the OR suite on procedure day;
3. Providing necessary procedure information in a blinded fashion to the study coordinator for eCRF entry.

6.3.2. Study devices

All study devices will be blinded by coverage with a sterile drape. For subjects randomized to the DrugSorb™-ATR device, the unblinded perfusionist will monitor flow to ensure it stays within the protocol dictated range.

Subjects randomized to standard of care without DrugSorb™-ATR (i.e., control) will have a ***sham device*** in the operating room. The sham device is identical in appearance to an active DrugSorb™-ATR device. Sham devices are sealed, inactive, pre-assembled device sets containing liquid to mimic a primed, ready to use, device. They are permanently sealed and cannot be put online with the perfusion circuit. Sham devices are marked **"Not for human use"** and cannot be opened, and they will not support flow, as they are glued/sealed shut. These devices are clamped like the DrugSorb™-ATR device, but line connections are not made to it. Once installed, the sham device is covered with a sterile drape, and tubing lines approximate the positioning of the real DrugSorb™-ATR device.

Assembly of the blind space may be required in advance should the OR personnel be in the workspace during set up to preserve knowledge of treatment allocation. The FCE and/or unblinded perfusionist ensures the blind is maintained prior to, throughout, and post-surgery. Of note, the sham device and blinding scheme discussed above is identical to the model used in REFRESH II, which is an ongoing IDE study already approved by the FDA.

6.3.3. Unblinding Procedure

It is the intention of this study to unblind both the subject and the site study personnel at the completion of the overall study. This will occur **after** all necessary 30-day follow-up assessments are completed and all the data have been collected and verified for all subjects, and the clinical database has been "locked", or write-protected from further changes. If the subject develops a condition within the 30-day follow-up window, the subject and team will be unblinded ***only if doing so is necessary to make informed decisions about clinical care, or in the possibility of a UADE***.

Any subject that is unblinded prematurely for any reason shall continue to be followed in accordance with the protocol evaluations outlined. A subject is NOT automatically considered to be withdrawn if unblinding occurs earlier than anticipated.

If the site investigator believes there is reason to unblind either themselves or the subject (significant change in subject's health status related to the possible use of the device, withdrawal or discontinuation of study participation), the site will contact the Sponsor to discuss the subject's circumstances, at which time the Sponsor, if in agreement with the site's request, may approve release of the blinding information by the unblinded Sponsor designee.

6.4. Field Clinical Engineers

Support by a Field Clinical Engineer (FCE), as designated by the Sponsor, may be offered to assist with set up of the blind and provide guidance during the procedure. In instances where the Sponsor designated FCE has previously observed set-up of the investigational device and has found the unblinded perfusionist(s) skilled and competent to manage study procedures, a waiver of FCE assistance may be granted. All such waivers of FCE assistance will be documented and retained in the study file.

The FCE will observe and proctor the unblinded perfusionist as he or she assembles the DrugSorb™-ATR cartridge and peripheral FDA-approved components as specified in the Instructions for Use (IFU). The unblinded perfusionist is responsible for the final hookup to the hospital perfusion apparatus. The Sponsor FCE will be available through-out the procedure to provide additional support to the perfusionist as needed. This approach is consistent with site expectations for study support and will further ensure study subject safety in a novel device trial. In addition, the presence of the FCE will likely reduce variability in study related procedures and ensure their timely execution (i.e., serial blood sampling for drug levels).

6.5. Device Quality Complaints: Deficiencies, Malfunctions, and Observations

If there is a device deficiency, malfunction, or other observation with the DrugSorb™-ATR device (i.e., device quality complaint) the Investigator (or designee) is required to complete the Device Deficiency/Observation eCRF and to notify the Sponsor immediately and indicate if the observation resulted in an adverse event and indicate if complications are related to the device, procedure, or underlying disease. If the device quality complaint is associated with an SAE, SADE, or UADE, the Investigator will be required to enter the adverse event within 24hrs of awareness, and this information will be transferred to the Contract Research Organization (CRO) and Sponsor through automated notification.

In the event of any suspected device problem, the device shall be returned to the Sponsor for analysis. Instructions for returning the investigational device are included in the Study Reference Manual. If the investigator cannot determine the cause of the event, it should be classified as unknown.

7. STUDY OVERSIGHT

7.1. Data and Safety Monitoring Board (DSMB)

This is an independent committee that will be charged with ensuring the safety of the subjects enrolled in the clinical study. The Data Safety Monitoring Board (DSMB) will be comprised of four members: three clinicians and one biostatistician with relevant clinical/medical experience with the indication/disease under clinical investigation. The membership of the committee will be independent of the investigative sites and study sponsor to reduce potential for perception of bias and to remain free of potential conflicts of interest. The policies and procedures governing the DSMB will be provided in a Charter that will be reviewed and ratified by the membership within a reasonable timeframe relative to the enrollment of the first few subjects entering the study.

Included in the charter will be a mission statement, operating procedures, and proposed monitoring criteria. There will be at least 4 DSMB meetings in the course of the trial. A kick-off meeting of the DSMB in anticipation of the start of enrollment and 3 safety reviews scheduled after 40 patients have been enrolled, after 80 patients have been enrolled, and a final review after database lock. The DSMB will meet at a minimum once per 6 months if a meeting is not already triggered by the above scheduled enrollment timeframes. Written recommendations from the DSMB will be provided to the study sponsor following each safety review meeting.

7.2. Clinical Events Committee (CEC)

An independent group of physicians that are not involved in the clinical investigations will act as the Clinical Events Committee (CEC). The CEC will be responsible for the review and adjudication of study effectiveness and safety endpoints that occur within 30 days post-operation according to standardized definitions. Policies and procedures governing the work of the CEC and the definitions used in the adjudication process will be provided in the CEC charter, which will be developed prior to the start of study enrollment.

7.3. Executive Committee

This committee shall serve as overall governance of the trial and will comprise of clinicians with relevant clinical/medical experience within the indication/disease under clinical investigation and who also have significant experience in overseeing clinical studies. The Executive Committee shall provide advice to the Sponsor with regard to the conduct and any necessary adjustments to the trial protocol and/or study execution. The Executive Committee will also advise the Sponsor in the case that any decisions are necessary in response to recommendations provided by the independent Data and Safety Monitoring Board.

7.4. Central Laboratory

A central laboratory shall be utilized to analyze some of the blood samples collected in this study. The sample size and shipping requirements are provided to the sites in the Study Laboratory Manual. All sites will be trained on the collection, preparation, and shipping for central laboratory samples.

8. STUDY MONITORING

The CRO will monitor and manage the data for the investigational study on behalf of the Sponsor, CytoSorbents, Inc. Some co-monitoring and remote data checking will also be done by qualified CytoSorbents personnel. A study-specific Monitoring Plan will be created to ensure protocol compliance and adherence to applicable regulatory requirements. The monitoring process will begin with site initiation activities and continue until completion of the study closeout visit. Clinical monitors will verify subject data and ensure compliance is consistent with Good Clinical Practice (GCP), clinical protocol and other study requirements, according to the guidelines per the Monitoring Plan, set forth in CROs monitoring Standard Operating Procedures (SOPs), and 21 CRF Part 812.

8.1. Monitor Training

The designated monitors and/or representatives of the Sponsor will be trained to monitor study progress including but not limited to the protocol and eCRFs, and per the Monitoring Plan.

8.2. Site/Investigator Training

The Sponsor is responsible for providing training to the Investigator and appropriate clinical site personnel on the following topics:

- Protocol
- Electronic case report form (eCRF) data entry and management
- Procedure/Laboratory/other testing requirements
- DrugSorb™-ATR Device

8.3. Site Monitoring

Completed eCRFs will be verified by the monitor both in person at the investigational sites and

remotely at regular intervals throughout the study. The Investigator will allow the monitor and/or representative of the Sponsor, and any regulatory body to review and inspect the study files, subject eCRFs, subject medical records and other related study documents as required. All eCRFs will be reviewed for completeness and clarity. Missing or unclear data will be investigated by the monitor and will be retrieved, clarified and entered by study personnel as necessary throughout the study. CytoSorbents, Inc., or their authorized representative may request additional documentation from the Investigator such as physician procedure notes or physician written summaries when adverse events are observed and reported.

8.4. Regulatory Agency Inspection

In the event that an Investigator is contacted by a regulatory agency regarding this study, the Investigator will notify the Sponsor or its designee immediately. The Investigator and research coordinator must be available to respond to reasonable requests and queries made during the inspection process. The Investigator must provide the Sponsor or designee with copies of all correspondence that may affect the review of the current trial (e.g., Form FDA 483, Inspectional Observations and Warning Letters). The Sponsor may provide needed assistance in responding to regulatory audits.

9. STUDY ASSESSMENTS AND PROCEDURES

An outline of study assessments, procedures, labs, and associated time windows are given in the **Schedule of Assessments** in Appendix 4. Subjects will be evaluated through the Follow-up evaluation at 30 days post-operation. Assessments and procedures that are recorded as Standard of Care (SOC) are optional and may be recorded if they are performed in accordance with SOC at the particular institution. Failure to record an assessment/procedure that is listed as SOC will not be a violation of protocol. Required assessments and procedures (not denoted as SOC) that are not completed or that are completed outside of the specified windows will be recorded as a protocol deviation (**Section 13.2**, **13.3**).

Study outcomes will be assessed as part of blood products and drainage volume, laboratory parameters, and documentation of clinical events and/or treatments. Reference **Section 4.3** for the full list of study endpoints. Definitions of analysis populations and description of statistical analyses endpoints is briefly described in **Section 11** and detailed in the Statistical Analysis Plan (SAP) for the study.

9.1. Procedures and Assessments by Study Phase

Subjects are considered enrolled in the study at the time which consent or assent (in the case of a proxy providing permission for an incapacitated subject) to participate in the study is provided. Details on the consent process are provided in **Section** 4.4.3 and the ethics of consenting non-vulnerable and vulnerable (incapacitated) populations are detailed in Appendix 3.

Subjects who do not meet study entry (inclusion/exclusion) criteria are screening failures and will exit the study. Treated subjects will be followed up through 30 days after the surgical procedure.

The start of the investigation is defined as the date of consent to enroll the first prospective subject. The end of the investigation is defined as the date of the last subject's last contact or assessment (whether scheduled or unscheduled).

The investigation is divided operationally into 6 phases:

- Screening Phase – the period between the time consent/assent is provided for study

participation and the start of the surgical procedure with CPB

- Pre-CPB Phase – the period within 2 hours of start of the operation with CPB (time of skin incision). *Note: The Pre-CPB Phase may overlap with the Screening phase.*

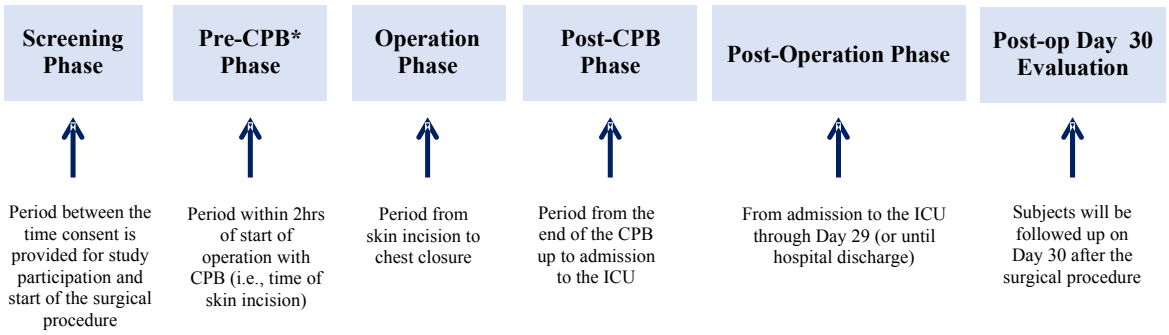
- Operation Phase – the start of the surgical procedure (defined as skin incision) until chest closure.

- Post-CPB Phase – the period from the end of CPB up to admission to the Intensive Care Unit (ICU). *Blood sampling for drug removal obtained in the post-CPB phase should be drawn as soon as possible following the end of CPB, and no later than 30 min after the subject has been disconnected from the CPB circuit.*

- Post-operation Phase – from admission to the ICU through Day 29 or the point of discharge from hospitalization, whichever is sooner. ***Discharge from hospitalization*** means the date of initial discharge from the hospital in which the cardiothoracic surgery was completed (i.e., index procedure) irrespective of discharge to home care, secondary care or other rehabilitation unit.

- Day 30 Evaluation Post-Cardiothoracic Surgery – The subject status on postoperative day 30 will be evaluated by telephone contact, in-person follow-up visit, or review of medical records. Assessment of mortality (i.e., vitals status), blood product transfusions, and other adverse events will be performed.

An overview of the investigation design is shown in **Figure 5**.



* Pre-CPB phase may overlap with the Screening Phase.

Figure 5. Investigation Schematic

9.1.1. Screening Phase and the Pre-CPB Phase

The Screening Phase through the Pre-CPB Phase is the period bound by the time that consent is provided for study participation and the start time of CPB. Subjects are qualified for study participation by confirmation of meeting all the inclusion and none of the exclusion criteria.

Each enrolled subject will be assigned a unique Subject Number consisting of a Site Number assigned by the Sponsor or designee, and a number which is sequentially assigned to all subjects screened at the investigation sites (e.g., XXX-YYY, where XXX is the site number and YYY is the subject number). The Subject Number will be used as a subject identification for each subject throughout the

investigation.

Screening and pre-CPB assessments should be completed as detailed in **Table 6**. As discussed in **Section 1.1,** all subjects undergoing CABG or with recent coronary stent placement (within prior 6 months) should have aspirin continued going into surgery. An overview of antithrombotic and anticoagulation management for study subjects is provided in Appendix 4, **Table 5**. During Screening, if consented subjects enter the Operation Phase without ***post-consent*** clinical chemistry, cardiac troponin, hematology, or coagulation tests to record, the last pre-consent laboratory values MAY be used.

Pre-randomization stratification

Pre-randomization stratification will be performed in on two levels (see **Section 6.1** for details):

1. By study site;
2. By the planned surgical procedure:
    - Isolated CABG (irrespective of number of grafts); or
    - All other cardiothoracic procedures.

Randomization

Subjects will be prospectively randomized in a one to one (1:1) fashion to either the control arm (SOC) or to the investigation arm (SOC + DrugSorb™-ATR device), as detailed in **Section 6.2**.

9.1.2. Operation Phase

The Operation Phase will be initiated at the time of first incision. During the Operation Phase, the subject will either undergo standard CPB, or CPB + DrugSorb™-ATR according to randomization.

Subjects randomized to the control arm will receive standard of care in which a sham device will be in place parallel to the CPB circuit, but through which no blood will circulate. Refer to **Section 6.3** for details.

In the treatment arm, DrugSorb™-ATR treatment will initiate with the start of CPB and continue through the end of CPB. Per the Instructions for Use (IFU) and under the guidance of a Field Clinical Engineer, the DrugSorb™-ATR device will be placed into a parallel bypass circuit to the main blood flow in a standard heart-lung machine circuit and primed for use in preparation for the Operation Phase. Throughout the treatment session, the DrugSorb™-ATR device will be monitored for blood leaks, flow changes, and/or clots. Any adverse device events and/or device observations must be recorded by indicating the location of leaks and/or by recording the size of any clots present. DrugSorb™-ATR treatment flow rates will be controlled utilizing a roller clamp placed on the distal, superior line above the DrugSorb™-ATR prior to returning to the reservoir. Flow rate will be measured using a Sponsor provided Transonic (or equivalent) ultrasonic flow meter and probe, also on the inlet line below the DrugSorb™-ATR device. **The blood flow rate of the device will be adjusted to 500mL/min ±100mL/min (minimum above 400mL/min is acceptable)**.

During the operation phase, arterial blood gas analysis will be obtained at the following time periods: within 30min pre-CPB, 30 ±15min into CPB, within 30min post-CPB, and upon admission to the ICU. Activated clotting time will be obtained once at 30 ±15min into CPB, and once within 30min post-protamine administration. All other assessments including monitoring of transfusions, will be performed as detailed in **Table 6** of Appendix 4. Intraoperative transfusions will be administered at the discretion of the investigator in accordance with standard practices but should follow Best Clinical

Practice Guidelines.

9.1.3. Postoperative phase through 30-day evaluation

Subjects will undergo scheduled study procedures as indicated in the Schedule of Assessments in Appendix 4 until the point of discharge from index hospitalization. A Follow-up Evaluation will be performed 30 days after the index operation for vital status/mortality check. This can be done via telephone contact, in-person follow-up visit, or review of medical records.

Postoperative Antithrombotic Management:

Approaches to antiplatelet and anticoagulation management during the study are listed below and summarized in **Table 5**. Antiplatelet therapy in the postoperative setting is determined by whether or not the study subject had ACS or recent stent placement:

1. Any ACS subjects who were not on aspirin in the preoperative setting should be initiated on aspirin at 6 hours post-op, per institutional protocols. In ACS subjects, or those with coronary stent placement within the prior 6 months, ticagrelor (or the treating physician's choice $P2Y_{12}$ inhibitor for DAPT, in accordance with standard clinical guidelines) should be resumed on postoperative day 1 if there is no concern for bleeding. Otherwise, ticagrelor/DAPT should be resumed as soon as deemed safe by the surgeon when weighing benefits of improved graft or stent patency against risk of bleeding.
2. In the remaining subjects, antithrombotic management should be per institutional protocols.

Postoperative anticoagulation for venous thromboprophylaxis in all subjects should be administered according to standardized institutional protocols.

9.2. Safety and Tolerability Assessments

9.2.1. Adverse Events

Throughout the study, the Investigator or designee will determine adverse event (AE) occurrences. AE definitions, assignment of severity/seriousness/causality, and procedures for reporting SAEs, SADEs, and UADEs are detailed in Appendix 1.

The condition of each subject will be monitored from the time of signing the informed consent form (ICF; assent or consent) to the postoperative day 30 assessment. Subjects will be observed for any signs or symptoms and if possible, asked about their condition by open questioning, such as "How have you been feeling since you were last asked?", at least once each day while in hospital and at each investigation visit. Subjects will also be encouraged to spontaneously report AEs occurring at any other time during the investigation.

If an AE occurs, appropriate diagnostic and therapeutic measures are to be taken and the investigation treatment may be discontinued if appropriate. Follow-up evaluations of the subject are to be performed until the subject recovers or until the clinical Investigator considers the situation to be no longer clinically significant.

Adverse events are monitored and registered on the AE form of the eCRF. In absence of a specific diagnosis, an individual AE form has to be filled in for each sign or symptom. Changes from baseline laboratory values which are abnormal values and that are classified as clinically significant by the investigator (e.g., requiring medical intervention) must be recorded as AEs.

Persistent AEs will be entered once in the eCRF until they are resolved or if a new event has to be documented due to deterioration. These AEs will be carefully monitored. If an AE is still not resolved at the end of the investigation, this will be documented as ongoing. For recurrent AEs (i.e., AEs of the same nature, but with a different date of onset), an individual AE form has to be completed for each of them.

Bleeding event AEs
Bleeding events are to be recorded as AE/SAEs by the Investigator or designee and will be classified according to the Universal Definition of Perioperative Bleeding (UDPB) in adult cardiac surgery. [17] Classifications are based on criteria presented in **Table 1** and will be determined based on the relevant data entered within the eCRFs. Of note, UDPB counts transfusions of PRBCs, platelets, FFP, and Cryoppt beginning at chest closure. While intra-operative transfusions of these blood products prior to chest closure will be documented, they will not be counted as part of the UDPB classification or contribute to the primary endpoint. Preoperative transfusions are not counted in the UDPB classification. Transfusions of PCC and rFVIIa are counted beginning at the start of the procedure for UDPB. Measurement of CTD volume begins at chest closure for UDPB classification. All bleeding event AEs classified as moderate, severe, or massive (Classes 2, 3 or 4) based on UDPB criteria will be referred to the CEC for adjudication of UDPB bleeding class. Details on the process for adjudication and relevant definitions are provided in the CEC Charter.

Postoperative Ischemic Events:

Postoperative ischemic events occurring during the index hospitalization will be captured as safety endpoints in this study. This is with the intent of evaluating any potential risk for ischemic rebound in the setting of ticagrelor removal. Postoperative ischemic events include myocardial infarction (MI), stroke, and urgent coronary revascularization. Of note, given the occasional complexities of distinguishing ischemic from hemorrhagic stroke (i.e., ischemic with hemorrhagic conversion), *all* postoperative strokes occurring during the index hospitalization will be captured within the safety endpoint.

All reported safety events occurring within 30 days of the study procedure that meet programed criteria for cardiac ischemia or stroke will be submitted to the CEC for endpoint adjudication. All coronary revascularization procedures (regardless of open or percutaneous) that occur post-index procedure and during the follow-up period will be adjudicated by the CEC for the potential safety endpoint of *urgent coronary revascularization*. Details on endpoint definitions, adjudication criteria, and all other CEC processes/procedures are detailed in the CEC charter.

Postoperative Mortality or AEs Resulting in Death

All deaths (including AEs resulting in death) that occur within 30 days of the study procedure will be adjudicated by the CEC for endpoint criteria. This includes assessment of the timing and nature of the mortality (cardiac vs. non-cardiac death). *For the purposes of this study, fatal bleeding will be considered a type of cardiac death.* Details on endpoint definitions, adjudication criteria, and all other CEC processes/procedures are detailed in the CEC charter.

9.2.2. Medical History

Medical history will be obtained at Screening and should include demographic information (date of birth, race, ethnicity) and subject’s medical and surgical history. The medical history must be documented in the subject's eCRF.

9.2.3. Clinical Laboratory Evaluations

Blood samples will be collected and documented by the Investigator (or designee) for clinical laboratory evaluations (including clinical chemistry, hematology, and coagulation tests) at the times indicated in the Schedule of Assessments in Appendix 4. Clinical laboratory evaluations are listed in Appendix 2. **Of note:** if multiple sets of labs are obtained for a subject within the same post-operative day (either as part of standard institutional protocols, or due to changes in the subject's clinical picture), the lab assessments obtained at the time which *most closely approximates* 24hrs, 48hrs, 72hrs, etc., post-op should be the values entered into the EDC for study purposes.

Instructions for the collection and storage of study samples that will be analyzed by the Central Laboratory are provided in the Study Laboratory Manual.

9.2.4. Vital Signs

Supine blood pressure, pulse rate, respiratory rate, oxygen saturation, and body temperature will be assessed at the times indicated in the Schedule of Assessments in Appendix 4. Vital signs may also be performed at other times if judged to be clinically appropriate, or if the ongoing review of the data suggests a more detailed assessment of vital signs is required.

All measurements will be performed singly and repeated once if outside the relevant clinical reference range.

9.2.5. Physical Examination

Body mass index will be calculated using the subject's body weight and height at the time of screening (Schedule of Assessments, Appendix 4). A physical exam (PE) will be performed and documented at the time of screening/subject enrollment. Physical exams performed as part of standard of care on the day of screening but occurring prior to signing of informed consent may be documented as the screening PE. A physical exam will be repeated on the day of the procedure, if the day of the procedure is different than the day of screening.

9.2.6. Other Assessments: Blood Products and Blood Loss

Intraoperative and postoperative blood loss and chest drainage volumes (chest drainage includes output from all chest and mediastinal tubes) will be measured and documented at the times indicated in the Schedule of Assessments in Appendix 4. Cellsaver will ***not*** be included in the calculation of blood product transfusions, as this is volume that would normally be given back as part of standard of care. Chest tube drainage will be recorded in the corresponding *Chest Tube Drainage eCRF* for at least 24hrs post-operation, unless unable to do so (i.e., subject death prior to 24hrs). Volume of blood loss not coming from chest/mediastinal drainage will be documented separately, in the corresponding *Blood Loss (Non-Chest Drainage) eCRF*. Blood products received by the subject will be recorded in the corresponding *Transfusion eCRF*.

9.3. Blood Sampling for Drug Removal

Blood samples for the analysis of plasma ticagrelor concentrations will be collected at the times indicated in the Schedule of Assessments in Appendix 4 and will be stored until analysis. A pre-CPB sample will be obtained prior to the start of cardiopulmonary bypass, and up to 2hrs pre-start of surgery (i.e., time of skin incision). While the subject is on CPB, serial samples will be drawn at 30±15min following initiation of CPB, at 60min, at 90min, and at 120min of CPB time. A post-CPB sample will be obtained as soon as possible following the end of CPB, and no later than 30min after the subject has been disconnected from the CPB circuit.

If the total CPB time required for the procedure is <120min (2hrs), the serial sampling will only be

performed through the required duration of CPB. For procedures requiring >120min (2hrs) of CPB time, serial sampling will ***not*** extend beyond this time point, as the incremental change is expected to be minimal compared to the post-CPB value. Processing, storage, and shipping instructions for these blood samples will be provided by the Sponsor (or designee) to the investigation sites, and detailed in the Study Laboratory Manual. Samples will be stored and analyzed at a designated bioanalytical laboratory using a validated assay. Any residual samples will be destroyed at the completion of the final investigation report or if the subject withdraws assent/consent to use the sample for the research purposes of the investigation.

10. CONCOMITANT MEDICATIONS

Medication history and concomitant medications will be recorded in the eCRF. The medication history will include all acute and chronic prescription and over-the-counter medications taken during the 30 days prior to Screening. Medication history will be repeated on the day of the procedure if different from the day of screening.

All medications administered during the Screening, Pre-CPB, Intraoperative, Post-CPB, and during the Postoperative Phases must be collected.

Study subjects may, in addition to ticagrelor, also be receiving other antithrombotic medications during their current hospitalization that could contribute to bleeding. The use of antithrombotic medications will be reviewed during the screening period. The type of agent and the timing of administration could confound the results of the study and are therefore listed as prohibited medications (see Appendix 5 for details). Subjects on prohibited medications at the time of surgery cannot be randomized. Each antithrombotic medication is categorized as allowed or prohibited in the study, and the reason for this categorization is provided.

Prior and concomitant medications will be coded using the latest version of the WHO Drug Dictionary, based on Anatomical Therapeutic Chemical classification and Preferred Name.

There are no protocol-specified prohibited medications during the Postoperative phase of the study.

11. STATISTICAL CONSIDERATIONS

General statistical considerations: descriptive summaries will be presented using mean with standard deviation (SD), median, minimum and maximum for continuous variables and as count and percent of subjects for categorical variables. Inferential statistical tests will be two-sided, and use an alpha (α) critical value of 0.05, unless noted otherwise. Statistical analysis will be carried out using SAS Version 9.4 or later and/or R software language.

11.1. Statistical Power and Sample Size Determination

Up to 140 subjects meeting the study inclusion criteria (**Section 4.4.1**) will be randomized in a 1:1 ratio to the treatment and control arms. As noted above (**Section 6.2**), in order to maintain the balance between sites in terms of numbers of subjects randomized, study sites will be capped at randomizing a maximum of 15% of the overall study sample. Allowing for 5% dropouts, at total of 114 subjects (57 per arm) are expected to be evaluable for effectiveness and safety. Sample size is based on assumed effect size for the primary effectiveness Win Ratio sub-components (**Table 3**), and can be calculated via an iterative simulation process with programming code available in an appendix to Redfors et al. (2019).[11] With a Finkelstein – Schoenfeld test, a total of 57 subjects per arm ensures power of $\geq$99.7% for the primary effectiveness endpoint at the final analysis, using a two-sided alpha (α) of 0.05. [10] With this same per arm sample size, power for the key secondary endpoint is estimated at >99.9% assuming a 40% ± 40% mean difference between treatment and control, based on a two-

sample t-test assuming equal variance and a two-sided alpha of 0.05. For the 24-hour CTD secondary endpoint, assuming a treatment arm volume of 480 ± 253 mL and control arm volume of 800 ± 253 mL [8] [a discount is applied (see **Table 3** for details) to bring the Active arm up to ~40% reduction on the Control arm], power is similarly estimated at >99.9%. Power for comparisons of platelet transfusions between the treatment arm (0.32 ± 0.9 units) and control arm (1.6 ± 2.2 units) [13] is estimated at 98.0%, based on a two-sample t-test assuming unequal variance and a two-sided alpha of 0.05. Similarly, power for PRBC transfusions between the treatment arm (1.3 ± 2.1 units) and control arm (4.4 ± 5.7) [13] is estimated at 96.7%.

Overall study sample size is designed to provide adequate power for the primary effectiveness endpoint, the key secondary endpoint, and succeeding three secondary endpoints. Sample size and power for all secondary endpoints were calculated using PASS 2021 (NCSS, LLC. Kaysville, UT, USA, ncss.com/software/pass).

The null hypothesis for the primary composite endpoint is represented by:
H_0: The distributions of the components are the same in the two treatment groups.
The alternative hypothesis for the primary composite endpoint is represented by:
H_A: For at least one component, the distribution is different between the treatment groups.

Table 3. Win Ratio Effect Size Assumptions with Power and Sample Size Estimates

n Per Group	Effect Size						Power
	Component #1		Component #2		Component #3		
	Fatal Bleeding		UDPB (Class ≥2)		24hr CTD		
	Treatment Event	Control Event	Treatment Event	Control Event	Treatment Mean (SD)	Control Mean (SD)	
N=57	3.0%	3.0%	24.3%	40.5%	480 (253)	800 (253)	**≥99.7%**

Notes: n = number; UDPB = Universal Definition of Perioperative Bleeding; CTD = chest tube drainage (volume [mL]).
Component #1 minimum rates of 3.0% assumed as a conservative approach.
Component #2 rates based on Russo et al. (2019), however, with a discount applied to bring the Treatment arm up to ~40% reduction on the Control arm. [14]
Component #3 rates based on Hassan et al. (2019), however, with a discount applied to bring the Treatment arm up to ~40% reduction on the Control arm. [8]

11.2. Analysis Populations

Enrolled subjects include all subjects who provide informed assent/consent. Enrolled subjects who do not meet criteria for study eligibility are deemed screening failures and will exit the study.

The Intent-to-Treat (ITT) Population will include all subjects who are randomized.

The modified Intent-to-Treat (mITT) Population includes all randomized subjects who undergo the index surgical procedure **and** receive a study device (whether DrugSorb™-ATR or *sham*). The primary analyses of the trial will be performed on the mITT Population. Baseline demographic and clinical variables will be summarized for each of the treatment groups in the mITT population. So long as the mITT and ITT populations are **not** identical, the ITT subjects who do not fall within the mITT population will be presented in a listing, including the reasons for why they did not receive a study device.

The Per Protocol (PP) Population will include all mITT subjects who have no major protocol violations. Analysis of the primary efficacy endpoint will be performed in the PP population as a supplemental analysis.

The Safety Analysis (SA) Population will include all enrolled subjects who are treated with a study device.

11.3. Effectiveness Analysis

The primary effectiveness endpoint will be evaluated using the Win Ratio method (Pocock, et al., 2012) of analysis for a hierarchical composite endpoint based on the Finkelstein-Schoenfeld test (Finkelstein and Schoenfeld, 1999; Pocock, et al., 2012) with three components ranked in order of clinical importance: a) fatal perioperative bleeding events (occurring within 48hrs post-index procedure), b) moderate, severe, or massive perioperative bleeding events according to the Universal Definition of Perioperative Bleeding in Cardiac Surgery (UDPB) classification ≥2, and c) 24-hour chest tube drainage (mL) following surgery. [9] [10] The Win Ratio assigns "wins", losses", or "ties" in sequential comparisons between treatment and control arm subjects according to the hierarchical order of the components of the primary composite endpoint. There are two key advantages to the Win Ratio method of analysis. First, the hierarchical assessment of the individual components of the composite endpoint according to their clinical significance. Second, the opportunity for different types of components, such as categorical versus continuous, to all be included thereby capturing all available information from each component to increase statistical power. [9] The estimated Win Ratio along with a two-sided 95% CI will be provided between the treatment and control arm. The details of the primary effectiveness analysis will be provided in the SAP.

The key secondary effectiveness endpoint is a drug removal endpoint, namely the percent change in pre-CBP vs. post-CPB ticagrelor blood levels as measured by liquid chromatography/tandem mass spectrometry. Blood samples for drug removal analyses will be collected and analyzed by a central core laboratory.

Change from baseline in blood concentration of ticagrelor is defined as:

$$\frac{\text{pre-CPB [ticagrelor]blood - post-CPB [ticagrelor]blood}}{\text{pre-CPB [ticagrelor]blood}} * 100\%$$

Benchtop studies of drug removal by the DrugSorb™-ATR device (CytoSorbents, unpublished data) demonstrate concentration and time dependent absolute drug removal. Based on these benchtop studies, a conservative estimate of 40% reduction in blood concentration of ticagrelor between pre- and post- DrugSorb™-ATR removal is expected, with a standard deviation of 40%, in the treatment arm. Minimal change is expected in the control arm. A two-sample t-test will be used to evaluate the difference between treatment arms. Due to highly variable baseline ticagrelor blood levels in the above benchtop studies, percent change from baseline will be analyzed as opposed to observed values. We anticipate drug removal data from other clinical studies in this application to become available during the course of the study and we plan to update the above assumption if necessary based on *in vivo* data.

Additional powered secondary endpoints include 24-hour CTD (volume [mL]), total platelet transfusions during the index hospitalization (volume [mL] and units), and total PRBC transfusions during the index hospitalization (volume [mL] and units). Twenty-four-hour CTD (mL) will be assessed via two-sample t-test for mean difference. In the event the assumptions for a two-sample t-test are not met, a nonparametric test such as a Mann-Whitney test will be employed, with median and range values provided in the output. The transfusion endpoints will all be analyzed using two-sample t-tests for mean differences, and Fisher-Freeman-Halton exact tests for units. In the event the assumptions for a two-sample t-test are not met, a nonparametric test such as a Mann-Whitney test will be employed, with median and range values provided in the output. Other secondary endpoints include the remaining Win Ratio component parts: proportions of fatal perioperative bleeding events will be assessed via Fisher's exact test; and proportions of UDPB events (by category) will be

assessed via a Fisher-Freeman-Halton exact test. All surgical re-exploration for excessive bleeding, including those events occurring beyond the timeframe captured within the UDPB component of the primary endpoint will be captured as a secondary endpoint. Time to re-exploration will be taken into account.

Type I error (alpha, α) will be preserved from inflation due to multiplicity across the primary effectiveness, key secondary, and secondary endpoints via a hierarchical closed testing step-down approach. Only in the event that preceding endpoints are declared statistically significant at the alpha 0.05 level, can further endpoints also be declared significant. The order of hierarchical testing will follow the order of primary, key secondary, and secondary endpoints as listed in the paragraph above, namely: the primary endpoint will be tested first, followed by the key secondary endpoint (percent change in pre-CPB vs. post-CPB blood ticagrelor levels), followed by the first secondary endpoint (24-hour CTD), second secondary endpoint (platelet transfusions), and lastly (PRBC transfusions). Should all preceding statistical comparisons show results below their alpha cut-off values, further secondary endpoints will be evaluated: the proportion of fatal perioperative bleeding events, proportions of UDPB events (by category), and surgical re-exploration rates.

Other exploratory endpoints include:

- Area under the concentration time curve (AUC), using the trapezoidal approach, for intraoperative ticagrelor pharmacokinetic (PK) concentration
- Operative time (measured from start of skin incision to completion of chest closure)
- Duration of ICU stay
- Duration of hospital stay
- 30-day hospital re-admissions

Details on methods of analysis for exploratory endpoints will be provided in the SAP.

Further details regarding summary and analysis of effectiveness data will be provided in the SAP.

11.4. Subgroup Analysis

The primary effectiveness endpoint will also be analyzed across the clinically meaningful subgroups, including but not limited to those outlined below:

- Planned surgery type (CABG alone vs. all other types of surgery)
- Key demographic factors including age (<65 vs ≥65 years old) and sex (M/F)
- EuroScore II score
- STS Risk score (low, intermediate, high)
- NYHA heart failure class (1, 2, 3, 4)
- Left ventricular ejection fraction [according to the ACC classification: ≥50% (normal), 40-49% (mild dysfunction), 30-39% (moderate dysfunction), <30% (severe dysfunction)]
- Baseline thrombocytopenia (platelet count <150,000 μ/L, ≥150,000 μ/L)
- Prior MI (Y/N)
- Prior stroke (Y/N)
- Prior hypertension (Y/N)
- Prior hyperlipidemia (Y/N)
- Diabetes mellitus (Y/N)
- Chronic obstructive pulmonary disease/COPD (Y/N)
- Current or prior tobacco use (Y/N)
- Prior sternotomy (Y/N)
- Drug removal

Additional details on subgroup analyses will be provided in the SAP.

11.5. Treatment of Missing Data

Every effort will be taken to obtain data entry compliance of all critical fields during the course of the study. The study assumes up to 5% of the data may be missing. Reasons for missing data will be collected and a distribution of the prognostic factors in subjects with and without missing data will be compared to identify any confounding factors. Sensitivity analyses will be conducted to assess the sensitivity of the results to assumptions underlying the missingness mechanism. Details will be provided in the SAP.

11.6. Safety Analysis

All the safety endpoints will be analyzed in the SA Population. Additional safety analyses will be conducted on the mITT and PP Population if they are different from the SA population.

The incidence of all AEs occurring after the start of the CPB procedure will be summarized by treatment group using frequency and percentage. AEs that occur following informed consent but prior to the start of CPB will not be included in this safety analysis but will be provided in a listing. Within the Safety Analysis, AEs will be summarized by severity and relationship to the study device as determined by the Investigator (or designee). Discontinuations due to AEs, and SAEs will be summarized. All AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA®) according to system organ class and preferred term, prior to database lock.

Observed values for clinical laboratory test data and vital signs, along with change from baseline results, will be summarized by collection time point. A summary of clinically notable values will be provided.

All the safety data will be listed in the SA population. Further details regarding presentation and analysis of safety data will be detailed in the SAP.

11.7. Device Malfunctions/Deficiencies

A summary of device malfunctions/deficiencies will be provided by treatment arm. All malfunctions/deficiencies will be listed.

11.8. Disposition and Baseline Characteristics

Number and percentage of subjects discontinuing prematurely from the study will be provided by treatment group and by reason discontinued. All data for background and demographic variables will be summarized and listed by treatment group and subject. Relevant medical history, current medical conditions, and incidence of prior and concomitant medications will be summarized by treatment group as well as listed.

12. DATA HANDLING AND RECORD KEEPING

Each participating site will maintain appropriate medical and research records for this trial, in compliance with ICH E6 Section 4.9 and regulatory and institutional requirements for the protection of confidentiality of subjects. As part of participating in a manufacturer-sponsored study, each site will permit authorized representatives of the sponsor(s), the sponsor's designee, and regulatory agencies to examine (and when required by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits, and evaluation of the study safety and progress.

Source data are all information, original records of clinical findings, observations, or other activities

in a study necessary for the reconstruction and evaluation of the trial.

The Investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data.

12.1. Data Management Procedures

Electronic Case Report Forms (eCRFs) will be used to collect all subject data during the course of the study, which are part of a database that meets 21 CFR Part 11 requirements. eCRFs must be fully completed for each subject and electronically signed by the Investigator when complete.

Federal Regulations and Good Clinical Practice Guidelines require that Investigators maintain information in the study subject's medical records that corroborate data collected on the eCRFs. In order to comply with these regulatory requirements, the following information should be maintained:

- Medical history/physical condition of the study subject before involvement in the study sufficient to verify protocol entry criteria.
- Dated and signed notes on the day of entry into the study including the study Investigator, study name, subject number assigned and a statement that consent was obtained.
- Dated and signed notes from each study subject visit with reference to the CRFs for further information, if appropriate (for specific results of procedures and exams).
- Information related to adverse event(s).
- Study subject's condition upon completion of or withdrawal from the study.
- Discharge summaries/procedure reports.

12.2. Subject Data Protection

Subjects will be assigned a unique identifier and will not be identified by name in electronic Case Report Forms (eCRFs), investigation-related forms, investigation reports, or any related publications. Subject and Investigator personal data will be treated in compliance with all applicable laws and regulations. In the event the clinical investigation plan (CIP), investigation report, or investigation data are included in a public registry, all identifiable information from individual subjects or Investigators will be redacted according to applicable laws and regulations.

The subject must be informed that his/her personal investigation-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the subject. The subject must also be informed that his/her investigation-related data may be examined by Sponsor or Contract Research Organization (CRO) auditors or other authorized personnel appointed by the Sponsor, by appropriate EC members, and by inspectors from regulatory authorities.

12.3. Data retention

Maintenance of study records should be obtained for a period of five (5) years after the latter of two occurrences:

1. The date when the investigation is terminated or completed, or
2. The date that the records are no longer needed to support a regulatory approval.

These documents should be retained for a longer period, however if required by local regulations. No records will be destroyed without the written consent of the sponsor, if applicable. It is the responsibility of the Sponsor to inform the Investigator when these documents no longer need to be

retained.

12.4. Investigator Records

Investigators will maintain complete, accurate, and current study records. Investigator records shall include the following materials:

- **Correspondence:** All significant correspondence with another investigator, an IRB, the sponsor, a monitor, or FDA, including required reports.
- **Subject Records:** Signed informed consent forms, copies of supporting documents (laboratory reports, reports of diagnostic tests, medical records, etc.) and records of exposure of each subject to the device. Informed consent must comply with FDA regulations (21 CFR, part 50).
- **Clinical Investigational Plan/Protocol:** A current copy of the Clinical Study Protocol and amendments including Instructions for Use of the DrugSorb™-ATR device and copies of the eCRFs.
- **Institutional Review Board (IRB) Information:** All information pertaining to IRB review and approval of this clinical study including a copy of the IRB letter approving the clinical study, a blank informed consent form approved by the IRB, and certification from the IRB Chairman that the IRB complies with FDA regulations (21CFR, part 56), and that the IRB approved the clinical study protocol.
- **Investigator Agreements:** Copies of the signed Investigator, Sub-Investigator Agreements with accompanying curriculum vitae. Signed Protocol pages.
- **Study Documents:** Including Investigational Device Accountability logs (including device shipment list/packing lists), Screening and Enrollment logs, and Site Visit logs
- **Other:** Any other records that may be required by applicable state or federal laws.

12.5. Investigator Reports

The Investigator will prepare and submit the designated reports listed in **Table 4**.

Table 4. Responsibilities for Preparing and Submitting Reports

Type of Report	Prepared by the Investigator for:	Time of Notification/Report Completion
Enrollment Notification eCRF	Sponsor	Within 24 hours of the subject signing the ICF
SAE/SADE/UADE eCRF	Sponsor	Within 24 hours of knowledge or as required by the IRB
All other eCRFs	Sponsor and IRB (as required)	Within 10 business days (or as required by IRB for AE eCRFs)
Device deficiency or device observation eCRF	Sponsor	Within 24 hours of knowledge
Subject Death or withdrawal	Sponsor and IRB (as required)	Within 24 hours of knowledge
Withdrawal of IRB or FDA Approval	Sponsor	Within 24 hours of knowledge
Informed Consent Not Obtained	Sponsor and IRB	Within 24 hours of knowledge or as required by IRB
Progress report	Sponsor and IRB	Annually
Final summary report	Sponsor, IRB, and FDA	Within six months of study

		completion
Other reports	Sponsor and IRB and FDA	As needed

13. QUALITY CONTROL AND ASSURANCE

13.1. Site and Investigator Selection

The Sponsor selects qualified investigators with appropriate experience at health care facilities with adequate resources to participate in this study. The investigational sites will be selected using combined current assessments of site and investigator qualifications.

13.2. Protocol Deviations

An Investigator is not allowed to deviate from the Protocol without the prior written approval of the Sponsor. Under emergency circumstances, deviations from the Protocol to protect the rights, safety and well-being of human subjects may proceed without prior approval of the sponsor and the IRB. Such deviations shall be documented and reported to the sponsor and the IRB (as required) as soon as possible.

A protocol deviation is a failure to comply with the requirements specified within this clinical study protocol. Examples of protocol deviations may include enrollment of a study subject who does not meet all of the inclusion/exclusion criteria specified in the protocol, visits performed outside of the protocol specified visit window, and missed study visits. Each investigator shall conduct this clinical study in accordance with this clinical study protocol, regulatory body regulations, Good Clinical Practices, and any conditions of approval imposed by their IRB.

All deviations are reviewed and assessed for their impact on subject safety by the Sponsor or designee. The PI and study staff are responsible for knowing and adhering to their IRB reporting requirements.

- The protocol deviations for this protocol consist of, but not limited to the following:
- Failure to obtain subject's informed consent prior to any study-related activities;
- Failure to conduct protocol required clinical follow-ups;
- Failure to conduct protocol required clinical follow-ups within time windows; and,
- Failure to report serious adverse events according to protocol requirements.

In the event of any deviation from the protocol, the Investigator will be notified of the site's non-compliance. Corrective actions will be required, if necessary. Continued protocol deviations despite re-education of the study site personnel or persistent protocol deviation may result in termination of the site's study participation. Subjects enrolled at these sites will continue to be followed per the clinical protocol.

13.3. Protocol Deviation Process

Investigators must report protocol deviations to the Sponsor within 10 working days of investigational site knowledge of the deviation by entering data into the protocol deviation log. Any protocol deviations that affect the rights, safety or well-being of the subject or the scientific integrity of the clinical investigation, including those which occur under emergency circumstances must be reported within 24 hours to the Sponsor and IRB if required by the IRB.

13.4. Corrective/Preventative Action

The Sponsor reserves the right to terminate an investigational site from the study for any of the following reasons:

- Repeated failure to complete Electronic Case Report Forms (eCRFs);
- Failure to obtain Informed Consent;
- Failure to report Serious Adverse Events within 24 hours of knowledge;
- Loss of or unaccountable investigational device inventory;
- Repeated protocol violations;
- Failure to enroll an adequate number of subjects

13.5. Data Quality Assurance

The following data quality steps will be implemented:

- All subject data relating to the investigation will be recorded on eCRFs unless directly transmitted to the Sponsor or designee electronically (e.g., laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by electronically signing the eCRF.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The Investigator must permit investigation-related monitoring, audits, and regulatory agency inspections and provide direct access to source data documents.
- The Sponsor or designee is responsible for the data management of this investigation including quality checking of the data. Predefined, agreed risks, monitoring thresholds, quality tolerance thresholds, controls, and mitigation plans will be documented.
- An Investigation Monitor will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of subjects are being protected; and that the investigation is being conducted in accordance with the currently approved CIP and any other investigation agreements, ISO GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this investigation must be retained by the Investigator in the investigation site archive for at least 5 years after the end of the investigation unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

14. TERMINATION OF STUDY OR STUDY SITE PARTICIPATION

The Sponsor may terminate the study at any time. Reasons for study termination may include but are not limited to any of the following:

- Adverse events unknown to date (i.e., not previously reported in any similar investigation or in market use with respect to their nature, severity, and/or duration).
- Increased frequency, severity, and/or duration of known, anticipated, or previously reported AEs.
- Medical or ethical reasons affecting the continued performance of the investigation.
- Difficulties in the recruitment of subjects.
- Cancellation of device development.

If the study is terminated prior to the completion of expected enrollment for any reason, all participating centers will be notified within five working days. All subjects already enrolled will

continue to be followed for the planned course of study described in this protocol. The study will be terminated following the final follow-up visit of the last enrolled subject.

In addition to the corrective actions listed in **Section 13.4**, the Sponsor reserves the right to terminate study site participation and remove appropriate study materials at any time. Specific instances that may precipitate such termination include but are not limited to the following:

- Failure to meet minimum subject enrollment requirements
- Failure to comply with protocol specified procedures and documentation
- Failure to comply with Good Clinical Practice

The site Investigator may also discontinue study participation with suitable written notice to the Sponsor.

15. ETHICS/PROTECTION OF HUMAN SUBJECTS

15.1. Statements of Compliance

This clinical investigation shall be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and 21 CFR Part 812, 50, 54, 56. The clinical investigation shall not begin until the required approval from the IRB has been obtained, if appropriate. Any additional requirements imposed by the IRB, or regulatory authority shall be followed.

15.2. Institutional Review Board (IRB)

Each participating institution must provide for the review and approval of this protocol and the associated informed consent documents and recruitment material by an appropriate IRB. Any major amendments to the protocol or consent materials must also be approved before they are placed into use.

15.3. Informed Consent Process

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout an individual's study participation. Discussion of risks and possible benefits of this therapy will be provided to the subjects and their families. Consent forms describing in detail the study interventions/products, study procedures, and risks are given to the subject and written documentation of informed consent is required prior to starting intervention/ administering study product.

Consent may be provided by 1) individual subject providing informed consent; 2) assent of a guardian, healthcare proxy, or welfare attorney on behalf of a subject without capacity to consent (vulnerable or incapacitated individual). Details of the process for obtaining and documenting informed consent are provided in Appendix 3. Failure to obtain informed consent prior to initiation of study treatments will need to be documented as a protocol deviation and be reported in accordance with regulations.

15.4. Subject Confidentiality

Confidentiality of data shall be observed by all parties involved at all times throughout the clinical investigation. All data shall be secured against unauthorized access.

The privacy of each subject and confidentiality of his/her information shall be preserved in reports and when publishing any data. The Principal Investigator or institution shall provide direct access to

source data during and after the clinical investigation for monitoring, audits, IRB review and regulatory authority inspections. As required, the Principal Investigator or institution shall obtain permission for direct access to source documents from the subject, hospital administration and national regulatory authorities before starting the clinical investigation.

16. PROTOCOL AMENDMENTS

The Protocol, CRFs, ICF and other subject information, or other clinical investigation documents shall be amended as needed throughout the clinical investigation, and a justification statement shall be included with each amended section of the document. Proposed amendments to the Protocol shall be agreed upon between the Sponsor and Principal Investigator(s), or the coordinating investigator. The amendments to the Protocol and the subject's informed consent form shall be notified to, or approved by, the IRB and regulatory authorities as required. For non-substantial changes (e.g., minor logistical or administrative changes, change of monitor(s), telephone numbers, renewal of insurance) not affecting the rights, safety and well-being of human subjects or not related to the clinical investigation objectives or endpoints, a simple notification to the IRB and, where appropriate, regulatory authorities can be sufficient. The version number and date of amendments shall be documented.

17. PUBLICATION POLICY

CytoSorbents manages its clinical studies in an ethical and rigorously scientific manner, working with leading experts in the field, to clearly and publicly demonstrate the benefits, risks, and value of the DrugSorb™-ATR Device to caregivers and study subjects alike. We accept the obligation to facilitate publication of medically important clinical data in a timely, objective, accurate, and balanced manner, regardless of the outcome of this trial. To ensure that an accurate record of the study data is presented to the public, CytoSorbents understands the need to allow sufficient time for careful preparation, analysis, interpretation, and review of study data and reports prior to their dissemination.

Safety and Efficacy Data generated for all prespecified primary and secondary endpoints, shall be compiled, analyzed, reviewed, and published in the following manner:

- The Principal Investigator(s) and Sponsor shall compile and disseminate a clinical summary report that shall be disseminated to CytoSorbents (as Sponsor), all participating local and central IRBs, and the FDA. Data from this Summary Report shall also be published on the ClinicalTrials.Gov website simultaneously.
- Following database closure, a study publication shall be submitted to a peer reviewed journal within 18 months of database closure. In the event that the study is terminated early, a publication of this data will be submitted within 12 months of database closure.

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20. APPENDICES

Appendix 1: Adverse Event Reporting

An adverse event (AE) is any untoward medical occurrence (signs, symptoms, abnormal laboratory findings) in a subject regardless of relationship to the device or procedure. Throughout the study, the Investigator or designee will determine adverse event (AE) occurrences. All AEs that occur starting from subject enrollment through follow-up will be reported. As a matter of semantics, AEs that are new onset or worsen in severity ***after the start of the cardiopulmonary bypass procedure*** are considered Treatment-emergent AEs. This term does ***not*** include adverse events occurring *prior* to the start of CPB but *after* the signing of the ICF (assent or consent). As previously discussed in **Section 11.6**, only the treatment-emergent AEs will be included in the safety analysis. This will be further detailed in the SAP.

Each adverse event is considered to be either anticipated or unanticipated as described below. The site is required to report the classes of adverse events that occur in the study (AE, SAE, and UADE) as described further below.

Severity Assessment

The Investigator will assess each adverse event for severity in accordance with the following categories: mild, moderate, severe, life-threatening, or death.

The severity assessment is distinct from the seriousness assessment (see definition of SAE below).

Serious Adverse Events

A serious AE (SAE) is defined as any untoward medical occurrence that meets one or more of the following criteria:

- led to death;
- led to a life-threatening illness or injury;
- led to in-patient hospitalization or prolongation of existing hospitalization;
- led to disability or permanent damage to a body structure or body function;
- led to fetal distress, fetal death, congenital anomaly or birth defect;
- required medical or surgical intervention to prevent permanent impairment or damage; or
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered SAEs when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

<u>Definition of Hospitalization</u>
Adverse events requiring hospitalization or extended hospitalization should be considered serious. In general, hospitalization signifies that the subject has been detained (usually involving an overnight stay) at the hospital or emergency ward for observation and/or treatment. When in doubt as to whether hospitalization occurred or was necessary, the AE should be considered as serious. *Planned hospitalization for pre-existing condition, or a procedure required by the Clinical Investigation Plan, without a serious deterioration in health is not considered a serious adverse event*.

Serious AEs occurring after 30 days post-operation are to be reported to the Sponsor if, in the judgment of the Investigator, there is an association between the event and the previous use of the device under investigation.

Causality Assessment

The Investigator will assess each adverse event for relationship to the following (causality), and relationship classified as unrelated, unlikely related, possibly related, probably related, or definitely related:

> **Investigational Treatment/Device:** An investigational device/treatment-related adverse event is one which in the judgment of the Investigator, results as a consequence of the investigational device/treatment. Clinical judgement in conjunction with the relevant documents, such as the Investigator's Brochure and the Clinical Investigational Plan shall be applied in the determination of whether the AE might be related to the device/treatment. The presence of confounding factors, such as concomitant medication/treatment, the natural history of the underlying disease, other concurrent illness or risk factors shall be considered.
>
> **Surgical Procedure:** The investigator will distinguish between the events potentially related to CPB and the investigational device from those related to the underlying surgical procedures. A procedure-related adverse event is one which, in the judgment of the Investigator, results as a consequence of the subject's surgical procedure and is not specific to the investigational device/treatment used or the associated CPB circuit. Complications occurring during a procedure are considered not related to the device if the complication would have been applied to the subjects in the absence of the investigational device use/application. Adverse events that have previously been determined to be related to the investigational device should not also be assessed as being related to the surgical procedure.

Causality assessment will also be performed during CEC adjudication of relevant events. Guidelines for CEC causality assessments are provided in the CEC charter.

Action Taken for Adverse Events

The Investigator or designee will record the action taken for the AE within the electronic Case Report Form (eCRF) in accordance with the following categories: treatment interrupted, treatment withdrawn, medication, procedure/intervention, transfusion, other/unknown, or none.

Outcome

The Investigator or designee will record the outcome of the AE within the electronic Case Report Form (eCRF) in accordance with the following categories: resolved without sequelae, resolved with sequelae, ongoing, or resulted in mortality.

Follow-up of Adverse Events

Every reasonable effort will be made to follow up with subjects who have AEs. Any subject who has an ongoing AE that is related to the investigational medical device at the 30-day Follow-up Evaluation will be followed up, where possible, until resolution or stabilization. This will be completed at the Investigator's (or designee's) discretion. Any subject who has an ongoing AE that is not related to the investigational medical device at the 30-day Follow-up Evaluation can be closed out as ongoing at the Investigator's discretion.

Adverse Device Effect:

An adverse device effect (ADE) is an AE related to the use of an investigational medical device. This definition includes AEs resulting from insufficient or inadequate instructions for use, deployment,

installation, or operation, or any malfunction of the investigational medical device. The definition also includes any event resulting from use error or from intentional misuse of the investigational medical device. These events can be classified as either serious or not serious in accordance with the definition for SAEs above. Serious adverse device effects are also commonly referred to by the abbreviation SADE.

Unanticipated Adverse Device Effect:

An unanticipated adverse device effect (UADE) is any adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report. These events can be classified as either serious or not serious in accordance with the definition for SAEs above. In the event of a possible UADE, the subject blind may be broken as per **Section 6.3.3** above. This will enable confirmation of relationship between the adverse event and device exposure and facilitate appropriate safety procedures as well as regulatory reporting per guidelines.

Anticipated Adverse Events/Device Related Adverse Events

A variety of complications are expected to occur in subjects undergoing CPB and cardiothoracic surgery, regardless of whether or not DrugSorb™-ATR is used. These may include, but are not limited to:

Serious, but less common, risks:

- Bleeding during or after the surgery including bleeding in relation to anticoagulation
- Blood clots that can cause heart attack, stroke, or lung problems
- Heparin-induced thrombocytopenia
- Bypass induced thrombocytopenia
- Reduction in platelets
- Infection, including pneumonia
- Organ injury including:
    - Respiratory damage causing breathing problems or failure to wean from the ventilator
    - Cardiac dysrhythmias/arrhythmias
    - Kidney injury or renal failure
    - Cognitive impairment
- Death

Less serious, but more common risks and adverse events:

- Low-blood pressure
- Nausea and/or vomiting
- Hypothermia and/or Chills
- Allergic response to device materials
- Reduction in platelet count
- Reduction in white blood cell count
- Reduction in proteins (albumin, total protein)
- Coagulation within device
- Heparin-induced thrombocytopenia

Potential Adverse Device Events Directly Related to DrugSorb™-ATR:

- Removal of drugs and hormones
- Allergic response to device materials
- Reduction in platelet count
- Reduction in white blood cell count
- Reduction in proteins (albumin, total protein) which may increase with CPB duration.
- Reductions in serum calcium (as a consequence of reductions in albumin)
- Coagulation within device
- Infection
- Blood loss
- Hemolysis
- Device leakage
- Circuit leakage
- Death

Investigator Reporting:

The Investigator at each participating center is ultimately responsible for reporting adverse events to the Sponsor or its designee. The information to be reported on the adverse event should include the start date of the adverse event, treatment, resolution, and assessment of both the seriousness and the relationship to the investigational device. The Investigator (or designee) is required to complete the adverse event eCRF at each study visit if an adverse event occurs. One adverse event eCRF must be completed for each adverse event. The timing of mandatory Investigator reports is provided in **Table 4**.

If there is a device malfunction or other observation, the Device Observation CRF requires the Investigator to indicate if the observation resulted in an adverse event and indicate if complications are related to the device, procedure or underlying disease.

Sponsor Reporting:

Reports will be provided to the FDA as required under §812.150. The details will be provided in the Study Reference Manual for the trial.

Appendix 2: Clinical Laboratory Evaluations

Clinical chemistry:	Hematology:
Alanine aminotransferase [a] Albumin Alkaline phosphatase [a] Aspartate aminotransferase [a] Blood urea nitrogen Calcium Ionized Calcium [a] Chloride Creatinine Direct bilirubin [a] Gamma-glutamyl transferase [a] Glucose Potassium Sodium Total bilirubin [a] Total protein	Hematocrit Hemoglobin Platelet count Red blood cell count White blood cell (WBC) count Differential [a]
Coagulation tests:	**Other, including cardiac biomarkers**
Coagulation Panel: Activated partial thromboplastin time International normalized ratio Prothrombin time Fibrinogen [a] **Point of Care Test(s):** Activated clotting time (ACT) [*refer to Schedule of Assessments for specific timing of sampling*]	Serum pregnancy test[b] Cardiac troponin (cTn)[c]

[a] Performed only if part of routine standard of care. Sponsor agrees to forego the data if the assessments are not performed and recorded
[b] Performed in serum at Screening for all females of child-bearing potential. Pre-consent test results done during the current admission MAY be used. Pre-consent test results done before the current admission MAY NOT be used.
[c] Performed in serum Screening for all subjects. Post-op testing will be per institutional standard of care, or as indicated by symptoms and concern for perioperative myocardial infarction

Appendix 3: Regulatory and Ethical Considerations

This investigation will be conducted in accordance with the Clinical Investigation Plan (CIP) and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and 21 CFR Part 812, 50, 54, 56.
- Applicable International Organization for Standardization (ISO) ISO14155 Clinical investigation of medical devices for human subjects — Good clinical practice, Good Clinical Practice (GCP) Guidelines.

The CIP, CIP amendments, Informed Consent Form (ICF) along with associated information sheets, and other relevant documents must be submitted to an Ethics Committee (EC) by the Investigator and reviewed and approved by the EC and regulatory authority before the investigation is initiated.

Any substantial CIP amendments, likely to affect the safety of the subjects or the conduct of the study, will require EC, IRB, and regulatory authority approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to investigation subjects or any non-substantial changes, as defined by regulatory requirements.

Informed Consent for Non-vulnerable Populations

Subjects will be given an opportunity to ask questions about the investigation prior to providing consent for participation. Written documentation of informed consent is required prior to starting the intervention/administering the study product. Consent forms will be IRB-approved, and the subject will be asked to read and review the document. The subject should have the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate, unless study timeframes do not allow for such discussions. The subjects may withdraw consent at any time throughout the course of the trial.

A copy of the signed informed consent form will be given to the subject, and another will be maintained in the subject's records. The rights and welfare of the subjects will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in the study.

When informed consent of the subject is not possible because of the subject's medical condition, the informed consent of the legally authorized representative, if present, shall be requested (see the below section on ***Informed Consent for Vulnerable Populations***).

If informed consent is not obtained prior to any research procedures being conducted, the investigative site must notify the Sponsor and IRB within 24 hours of knowledge of the incident.

If new information becomes available, that can significantly affect a subject's future health and medical care, this information shall be provided to the subject(s) affected in written form. If relevant, all affected subjects shall be asked to confirm their continued informed consent in writing.

Informed Consent for Vulnerable Populations

Considering the nature of the clinical investigation as well as the clinical investigation population, is it likely that potential subjects may not be able to give voluntary written informed consent in advance of the procedure (vulnerable individual lacking capacity). A personal legally authorized representative (preferably the nearest relative or healthcare proxy) of the subject shall be consulted in the event the subject is unable to consent for themselves and this person will be the one responsible for assenting to

the subject participation in the clinical investigation. After the procedure is completed, the consent of the subject will be obtained as soon as the subject has recovered capacity. Upon regaining capacity, those subjects who do not wish to consent, may request that all data obtained under the assent be withdrawn from the study database.

Informed Consent for Subjects Unable to Read or Write

Informed consent shall be obtained through a supervised oral process if the subject or legally authorized representative is unable to read or write. An independent witness shall be present throughout the process. The written informed consent form and any other information shall be read aloud and explained to the prospective subject and his/her legally authorized representative and, whenever possible, shall sign and personally date the informed consent form. The witness also signs and personally dates the informed consent form attesting that the information was accurately explained, and that informed consent was freely given.

Disclosure

All information provided regarding the investigation, as well as all information collected and/or documented during the course of the investigation, will be regarded as confidential. The Investigator (or designee) agrees not to disclose such information in any way without prior written permission from the Sponsor.

Appendix 4: Schedule of Assessments

Table 5. Schedule of Antithrombotic and Anticoagulation Management

Time period	**Screening/ preoperative period**	**Operation**	**Postoperative day 1**	**>1 day post-operation**	**30-day follow-up**
Subjects with ACS or coronary stent placement within the previous 6 months					
Aspirin	X	X	X[a]	X	X
Ticagrelor/$P2Y_{12}$ inhibitor[b]	X[c]		X[d]	X	X
Thromboprophylaxis		SOC ---------- SOC			
All other subjects					
Aspirin	SOC	SOC	SOC	SOC	SOC
Ticagrelor/$P2Y_{12}$ inhibitor[b]	X[c]		SOC----------SOC		
Thromboprophylaxis		SOC ----------SOC			

[a]Subjects not previously on Aspirin in the preoperative setting should be initiated on Aspirin therapy at 6 hours post-op, per institutional protocols
[b]Choice of agent for postoperative DAPT is at the discretion of the treating physician, in accordance with standard clinical guidelines
[c]Timing of last dose must be consistent with the study inclusion criteria
[d]Resumption of ticagrelor therapy should be within 24hrs post-op if there is no clinical concern for bleeding. Otherwise, if concern for bleeding exists, ticagrelor should be resumed as soon as deemed clinically safe in the judgement of the surgeon. Known benefit of ticagrelor in postoperative graft/stent patency must be weighed against bleeding risks
SOC = per institutional protocols

Table 6: Schedule of Assessments

Study Procedures	**Screening**	**Pre-CPB**	**Operation**	**Post-CPB**	**Post-Operation**						**Follow-up Visit/End of Study/Early Termination**
Timepoint	Up to 2 days prior to the day of Operation	Within 2 hours before start of operation (i.e., skin incision)	From chest incision to chest closure	Within 30 min after end of CPB	ICU Admission	POD 1	POD 2	POD 3	POD 4	POD 5-29	POD 30 + 5 days
Informed consent/authorization [a]	X										
Inclusion/exclusion criteria	X										
Demographic information	X										
EuroScore II	X										
STS Risk Score	X										
Last pre-operation dose of ticagrelor (date, time, and dosage)	X										
Medication history within 30 days of study enrollment	X [r]										
Physical exam, height, weight [b]	X [r]										
Planned surgical procedure [c]	X										
Drug removal blood sampling [d]		X	X	X							
Medical history	X										
Concomitant medications	X	X	X		X	X	X	X	X	X [s]	X
EKG [e]	X				SOC [t]	SOC [t]	SOC [t]	SOC [t]	SOC [t]	SOC [t]	
Pregnancy test [f]	X										
Cardiac troponin (cTn) [g]	X				SOC [t]	SOC [t]	SOC [t]	SOC [t]	SOC [t]	SOC [t]	
Hematology [g]	X				X	X	X [u]	SOC	SOC	SOC	
Clinical chemistry [g]	X				X	X	X [u]	SOC	SOC	SOC	
Coagulation panel [g]	X				X	X	X [u]	SOC	SOC	SOC	
Vital signs [h]	X				SOC	X	X	SOC	SOC	SOC [s]	SOC
CPB duration [i]			X								
DrugSorb™ flow rate & flow duration [i]			X								
Surgical procedure type [j]			X								
Activated Clotting Time (ACT) [k]			X	X							

Study Procedures	**Screening**	**Pre-CPB**	**Operation**	**Post-CPB**	**Post-Operation**						**Follow-up Visit/End of Study/Early Termination**
Timepoint	Up to 2 days prior to the day of Operation	Within 2 hours before start of operation (i.e., skin incision)	From chest incision to chest closure	Within 30 min after end of CPB	ICU Admission	POD 1	POD 2	POD 3	POD 4	POD 5-29	POD 30 + 5 days
Arterial Blood Gas (ABG) [l]			X	X	X						
Blood products [m]	X----------X					X	X	X	X	X [s]	
Operation blood loss and drainage [m]			X								
Post-Operation chest tube drainage				X----------X							
Post-Op blood loss & bleeding [m]					X	X	X	X	X	X [s]	X
Daily assessment						X	X	X	X	X [s]	
Adverse events [n]	X	X	X	X	X	X	X	X	X	X	X
Ventilation and mechanical support [o]					X	X	X	SOC	SOC	SOC	
FiO2 [p]					X	X	X	SOC	SOC	SOC	
Vasopressor requirements [q]					X	X	X	SOC	SOC	SOC	

Abbreviations: AE = adverse event; CPB = cardiopulmonary bypass; D = day; h = hour; eCRF = electronic case report form; ICF = Informed Consent Form; ICU = Intensive Care Unit; POD = post-operative day; SOC = standard of care.

[a] Authorization or informed consent must be obtained at Screening (see Appendix 3)

[b] Body mass index will be calculated from the subject's height and weight measurements obtained at Screening or from the values in the medical record in the current hospital admission.

[c] Pre-randomization stratification will be performed based on the ***planned*** surgical procedure, which may differ from the performed procedure.

[d] Blood samples will be collected for the determination of plasma ticagrelor concentration at a designated bioanalytical laboratory using a validated assay. The pre-CPB blood sample will be drawn prior to the start of cardiopulmonary bypass and can be up to 2hrs prior to skin incision. The post-CPB blood sample will be drawn as soon as possible following the end of CPB, and no later than 30min after the subject has been disconnected from the CPB circuit. During the procedure, while the subject is on CPB, serial sampling will be obtained q30±15min up through 2hrs of CPB. If the procedure requires a CPB time of <2hrs, then sampling will be q30±15min only up through completion of the CPB.

[e] Baseline EKG is required on file within the subject's medical record pre-op but does not need to have been performed within the 2 days prior to the day of surgery. Post-op EKG is only mandated in the event of possible MI

[f] In all females of child-bearing potential. Performed in serum. Pre-consent test results done during the current admission MAY be used. Pre-consent test results done before the current admission MAY NOT be used.

[g] Refer to Appendix 2 for a list of evaluations in the hematology, clinical chemistry, cardiac biomarker, and coagulation tests. During Screening, if consented subjects enter the Operation Phase without post-consent evaluation of hematology, clinical chemistry, or coagulation tests to record, the last pre-consent laboratory values MAY be used. Post-op cTn is only mandated in the event of possible MI

[h] Vital signs include supine blood pressure, pulse rate, respiratory rate, oxygen saturation, and body temperature.

[i] Duration of CPB = time from the start of CBP to end of CPB, which may differ from duration of operation. Flow rate and flow duration for the device will be recorded q30±5min while patient is on CPB; flow rates are not mandated while subject is on hypothermic circulatory arrest (HCA).

[j] Details regarding the surgical type will be recorded. Delayed sternal closure will be recorded. ***Re-exploration/re-thoracotomy will be recorded according to the same schedule as AEs and documented in the re-operation eCRF***.

[k] ACT will be obtained once at 30min into CPB ±15min, and once within 30min post-protamine administration (post-CPB). Intraoperative ACT is documented in the ACT log, and not recorded in the

Coagulation Test eCRF.

[l] During the operation phase, arterial blood gas analysis will be obtained at the following time periods: within 30min pre-CPB, 30 ±15min into CPB, within 30min post-CPB, and upon admission to the ICU

[m] Blood product administration will be monitored and recorded from the point of consent through discharge. Cell Saver will ***not*** be included as blood product administration. Blood loss and bleeding events will be monitored and recorded through follow-up, and drainage will be monitored from chest closure to 12h post-op (for UDPB class) and continued from 12hr post-op through at least 24h post-operation. Measurement of drainage after 24h and through time of chest/mediastinal drain removal will be per SOC.

[n] All AEs will be recorded from point of authorization to participate in the study through the 30-day Follow-up. Serious AEs occurring after 30 days post-operation are to be reported to the Sponsor if, in the judgment of the Investigator, there is concern for potential association between the event and the use of the DrugSorb™-ATR device.

[o] If subject is intubated/requires mechanical ventilatory support, the maximum ventilation and mechanical support requirements will be recorded for each day.

[p] Documented in the ABG eCRF; only required if the subject is intubated or on mechanical ventilatory support

[q] The maximum vasopressor dosage will be recorded each day.

[r] Physical exam performed on the day of screening as part of standard of care but occurring prior to signing of informed consent *may* be used for the screening PE. The physical exam and medication history will be repeated on the day of the procedure, if the day of the procedure is different than the day of screening

[s] Assessments completed daily ***through hospital discharge***.

[t] In the advent of any cardiac ischemic AEs, EKG (to assess for Q waves) and cTn ***must*** be obtained. EKG will be provided as source documentation for CEC adjudication. cTn will be documented within the laboratory eCRF for CEC event adjudication

[u] Through postoperative day 2 only.

Appendix 5: Antithrombotic Medications Allowed/Disallowed

Aspirin – allowed

Ticagrelor – allowed

Clopidogrel – any use within 7 days disallowed (as may have confounding effects on bleeding)

Prasugrel – any use within 7 days disallowed (as may have confounding effects on bleeding)

Cangrelor – any use within 4 hours of (or during) the index procedure is disallowed (as may have confounding effects on bleeding)

Argatroban – any use within 4 hours of (or during) the index procedure is disallowed

Bivalirudin – any use within 2 hours of (or during) the index procedure is disallowed

Heparin – allowed

Low molecular weight heparin (e.g., enoxaparin) and fondaparinux – allowed

DOACs (e.g., apixaban, rivaroxaban, dabigatran and edoxaban) – any use within 5 days is disallowed, as it may have confounding effects on bleeding

Warfarin – recent use disallowed unless INR < 1.5 as otherwise may have confounding effects on bleeding

Tirofiban – any use within 8 hours disallowed as may have confounding effects on bleeding (restoration of platelet function normally occurs within approximately 4 hours)[1]

Eptifibatide – any use within 8 hours disallowed as may have confounding effects on bleeding (restoration of platelet function normally occurs within approximately 4 hours)[1]

Abciximab – any use within 5 days disallowed as may have confounding effects on bleeding (restoration of platelet function normally occurs within approximately 72 hours)[1]

References (for this appendix only):

1. Schrör K, Weber AA. Comparative Pharmacology of GP IIb/IIIa Antagonists. *J Thromb Thrombolysis*. 15:71–80.