OFFICIAL STUDY TITLE:

Ticagrelor CytoSorb® Hemoadsorption (TISORB): Prospective, Open, Multicenter, Single-arm Study to Demonstrate the Feasibility of the CytoSorb® 300 mL Device to Remove Ticagrelor During Cardiopulmonary Bypass in Patients on Ticagrelor Undergoing Emergent or Urgent Cardiothoracic Surgery

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SYNOPSIS

Title of investigation: Ticagrelor CytoSorb® Hemoadsorption (TISORB): Prospective, Open, Multi-center, Single-arm Study to Demonstrate the Feasibility of the CytoSorb® 300 mL Device to Remove Ticagrelor During Cardiopulmonary Bypass in Patients on Ticagrelor Undergoing Emergent or Urgent Cardiothoracic Surgery

Hypothesis:
CytoSorb® hemoadsorption of ticagrelor during emergent or urgent cardiothoracic surgery with cardiopulmonary bypass (CPB) in patients on ticagrelor increases post-operative platelet reactivity to adenosine diphosphate (ADP) above the level associated with increased bleeding risk (22 aggregation units [AU]) measured on the multiple electrode aggregometry (MEA) platform.

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 any drug that inhibits platelet function, the predominant safety concern with ticagrelor is the possibility of major bleeding events, either arising from personal illness or injury, or iatrogenic from invasive medical procedures. For patients on ticagrelor requiring cardiac surgery, the 2018 European Society of Cardiology/European Association for Cardio-Thoracic Surgery Guidelines recommend postponing surgery at least 3 days (or 72 hours) after ticagrelor discontinuation.[2] Nonetheless, the PLATO study showed that up to 5% of patients on ticagrelor may require cardiac surgery before the recommended washout period (defined here as the emergent patient), with all attendant serious morbidities from post-operative bleeding.[3,4] Likewise, patients on ticagrelor deemed clinically stable enough to attempt washout before cardiac surgery (defined here as the urgent patient) may benefit from surgery before washout. Currently, there is no intervention to address this significant unmet medical need from ticagrelor-induced coagulopathy in the emergent patient or the urgent patient that proceeds to surgery before washout of ticagrelor.

Due to the ability of the CytoSorb® device to bind hydrophobic small molecule drugs, the Sponsor has discovered that ticagrelor is rapidly and efficiently removed from whole blood by CytoSorb® hemoadsorption. Preclinical studies have demonstrated approximately 80% removal of ticagrelor from whole blood within 1.5 hours of CytoSorb® hemoadsorption (unpublished data).

A retrospective case-series study by the Asklepios Klinik St. Georg (Hamburg, Germany) evaluated the use of the CytoSorb® device in patients undergoing emergent cardiac surgery with CPB for ACS. Patients on ticagrelor that received CPB only (control) were compared to patients that received CytoSorb® hemoadsorption during the CPB procedure (treatment). Results showed an absence of the post-operative ticagrelor-induced coagulopathy after intra-operative CytoSorb® hemoadsorption of ticagrelor in the treatment cohort but not in the control cohort.[5] No device-related adverse events (AEs) or device malfunctions were reported.

Thus, as a result of these preclinical and clinical findings, the Sponsor proposes to conduct a prospective, open, multi-center, single-arm study to demonstrate the feasibility of the CytoSorb® device to remove ticagrelor during CPB, as measured by platelet reactivity to ADP, in patients on ticagrelor undergoing emergent or urgent cardiothoracic surgery. For the purposes of this study, the following definitions of urgent and emergent will be applied to the patient population:

Urgent patient – on presentation, the patient's clinical state does allow for the minimum recommended time to washout ticagrelor (i.e., 72 hours), irrespective of whether ticagrelor is continued after presentation to minimize thrombotic risk, as the patient does not have to go to surgery as soon as possible and the surgery can be scheduled accordingly.

Emergent patient – on presentation, or on subsequent evolution of the patient's clinical state after presentation, the patient's clinical state does not allow for washout of ticagrelor as the patient must go to surgery as soon as possible.

A single-arm study design is proposed due to the concerns of randomizing patients in a 2-arm study to sham device with known adverse post-operative bleeding outcomes from ticagrelor. Data from the single-arm study described herein will be compared with data obtained from an External Control Cohort. The external control cohort is governed under companion protocol(s) in which the patient population will be matched, to the extent possible, to the patient population in the TISORB protocol with respect to entry criteria, risk factors, health system, country, and collection of data points.

Objectives:
The primary objective of the study is to demonstrate intra-operative removal of ticagrelor by CytoSorb® hemoadsorption in patients on ticagrelor undergoing emergent or urgent cardiothoracic surgery requiring CPB, using platelet reactivity to ADP as a pharmacodynamic surrogate measure of ticagrelor levels in blood.

Endpoints:
Primary Effectiveness Endpoint:

- Change in ADP-induced platelet AU measured on the MEA platform immediately before and after CPB.

Primary Safety Endpoint:

- Assessment of device-related AEs during the study period.

Investigation design:
This study is a prospective, open, multi-center, single-arm pivotal study to evaluate the safety and effectiveness of the CytoSorb® 300 mL device to remove ticagrelor in patients undergoing emergent or urgent cardiothoracic surgery requiring CPB. Patients will be followed up through 30 days after admission to the ICU following the surgical procedure.

Number of patients:
Pharmacodynamic (Primary) Population: A target of 20 treated patients (no fewer than 18 and no more than 22)
Non-pharmacodynamic Population: Up to approximately 10 treated patients but no more than 12
Number of sites:
Up to 8 investigational sites will participate in the study.

Patients must meet all inclusion criteria to be eligible to participate in the study. Patients meeting any of the exclusion criteria are not eligible to participate in the study. Patients are assigned to the Pharmacodynamic or the Non-pharmacodynamic populations based on the second criteria provided below.

FIRST shared criteria to meet study eligibility and enter either the Pharmacodynamic Population or the Non-pharmacodynamic Population:

Inclusion criteria:

1. Males and females aged ≥18 and < 80 years with a body weight > 45kg.;
2. Cardiothoracic surgery requiring CPB ≤48 hours following the last dose of ticagrelor.

Exclusion criteria:

1. Any cardiothoracic surgery >48 hours after last dose of ticagrelor;
2. Any pre-operative coagulopathy unrelated to ticagrelor or standard of care to undergo surgery with CPB, inclusive of heparin induced thrombocytopenia, patients with a platelet count < 20,000 μ/L, and patients receiving prohibited antithrombotic medications (reference Section 8 and Appendix 6);
3. Presence or active treatment for sepsis;
4. Presence of significant active infection which, in the opinion of the Investigator, increases the risk to the patient or could confound the results of the study;
5. History or presence of significant pulmonary, hepatic, renal, hematologic, gastrointestinal, endocrine, immunologic, neurologic, or psychiatric disease which, in the opinion of the Investigator, increases risk to the patient or could confound the results of the study inclusive of patients in acute sickle cell crisis and those with allergies to device components;
6. Presence of end-stage renal disease or currently receiving renal replacement therapy;
7. Patients with a history of major organ transplantation and those currently receiving immunosuppressive medication (corticosteroids excluded) or who are profoundly immune suppressed;

8. Women of childbearing potential with a positive pregnancy test performed during the current admission or who are lactating;
9. Patients currently undergoing or with a history of treatment for cancer within the past 6 months without remission of disease. Treatment for basal cell carcinoma will be allowed.

SECOND criteria for eligible patient assignment to the Pharmacodynamic Population[a]:

1. ADP-induced AU ≤22 measured on the MEA platform within 2 hours before induction of anesthesia for surgery; **AND**
2. Thrombin-induced AU in the normal range measured on the MEA platform within 2 hours before induction of anesthesia for surgery; **AND**
3. Platelet counts ≥75,000/μL within 2 hours before induction of anesthesia for surgery.

SECOND criteria for eligible patient assignment to the Non-pharmacodynamic Population[a]:

1. ADP-induced AU >22 measured on the MEA platform within 2 hours before induction of anesthesia for surgery; **OR**
2. Thrombin-induced AU below the normal range measured on the MEA platform within 2 hours before induction of anesthesia for surgery; **OR**
3. Platelet counts <75,000/μL within 2 hours before induction of anesthesia for surgery.

[a] As clinically indicated, patients may proceed into surgery after initiation of these assays and before knowledge of the results of these assays. Assignment to either the Pharmacodynamic Population or the Non-pharmacodynamic Population is not a requisite for proceeding with surgery. Note that the SECOND criteria only allow patients to be assigned to either the Pharmacodynamic Population or the Non-pharmacodynamic Population.

Duration of patient participation in the investigation:
Duration of treatment with the CytoSorb® device is limited to the time that the patient undergoes surgery on CPB. Patients will undergo scheduled study procedures until the point of discharge from hospitalization. Discharge from hospitalization means the date of initial discharge from the hospital in which the cardiothoracic surgery was completed, irrespective of discharge to home care, secondary care or other rehabilitation unit. Patients will return to the investigative sites for a Follow-up Visit 30 days after the operation.

Test device:
The CytoSorb® device is a sorbent-filled hemoperfusion cartridge that is designed to adsorb ticagrelor and reduce circulating drug from blood. The device is placed into a parallel bypass circuit (between the oxygenator and the venous reservoir) in a standard heart-lung machine.

Statistical methods:
The primary effectiveness endpoint is the change in ADP-induced platelet AU measured on the MEA platform immediately before and after CPB. The Primary Analysis Population will include all assented/consented patients with both platelet counts and MEA AU to ADP and thrombin measured immediately before CPB that meet the SECOND criteria for the Pharmacodynamic Population. Studies showed that 22 AU in the MEA platform is the threshold below which the risk for cardiac surgery-associated bleeding from $P2Y_{12}$ inhibitors increases, with an AU mean ± standard deviation on $P2Y_{12}$ inhibitors of 15 ± 7.5 AU.[14,15] CytoSorb is expected to improve the AU to at least 22. Thus, the null statistical hypothesis is mean increase from pre to post CytoSorb is zero, and the alternative statistical hypothesis is that the mean increase exceeds zero (target mean increase is 7 units). For a single-arm study comparing observed mean increase following CytoSorb® treatment versus 0 AU increase, N=13 would have 87% power via T-test (alpha=0.025 1-sided) if the TRUE mean increase is 7. The proposed N=18-20 exceeds that with 96-98 % power. Addition of platelet counts[12] and thrombin-induced platelet aggregation[11,13] as controls in the MEA platform mitigates the risk of enrolling patients who will generate false-positive and false-negative pharmacodynamic results.

Analysis Populations
Patients are considered enrolled in the study at the time of informed assent/consent. Enrolled patients who do not meet the FIRST shared criteria to enter either the Pharmacodynamic Population or the Non-pharmacodynamic Population are screening failures and will exit the study.

The **Pharmacodynamic Population** (Primary Analysis Population) will enroll patients that meet ALL of the 3 SECOND criteria for assignment to this population. The Non-pharmacodynamic Population is excluded from this population.

The **Non-pharmacodynamic Population** will enroll patients that meet ANY one of the 3 SECOND criteria for assignment to this population.

All AEs will be listed and summarized using descriptive methodology. The incidence of AEs will be presented by severity and by association with the CytoSorb® 300 mL device 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 and the change from baseline will be listed, as well as a summary of clinically notable values. No inferential statistical analyses are planned.

Platelet counts done at the time of MEA platform testing will be listed and summarized using descriptive methodology. Results of the MEA platform testing will be listed and summarized using descriptive methodology.

Safety oversight committees:
An independent group of physicians and a statistician that are not involved in the clinical investigation will act as the Data Safety Monitoring Board (DSMB). The DSMB will oversee the safety of patients enrolled in the study. The policies and procedures governing the DSMB will be provided in a Charter that will be reviewed and ratified by the membership before the start of study enrollment. The physicians of the DMSB will also provide clinical event (CE) adjudication and will comprise the CE sub-group of the DSMB. The CE sub-group will be responsible for the review and validation of specified AEs (including all unanticipated adverse device effects (UADE), serious unanticipated adverse device effects (SUADE), serious AEs (SAE), and serious adverse device effects (SADE)) that occur up to the 30-day follow-up visit per the policies and procedures detailed in the DSMB Charter.