Background

Last year, Terumo Blood and Cell Technologies and Marker Therapeutics AG ("Marker") combined efforts to explore the integration of the D2000 Plasma Adsorption Column with the Spectra Optia system and its secondary plasma device (SPD) protocol and gain future insights around the development of our future SPD or selective removal capabilities. After the announcement of the COVID-19 pandemic in February, we submitted our application in March 2020 for an emergency use authorization (EUA) from the FDA. The EUA was obtained on April 9, 2020.

Under the EUA, the companies are working together in up to 15 U.S. sites to treat patients in the ICU with severe COVID-19 using the selective removal application and gather the needed data to demonstrate the safety, clinical efficacy and outcomes related to this procedure. We are authorized to treat up to 2,000 patients under the EUA with an interim analysis of the data once 40 patients are treated.

Study Objective

The objective of the study is to gather the data about the performance of the D2000 Column and assess its ability to reduce morbidity and mortality associated with patients 18 years old or older with diagnosed respiratory failure and COVID-19 infection. The primary outcome is all-cause mortality, with a secondary outcome of change in patients’ sequential organ failure assessment (SOFA) scores.

Differences and Similarities Between Therapeutic Plasma Exchange (TPE) and SPD

Both TPE and SPD procedures work with the patient’s plasma.

<table>
<thead>
<tr>
<th>TPE</th>
<th>SPD</th>
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<tbody>
<tr>
<td>Plasma is exchanged</td>
<td>Plasma is treated</td>
</tr>
<tr>
<td>Removes disease mediators and healthy factors like fibrinogen in the plasma</td>
<td>Removes the targeted disease mediators</td>
</tr>
<tr>
<td>Replacement fluid is required</td>
<td>No replacement fluid is required</td>
</tr>
<tr>
<td>Healthy factors can be replaced by use of replacement fluid</td>
<td>Healthy factors cannot be replaced by use of replacement fluid</td>
</tr>
<tr>
<td>Procedure time is approximately 90 to 120 minutes</td>
<td>Procedure time is approximately 120 to 180 minutes</td>
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Selective removal uses an extracorporeal device, such as Spectra Optia, with a secondary device that selectively targets and removes pathologic components and disease mediators from either whole blood or plasma and returns the blood or plasma to the patient. Depending on the method and the devices, selective removal may be referred to as: \(^1\)

### Adsorption Cytapheresis

Whole blood passes through a column/filter that selectively adsorbs disease mediators \(^1\)

### Immunoadsorption (IA)

Primary device separates plasma from red blood cells and a secondary column binds and removes disease mediators \(^1\)

### Cascade Filtration/Double Filtration Plasmapheresis (DFPP)

Primary filter separates plasma from red blood cells and a secondary filter removes disease mediators based on size \(^1\)

#### Several selective removal options on the market today are being explored for the treatment of patients with COVID-19, including:

**Plasma Adsorption**

**Hemadsorption/Adsorptive Cytapheresis** \(^2\)
- Jafron HA330 is used outside the United States only.

**Secondary Plasma Device (SPD) on Spectra Optia**
- Selective removal, when performed on Spectra Optia, is referred to as the secondary plasma device or SPD protocol. Terumo Blood and Cell Technologies launched the protocol outside the U.S. in 2011.
- SPD has become common with many indications and may be used as an alternative to plasma exchange outside the U.S.
- It is an extension of the therapeutic plasma exchange (TPE) protocol.
- The SPD protocol can accommodate a variety of columns and filters for selective removal of disease mediators.

**SPD + D2000 Column** \(^3\)
- The system separates plasma from the patient’s whole blood; plasma removal efficiency is 80% to 87%, the same as with TPE.
- Plasma is sent from the centrifuge through the D2000 Column for the removal of the disease mediators.
- The plasma, now called treated plasma, exits the column and is sent to a treated plasma bag.
- From the treated plasma bag, the system uses the replace pump to send the treated plasma to the reservoir, where it is mixed with the patient’s red blood cells (RBCs) and then returned to the patient.
Marker Therapeutics AG D2000 Adsorption Column:
Applications to COVID-19

- Marker’s patented D2000 Adsorption Column mediates severe inflammation in acute respiratory distress syndrome (ARDS) – the most common end-stage condition associated with severe COVID-19 cases.¹
- The D2000 has been successfully used on six patients with pneumonia and ARDS-related pulmonary issues, including severe H1N1.
- The D2000 was awarded a CE mark with a broad indication for use that facilitates a responsible and quick rollout in the EU.

The D2000 is a disposable extracorporeal adsorption column used to remove a broad range of inflammatory cytokines, toxins, metabolic waste and poisons from blood plasma. The D2000 may manage the cytokine storm associated with severe COVID-19 patients to reduce mortality risk.

Patients receive daily 2- to 4-hour treatments using plasmapheresis or other equipment. The D2000 Column may be used with the SPD protocol on Spectra Optia in the U.S.

The D2000 treats plasma to prevent damage to blood cells (hemolysis), contains a proprietary non-ionic blend of adsorptive media with no impact on a patient’s electrolyte balance and provides an extremely large adsorbent surface area of 2.1 million square feet. It has low pressure drop and priming volume.

D2000 Clinical Results/Case Studies

- D2000 lab tests substantiate reduction of a broad range of cytokines and toxins in plasma.
- No adverse events have been reported from more than 160 applications on over 50 patients.
- Visible results are shown in this chest X-ray of a Singapore ARDS patient following a single D2000 application.

The Goal

Our goal is to reduce mortality in this immediate crisis of the COVID-19 pandemic.

- Mortality risk is reduced once severe pneumonia or ARDS risk is reduced.

How the D2000 Column Works

As a patient’s plasma flows through the D2000 Column, a broad range of inflammatory molecules bind to the adsorbent materials, thereby reducing the concentration of these molecules in the patient’s circulating plasma. The device does not treat the virus or other complications directly. Instead, it removes a large proportion of the inflammatory cytokines and other inflammatory molecules from plasma to help mediate an uncontrolled inflammatory response.
Attendee Questions and Answers

Q. How do I gain access to this therapy? Can I purchase the columns or participate in the study?

A. Both devices are CE marked and may be used outside of the U.S. today. The therapy is available through the EUA granted by the FDA on April 9 (EUA 200148). Given the unprecedented circumstances and the need to collect safety and efficacy data for COVID-19-related treatments, Terumo Blood and Cell Technologies and Marker Therapeutics AG are strategically managing the ability to meet demand at this time. A clinical study is being conducted in the U.S. to collect health data around safety and efficacy. Currently 15 sites are enrolling participants in the study. If you are interested in participating or have questions, please send inquiries to EUA.inquiries@terumobct.com or covid19@markerhealth.com.

Q. Can you explain the details of the study? Is this a clinical trial? What are the study endpoints? Are adverse events being tracked?

A. This is not a traditional clinical trial. Under the FDA-authorized EUA allowing the emergency use of a currently unapproved therapy to treat patients in crisis, we are collecting patient data. The FDA reviewed and granted authorization to perform the study with the following endpoints: mortality at day 28 and SOFA score. Adverse events are tracked as defined through the study protocol.

Q. What are the procedural endpoints for the study (i.e., plasma flow rates and volume of plasma to be treated)?

A. Based on the attending physician’s discretion, the course of each daily treatment is expected to take 2 to 4 hours and use one D2000 Column. Patients on average receive three to five total treatments during their course of therapy; however, a patient can receive up to 14 treatments at the physician’s discretion. During each procedure, 1.5 patient plasma volumes are treated. Plasma flow through the column is up to 50 mL/min with a plasma pressure limit of 300 mmHg. The anticoagulant used is citrate anticoagulant ACD-A.

Q. How does the therapy work?

A. The D2000 Plasma Adsorption Column adsorbs a broad spectrum of inflammatory mediators circulated in the plasma and may assist in managing the cytokine storm in hyper-inflammatory patients. Uncontrolled, cytokine storms can lead to multiple organ failure and death and are the predominant path to mortality in COVID-19.

The D2000 Column consists of a proprietary blend of biologically safe adsorption materials that reduce the circulating cytokine, toxin, and metabolic waste load in a hyper-inflammatory patient’s plasma.

The adsorbents have been demonstrated to remove statistically significant proportions of TNF-alpha, IL-1B, IL-3, IL-6, IL-8, MCP-1, IL-10, and IFN-gamma in bench testing and clinical settings.

The Spectra Optia system running the SPD protocol uses a disposable tubing set to separate plasma from the patient’s blood, which is then passed through the D2000 Column to significantly reduce cytokine levels. The treated plasma is recombined with the blood and returned to the patient.

Q. From the previous safety and efficacy testing, can you provide background and/or data to support the information shared?

A. In early clinical trials performed in the U.S., India, Singapore and Turkey, the D2000 Column was applied to 47 patients in over 140 applications with no adverse events. Over 20 treatments for COVID-19 have been performed to date in the U.S. Full results/data are not publicly available at this time.

View On-Demand Webinar
This presentation can be viewed on-demand at: https://bit.ly/2E7iMTZ

What’s Next
Clinical data from the study will be shared in a follow-up webinar on August 26, 2020. Please pre-register for this webinar at: https://bit.ly/32HCM9J

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Share this summary or the link to the on-demand recording of the webinar.