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Anita Dushyanth, PhD
adushyanth@zacks.com
Ph (312) 265-9434

scr.zacks.com

10 S. Riverside Plaza, Chicago, IL 60606

CytoSorbents Corporation (CTSO-NASDAQ)

Q1'2020: CTSO Nabs FDA breakthrough designation and European approval for ticagrelor removal, Q1 Product revenue sets new record, Moving PT to $15/share

Based on our 10-year DCF model, which uses a 10% discount rate and a 2% terminal growth rate, the shares are valued at approximately $15.00.

Current Price (05/18/2020)	$10.57
Valuation	**$15.00**

OUTLOOK

Product sales continued their rapid climb upward, setting a new record high (of $8.15M, +78% yoy, +22% qoq). We think this is at least partially attributable to the surge in demand for CytoSorb device for COVID-19 patients as well as the company's incremental shift towards 'owning' a greater portion of the sales channels, which can have several benefits including higher margins. We see several catalysts that begin to make either an initial or a greater impact including Fresenius entering S. Korea, assignment of reimbursement amount in Switzerland, expansion into other countries, growing awareness of the potential utility of CytoSorb in various indications and adoption driven by case studies, investigator-initiated studies, supportive feedback from hospitals and critical care professionals, KOL interest and (potentially positive results of) the ongoing REMOVE and REFRESH 2-AKI studies. HemoDefend, a U.S. pivotal study for which could begin in the coming months, represents another potential near-term catalyst.

SUMMARY DATA

52-Week High	**$10.59**
52-Week Low	**$3.61**
One-Year Return (%)	**49.64**
Beta	**0.52**
Average Daily Volume (sh)	**824,566**
Shares Outstanding (mil)	**36**
Market Capitalization ($mil)	**$375**
Short Interest Ratio (days)	**N/A**
Institutional Ownership (%)	**27**
Insider Ownership (%)	**6**
Annual Cash Dividend	**$0.00**
Dividend Yield (%)	**0.00**
5-Yr. Historical Growth Rates	
Sales (%)	**54.1**
Earnings Per Share (%)	**N/A**
Dividend (%)	**N/A**
P/E using TTM EPS	**N/A**
P/E using 2019 Estimate	**N/A**
P/E using 2020 Estimate	**N/A**
Zacks Rank	**N/A**

Risk Level	**Above Avg.,**
Type of Stock	**Small-Growth**
Industry	**Med Products**

ZACKS ESTIMATES

Revenue
(in '000 of $)

	Q1 (Mar)	Q2 (Jun)	Q3 (Sep)	Q4 (Dec)	Year (Dec)
2019	$5,192 A	$6,233 A	$6,095 A	$7,430 A	$24,950 A
2020	$8,707 A	$9,348 E	$8,053 E	$8,484 E	$34,622 E
2021					$46,791 E
2022					$57,400 E

Earnings per Share

	Q1 (Mar)	Q2 (Jun)	Q3 (Sep)	Q4 (Dec)	Year (Dec)
2019	-0.15 A	-0.14 A	-0.21 A	-0.16 A	-0.60 A
2020	-0.10 A	-0.06 E	-0.09 E	-0.07 E	-0.31 E
2021					-0.09 E
2022					0.11 E

Zacks Projected EPS Growth Rate - Next 5 Years % **N/A**

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Recent Highlights

- **Record Revenue, Margins**: Q1 set records on product revenue. Achieved guidance on product margins which widened to 80% by Q4 2019, are benefitting from growth in direct sales (proportionally as well as in aggregate) and achieved more product efficiencies
- **CE Mark Renewal**: on August 15th, 2019 CytoSorbents announced that they received renewal of its European Union CE Mark through May 2024 and ISO 13485 to September 2022, ensuring no interruptions to international commercialization
- **REFRESH 2-AKI**: Guiding to reach 50% mark (i.e. 200 patients) by Q4 2020-Q1 2021 and, if all goes to plan, make PMA filing by ~mid-2022. Continued progress in REFRESH 2-AKI is what represents the most significant potential pipeline-related value enhancement in our opinion
- **REMOVE**: rapid enrollment pace continues with 288 patients (of planned 250) through. Data analysis to follow. Guiding for topline data by mid-2020 which we think will represent a potential value-inflection event in CTSO's share price
- **Commercialization Footprint Expanding:** CTSO's footprint continues to grow and now encompasses 58 countries and counting. Regulatory clearances anticipated in S. Korea, a substantial market. CTSO's direct territories recently increased to 10. Direct sales bring enhanced margins, as well as other benefits
- **HemoDefend U.S. Clinical Trial:** CTSO expects to seek U.S. regulatory approval to commence a pivotal study for HemoDefend. Study could begin and finish by mid-next year and, if all goes smoothly, HemoDefend could be on the U.S. market shortly afterwards. Progress on this pursuit also holds value-inflection opportunity in our opinion
- **Extended CytoSorb distribution to 58 countries:** In addition to selling through distributors, the company extended its sales using direct sales force in 10 countries.

Q1'2020: CTSO *Nabs FDA breakthrough designation and European approval for ticagrelor removal, Q1 Product revenue sets new record, Moving PT to $15/share*

COVID-19: A new opportunity for CytoSorb

The company operates in several countries, including Italy, Iran, Germany, France, Spain, Hong Kong, that are affected by COVID-19. As a reminder, COVID-19 is caused by SARS-CoV-2, the novel coronavirus. SARS-CoV-2 causes cytokine storm, where the immune system releases an excess of cytokines that cause systemic inflammatory response syndrome which results in organ failure and eventually death. This feature is typical in patients having respiratory illness, sepsis, burn injury, trauma, liver failure, complications in cardiac surgery, etc. Initially, CytoSorb was specifically added to coronavirus treatment guidelines in Italy and Panama.

In February 2020, Cytosorbents inked an agreement with China Medical System Holdings Limited (CMS), a well-established, specialty pharma, to treat critically-ill patients in China with COVID-19 infection using CytoSorb. CytoSorb was introduced to four hospitals in Wuhan, China. The therapy was evaluated in 17 severe COVID-19 coronavirus patients with a systemic inflammatory response who were treated with either continuous renal replacement therapy (CRRT) or extracorporeal membrane oxygenation (ECMO).

Subsequently, in April 2020, the FDA has granted Emergency Use Authorization (EUA) of CytoSorb for use in patients with COVID-19 infection. The EUA allows CytoSorb to be sold commercially to hospitals in the U.S. and used on patients that have acute lung injury or acute respiratory distress syndrome (ARDS) or life-threatening illness resulting in respiratory failure, septic shock, and/or multiple organ dysfunction or failure. The company has recommended the use of four cartridges per patient and tailor the need as necessary. The treatment was terminated if specific clinical outcomes, such as reduction in inflammatory mediators, reversal of shock or removing mechanical ventilators, were achieved. Initial feedback from the physicians, based on preliminary clinical evidence, seem to indicate that CytoSorb may be beneficial if utilized in the early acute phase of the COVID-19 infection.

To date, CytoSorb has been used in more than 750 patients infected with COVID-19 in Italy, China, Germany and France, of which, 25 patients are from the U.S. (EUA authorization). Preliminary feedback from physicians point to the fact that CytoSorb use has generally been associated with a marked reduction in cytokine storm and inflammation, improved lung function, weaning from mechanical ventilation and a reversal of shock. Also based on these preliminary reports, CytoSorb has been specifically recommended in the Italy Brescia Renal COVID Task Force Guidelines to treat patients with severe COVID-19 infection and Stage 3 renal failure on continuous renal replacement therapy. CytoSorb has also been recommended in the National Treatment Guidelines from Panama for Adult COVID-19 patients if they have either refractory shock or severe/refractory respiratory failure requiring either high ventilator support or ECMO.

One of the benefits that emerged from the COVID crisis is that it has thrust the company into the spotlight. In a fairly short period of time CytoSorb has garnered meaningful interest from several geographies to treat COVID-19. CytoSorb's apparent early success in treating COVID-19 patients is encouraging, particularly as it may relate to CytoSorb's effective utility in other critical care illnesses that are associated with cytokine storm. Future recommendations and potentially published manuscripts from some of these investigator-initiated studies, could wield meaningful influence - the fruits of which we think may be seen in the short-to-mid term. This growing interest in CytoSorb to treat "cytokine storm" is what we think will be pivotal in accelerating uptake and interest of CytoSorb for clinical use as well as providing support for initiation of U.S. clinical studies. We view FDA's EUA authorization of CytoSorb as a meaningful milestone towards eventual approval and commencement of larger U.S. studies in support of a regulatory filing.

While the initial positive results seen with the use of CytoSorb in COVID-19 patients worldwide are very encouraging, we continue to see other catalysts either having an initial influence on sales or making a more significant impact. This includes assignment of reimbursement amount in Switzerland (possibly within the next 12 months), and adoption driven by case studies, investigator-initiated studies, KOL interest and (potentially positive results of) the ongoing REMOVE and REFRESH 2-AKI studies. HemoDefend, a U.S. pivotal study for which could begin in the coming months, represents another potential near-term catalyst.

As before, Germany continues to account for the majority of sales. Germany accounted for about 60% of sales during Q1, and is a very important country as the largest medical device market in the European Union and the third largest in the world. Sales from Germany grew 59% yoy and were up 18% on a sequential basis through Q1 2020. Q1 also set a record on direct sales, which were $6.4M. Direct sales have climbed as a proportion of total product sales increasing from 74.3% in Q4 2019 to 78.6% in Q1 2020. With the new direct territories coming online, we could see direct sales growth steepen even further.

Much of the recent growth has been attributed to improved reimbursement in Germany and expanding use and utility of CytoSorb to address a growing list of critical care conditions. And while Germany has been a significant contributor to revenue, that market may still remain relatively untapped given their significant population and large hospital network. Management has indicated that adoption in that country has been brisk and aided by strong support by certain KOLs. At least one hospital in Germany already generates over $1M in product sales for CTSO. With over 400 mid-to-large hospitals in the country, we think there is considerable near-term upside from that market. Switzerland could soon provide another catalyst to product sales as a dedicated procedure code for cytokine reduction went into effect on January 1, 2019. Assignment of a reimbursement amount is next, which could happen by the end of 2020. While Switzerland is only about 10% of the size of Germany (in population), if CTSO's direct-sales successes can be replicated there, we estimate incremental annual product revenue could be as much $1.2M.

With the new direct territories coming online, we could see direct sales growth steepen even further. Another catalyst that drives revenue upwards would be Fresenius Medical Care (FMC) launching in Mexico and eventually entering S.Korea. In March 2020, CytoSorb received marketing approval from COFEPRIS, the Federal Committee for Protection from Sanitary Risks (Comisión Federal para la Protección contra Riesgos Sanitarios), who are the regulatory authority in that country. Mexico is the second largest medical device market in Latin America after Brazil. Further, Mexico has reported approximately 1,100 COVID-19 infections to date and this statistic is expected to increase in the coming months as the pandemic spreads across the region. Fresenius has brought in a new head to lead the sales team in Mexico. He has extensive commercial experience and network connections, which is expected to spark strong interest and excitement in the therapy, helping to drive adoption in Mexico and meet/exceed growth objectives.

The eventual entry into Mexico and South Korea via the Fresenius co-marketing agreement will bring the total distribution footprint to about 58 countries, compared to 45 countries two years prior. Expansion of the geographic and distribution footprint as well as increasing commercial use in a growing number of indications have also benefitted product revenue. CytoSorb has been used in a host of conditions throughout much of the world. To-date CytoSorb has been used in more than 88k human treatments, up from 61k a year ago.

We expect that both aggregate and rate of utilization will continue to climb. The recent indication in COVID-19 could have the effect of further expanding use. Further label expansion and approval for use in the U.S. could follow. More importantly, there is little doubt in our minds that utilization is begetting more utilization and the reasons likely almost universally relate to the ever-growing amount of evidence supporting the utility (i.e. safety and effectiveness) of CytoSorb in various critical care applications. As many more of these experiences from single-patient case studies to relatively large, formal, randomized controlled studies are now making their way into published

manuscripts in leading industry journals, we think this will bode exceptionally well for generating additional awareness of CytoSorb and translating into greater adoption and utilization.

On the earnings call, management noted that their manufacturing facility is currently running near capacity and that they could supply $80M worth of business. The single-use cartridge is selling at a unit price of about $1000, which translates to producing 80k devices. Recently, there has been a sudden surge in demand for the CytoSorb device as it demonstrated its utility in COVID-19 patients. As of Q1, the company had backorders for roughly 3000 devices. While the company had established the production capacity to supply the near-term demand for the device, we think they will likely need to scale up and increase manufacturing capabilities in order to meet the growing demand in commercial and clinical testing. To meet this growing demand, we think management is likely to expand manufacturing capabilities by hiring additional staff to increase the hours of operation each day. In order to meet future demands, we think the company is likely to begin exploring new manufacturing sites that will help scale up their operations.

Financial Update:

CytoSorbents reported financial results for their first quarter ending March 31st 2020 and provided a business update.

Total revenue from product sales was $8.2M for Q1 which increased 78% yoy and 22% qoq. Sales growth was fueled by strength in core critical care and cardiac surgery markets. As the company had previously guided, Q1 2020 product sales exceeded Q1 2019 product sales driven by strength in direct sales from increased product demand. The record increase in product sales was also fueled by demand for CytoSorb in response to the coronavirus pandemic. In the earnings call, CEO Phillip Chan said the company has ramped up the production of CytoSorb and the manufacturing facility is running at near full capacity. The company had sales back order of approximately $2.7M. The company has rapidly scaled-up manufacturing with a goal to fulfill backorders by the end of Q2 2020. The ~$1.5M incremental revenue related to the surge in CytoSorb demand from the COVID-19 pandemic represents about 20% of the overall $8.2M revenue for Q1. Based on the estimate given by the company, we think that roughly 20-30% of the Q2 revenues could be directly related to the sales of CytoSorb to treat COVID-19 patients. While CytoSorb demand is likely to remain strong in the second quarter, we think the demand would likely weaken, extending through the rest of 2020, as the pandemic subsides resulting in lower revenues during this time. However, if there is a second and third resurgence from this virus, we could witness demand shooting up again for CytoSorb. Also, noteworthy as it relates to product sales reaching a new record, is that this a foreign exchange headwind negatively affected sales by $237k (or ~3% of product sales). Meanwhile, grant income was $551k in Q1. While we expect additional (and near-term) opportunities to score future grants, we expect overall revenues to soften a bit by decreasing grant revenues as grant-related activities have been suspended temporarily due to quarantine and physical distancing requirements because of COVID-19.

Product gross margins for Q1 were 76%, higher from 74% in Q1 2019 but lower from 80% in Q4 2019 due to increased costs required to rapidly scale-up CytoSorb production. We expect gross margins to widen to 80% and beyond as production efficiencies improve and once the initial costs associated with the increases in production capacity are met with. We currently model full year 2020 product margin of nearly 80%, or ~300 basis points better than 2019.

Meanwhile, grant income continues to help subsidize R&D as well as providing additional validation of CTSO's technology (particularly given the list of contracts has continually grown). We think CTSO will continue to look to monetize the successes of these grant-funded studies with further label extensions and in the development of new technologies (such as HemoDefend). That could provide additional optionality in terms of commercial programs that CTSO could pursue. As we explain below, we think HemoDefend may be a dark horse that is mostly being overlook by investors and the significance of continued development progress should not be underestimated.

Operating expenses increased slightly on a yoy basis as compared to Q1 2019. Operating expenses, which included about $150k worth of non-cash stock compensation, were $8.8M (including ~$0.8M in stock comp) in Q1 2020, compared to $7.7M (including ~$2M in stock comp) in Q1 2019. R&D spend decreased by ~$1M as compared to Q1 2019 due to the temporary pause in the REFRESH 2-AKI study that resulted in lower clinical trial costs. This decrease was offset by an increase in expenses related to increase in headcount of the sales and marketing staff. The direct sales force (including support staff) now stands at 79 people. While operating expenses have increased, these investments are expected to result in steepening of the revenue and, eventual, earnings curve.

Cash used in operating activities was $3.2M in Q1 2020 as compared to $4.2M in the comparable prior year period. The company exited the quarter with a strong cash position of approximately $26M. Of this amount, approximately

$13M was raised by utilizing the ATM facility. The company also received approximately $1M in cash from the approved sale of NOLs and R&D credits from the State of New Jersey in the Q1 2020. Management has guided that the cash runway is likely to extend well into 2021.
As of May 1, 2020, the company had about 41M common shares o/s on a diluted basis.

Operational Update:
CytoSorb has received multiple label expansions till date…
In 2018, CytoSorb received two label expansions, including increasing treatment time from six hours to 24 hours and use of the device for the removal of bilirubin and myoglobin in the treatment of liver failure and trauma, respectively. The indication for removal of bilirubin and myoglobin have further expanded its use. While CE Mark meant that clinicians had wide discretion in what conditions to employ CytoSorb, this label expansion adds credence for use in these specific indications. Additionally, it can provide a reimbursement benefit related to on-label (as opposed to, previous, off-label) use for these conditions.

CytoSorb approved in Europe for removal of anti-platelet drugs…
Earlier this year, CytoSorb was approved in the E.U. to remove ticagrelor, a blockbuster anti-platelet drug, during cardiopulmonary bypass in cardiothoracic surgery, with the goal of reducing the risk of costly and potentially fatal perioperative bleeding.

Adenosine diphosphate (ADP) receptor inhibitors (also known as $P2Y_{12}$ receptor inhibitors) are recommended either as monotherapy or as part of anti-platelet therapy for the prevention of cardiovascular events after cardiac surgery. The literature indicates that undergoing cardiac surgery while taking antiplatelet agents is associated with increased bleeding and other adverse events.
Ticagrelor (Astra Zeneca - Brilinta®, Brilique®) is one of the most commonly used anti-platelet drugs used in patients with acute coronary syndrome or in those who have stents. Ticagrelor is preferred in surgeries as it has a favorable safety profile and less response variability compared to other types of ADP inhibitors. Ticagrelor, marketed by Astra Zeneca and sold as Brilique® in the E.U. and Brilinta® in the U.S., with projected worldwide sales of more than $1.5 billion in 2019, with more than half of sales coming from Europe, emerging markets, and rest of world. Recently, CytoSorb was approved in the E.U for removal of rivaroxaban (Xarelto®- Bayer, Jansenn/Johnson & Johnson), a widely-used Factor Xa inhibitor and novel oral anticoagulant (NOAC), during cardiothoracic surgery requiring cardiopulmonary bypass. Cumulatively, more than 40 million people worldwide have been prescribed the drug. Rivaroxaban is used globally, with approximately $4.5 billion in 2019 sales outside the U.S. driven by Europe and Asia, and 2019 U.S. sales of $2.3 billion.

Apixaban and rivaroxaban are in the class of antibiotics called factor Xa inhibitors. CytoSorb can remove that too. Portola Pharma's Andexxa is only effective during the time of infusion. It also has a blackbox warning of being pro thrombotic, which is negative in patients undergoing cardiac surgery and also is a very expensive drug. we've demonstrated in a study that came out last year, showing that even taking into consideration the cost of the device that use of the device per patient would save hospitals a projected $5,000.

The patients requiring an emergent cardiac surgery such as coronary artery bypass graft surgery (CABG) are at high risk of bleeding and associated complications, and patients who could wait for the physiologic elimination of ticagrelor but would be at risk of ischemic complications are ideal candidates for CytoSorb device. The major risk of ADP receptor inhibitor use is bleeding; timely discontinuation of which is necessary when patients are undergoing cardiac surgery. There are no approved or cleared therapies in the U.S. to rapidly reverse the effects of, or remove ticagrelor in these patients. Of the three major $P2Y_{12}$ platelet inhibitors – clopidogrel (Plavix®, Bristol-Myers Squibb Co. and Sanofi SA), ticagrelor, and prasugrel - it is currently believed that only the effect of ticagrelor is theoretically reversible. Though Plavix is more frequently prescribed and inexpensive, it is inferior in working. However, because of the absence of an effective reversal agent, this safety advantage has never been realized. The company reported the results of an observational study that further supported this proposition with a compelling case that showed the potential for a significant reduction in bleeding risk, and another study highlighting an approximate $5,000 projected costs savings, when CytoSorb is used with patients on ticagrelor undergoing emergent cardiac surgery, in comparison to patient outcomes when CytoSorb was not used. CytoSorb makes for a compelling proposition in reducing bleeding risk and improving patient outcomes.

CytoSorb can rapidly reduce rivaroxaban during a typical CABG surgical procedure, so that waiting 2-3 days off the drug to allow the anticoagulant to be eliminated from the body is no longer necessary. According to the literature, an estimated 8-10% of patients on anticoagulant therapy will require emergent surgery at some point in their lifetime. Historically, in the case of cardiac surgery where the risk of postoperative bleeding is high, a 48-hour washout period is recommended for elective surgery. By reducing rivaroxaban during surgery, CytoSorb has the potential to eliminate the need for this delay, while decreasing the pro-thrombotic risks of being off of these agents,

while also reducing bleeding complications. For example, in a retrospective case series of patients (n=12) who required emergency cardiac surgery on rivaroxaban and could not delay surgery, the incidence of bleeding events (e.g. need for blood transfusions, re-thoracotomy rate, surgical drainage volume) and ICU and hospital time were all lower in those treated with CytoSorb compared to those that were not.

Since CytoSorb is being used in several cardiac surgery procedures, we believe this is another reason for health centers to have it stocked. Further, CytoSorb is the only device that reduces both ticagrelor and rivaroxaban, with a shelf life of 3 years at room temperature. Integration of CytoSorb into a cardiopulmonary bypass circuit for intraoperative use is seamless. We believe CytoSorb has the potential to replace expensive, and rapidly expiring biologic antidotes. Therefore, incorporating it into the standard practice of care for different classes of anti-thrombotics is likely to be cost effective. We believe this approval will serve as a springboard for CTSO to expand across the E.U. and to other important markets.

In April 2020, CytoSorb received the Breakthrough Designation from the FDA for the use of the device to reduce ticagrelor during urgent or emergent cardiac surgery. We think the approval decision from the European authorities will pave the way for entry into the U.S. market. CTSO is currently working on a plan to explore a path forward in the U.S. The additional supportive data from investigator-initiated studies from Europe could help bolster the approval process. Management is seeking advice from the FDA.

Clinical Update:

REFRESH 2-AKI study

This is a randomized, controlled, multi-center pivotal study designed to provide the key safety and efficacy data needed to support U.S. regulatory approval for using CytoSorb in cardiac surgery. follow the premarket approval (PMA) pathway. The study will enroll up to 400 patients at increased risk of cardiovascular surgery-associated AKI, undergoing elective, non-emergent open-heart surgery for either valve replacement, or aortic reconstruction with hypothermic cardiac arrest. The trial is evaluating the use of two CytoSorb cartridges in parallel during cardiac surgery to reduce the incidence or severity of acute kidney injury 48 hours after surgery in two populations: patients undergoing valve replacement surgery, and those undergoing aortic reconstruction with hypothermic cardiac arrest. CytoSorb has been used safely during complex cardiac surgery outside of the U.S. in a single cartridge configuration in thousands of surgeries.

REFRESH 2-AKI was also moving along and had accelerated since the protocol amendment was approved in September 2018. However, in November 2019, the Data Monitoring Committee (DMC) recommended to pause enrollment following a blinded, interim, milestone review of clinical study data. As of November 25, 2019, the study had enrolled 153 patients at 25 initiated sites. There are 25 sites active (up from 24 in August 2019) and others that should come online over the coming months. Rate of enrollment CTSO anticipates eventually having 30 to 35 sites active, which should further facilitate the pace of enrollment which management believes can increase to ~20 patients/month (which is consistent with the current patient/site/month enrollment rate assuming ~32 sites active).

Assuming a timely restart of the study expected in 2H 2020, we anticipate the interim analysis at 200 patients enrolled, where the DMC will evaluate the trial for safety by Q4 2020-Q1 2021. Assuming no unexpected issues from that analysis and pace of enrollment reaches ~20/month, CTSO anticipates enrollment will complete by the end of 2021. If all goes to plan, CTSO believes they can have data analysis completed and a PMA application submitted to FDA by ~mid-2022. While we think that timeline is not unrealistic, if it does get pushed back by several months or quarters from what management is proposing here, it would be largely immaterial from a valuation perspective in our opinion.

UK TISORB study

Research has shown that roughly 4% of patients that require emergency cardiothoracic surgery experience the risk of perioperative bleeding with potential negative clinical outcomes or even death. The European approval for the removal of anti-thrombotic agents (ticagrelor and rivaroxaban) during cardiac surgery has provided the label expansion and a potentially compelling commercial opportunity for CytoSorb. In order to collect additional supporting data, CytoSorbents initiated a 30-patient, multicenter study called the TISORB (Ticagrelor CytoSorb Hemoadsorption), in the U.K. in October 2019 to prospectively evaluate the removal of ticagrelor during cardiopulmonary bypass in patients on ticagrelor undergoing emergent cardiothoracic surgery.

The primary endpoint of the TISORB study is the change in platelet reactivity and ticagrelor blood concentration before and after cardiopulmonary bypass. A protocol amendment was submitted to expand the population of eligible patients to now include patients requiring urgent cardiac surgery, and third-party consent. These changes were approved by the UK Medicines and Healthcare products Regulatory Agency (MHRA) at the end of February, with approvals pending from the key regional ethics committees (RECs). The company intends to enroll thirty patients

who will have received ticagrelor within 48 hours of undergoing emergent or urgent cardiothoracic surgery with cardiopulmonary bypass. As of March 5, 2020, the Company has initiated six sites and one patient has been enrolled. Once REC approves, enrollment is expected to accelerate and be complete in the second half of 2020.

REMOVE study
As a reminder, REMOVE is evaluating safety and efficacy of CytoSorb in patients with infective endocarditis undergoing valve replacement surgery. Primary endpoint is the difference in mean SOFA (Sequential Organ Failure Assessment) scores between experimental and control arms. Secondary endpoints include 30-day mortality, changes in cytokine levels, need for supportive care therapies such as vasopressors, mechanical ventilation, and dialysis, incidence of stroke, and the length of intensive care unit and in-hospital stay.

This study could be a win-win for CytoSorbents potentially providing robust evidence of CytoSorb s utility in alarge and growing patient population (an already-completed 39-patient case study already indicated potential utility of CytoSorb in infective endocarditis, a growing problem among IV drug users which share dirty needles) and doing so at little or no cost to the company as the study is being fully funded by the German government. Jena University Hospital is primary sponsor - Jena has been an important partner of CTSO's over the years and manages the company s International CytoSorb registry. B.R.A.H.M.S. (a division of Thermo Fisher Scientific) and the Fraunhofer Institute for Interfacial Engineering and Biotechnology are co-collaborators.

This DSMB 50-patient evaluation was a critical milestone as not only does it indicate there are no serious safety concerns, but its success was also a prerequisite for the German government to continue funding the study. And it holds potentially even greater importance when considering that success of REMOVE could eventually inform or even help dictate the company s U.S. regulatory and commercialization decision-making (beyond their initial REFRESH / acute kidney injury program). Management recently noted that, given the robustness of the trial design, that it might be possible to use REMOVE
as primary support (assuming positive results) for a future FDA filing for an infective endocarditis indication. Positive results from this German study would certainly lend significant veracity to the likelihood of an eventual FDA approval for a similar indication whether it requires a U.S study or not.

As of March 31, 2020, the study had 288 patients enrolled. Data analysis will follow and, if all goes well, management believes they could be reporting topline data of REMOVE by mid-2020. Given the potential significance of the data as it relates to validating the safety and utility of CytoSorb in this indication (and resultant effect on spurring additional adoption and use of the device in currently-marketed territories) as well as the possible implications for U.S. regulatory purposes, **we expect that this REMOVE data readout will represent a potential value-inflection event in CTSO's share price** and, as such, will be something that we will be eagerly awaiting.

Recent publication of single center, 58-patient, infective endocarditis retrospective case series from University of Essen demonstrating a statistically improved hemodynamic stability at ICU admission, as well as lowered incidence of postoperative sepsis and death related to sepsis is encouraging.

CYTORELEASE Study
In order to evaluate the use of CytoSorb in treating Cytokine Release Syndrome (CRS) and inflammation of the brain called CAR-related Encephalopathy Syndrome (CRES), following CAR-T cell immunotherapy, the Hannover Medical School in Germany will commence the first clinical study, called CYTORELEASE, This is a randomized, controlled pilot study in 34 cancer patients who have received CAR-T cell immunotherapy and who have developed either severe CRS or CRES for a duration less than 6 hours. Patients will receive either standard of care therapy or standard of care therapy plus CytoSorb hemoadsorption. The primary endpoint of the study is a plasma reduction of the pro-inflammatory cytokine interleukin-6 (IL-6). Secondary and exploratory endpoints will examine other potential clinical benefits such as improvements in CRES, shock, and other organ injury. Hannover Medical School is currently screening patients for enrollment.

HemoDefend
In addition, management continues to anticipate being in a position to file an IDE to FDA (following successful requisite bench testing) and commence pivotal study of HemoDefend before the end of 2020. Management mentioned on the earnings call that they expect to complete bench testing by mid- 2020, file for an IDE in Q4 2020 begin the study shortly thereafter. Given a relatively straightforward FDA pathway, CTSO believes that (assuming all goes well) HemoDefend could launch in the U.S. by late next year. We reiterate that the potential for HemoDefend should not be underestimated.

More Evidence Supporting CytoSorb's Utility in HLH
Additional evidence appears to support the potential utility of CytoSorb in the treatment of hemophagocytic lymphohistiocytosis (HLH). Studies have shown that subjects with secondary HLH, which is often caused by virologic infection and characterized by a strong and sometimes uncontrollable immune response including cytokine release syndrome (CRS), can exhibit responses similar to cancer patients treated with certain immunotherapies. Severe CRS (i.e. severe inflammatory response with excessive and harmful levels of cytokines), which can lead to serious complications including organ failure and even death, has been associated with the use cancer immunotherapies, including Novartis' (NVS) Kymriah and Gilead's (GILD) Yescarta which were recently approved by FDA and in Europe for the treatment of certain blood cancers.

While these immunotherapies have shown extraordinary efficacy, mitigating risk of CRS remains problematic. While corticosteroids and tocilizumab have been used with some success in controlling CRS, there are drawbacks. This includes that corticosteroids are suspected of potentially comprising immunotherapy efficacy. Relative to tocilizumab, researchers have noted that its use should be avoided if macrophage activating syndrome (MAS) is suspected.

Early in 2017 CTSO appeared to be working towards a potential program in HLH / CRS. In Q1 of that year they announced that Dr. Carl June joined their scientific advisory board for the purpose of guiding their strategy in oncology. Dr. June is considered the pioneer of cancer immunotherapy and guided Novartis' Kymriah program. In March 2017 CTSO disclosed that "we have confirmed the interest in the therapy [CytoSorb], once available, as an adjunct to tocilizumab, and before high dose steroids are administered. We plan to continue to pursue applications of our therapy in the treatment of CRS in the United States, Europe, and elsewhere, as cancer immunotherapies continue to expand worldwide."

As we noted in early 2017, the similarity in CRS response in HLH and cancer patients treated with immunotherapies and CytoSorb's apparent early success in treating HLH patients (via reduction in inflammatory markers) was encouraging, particularly as it may relate to the leveraging the massive interest in and growth of the immunotherapy segment. Activity has clearly continued as evidenced by a recent case at Mount Sinai Beth Israel where CytoSorb was successfully used on a patient with poor prognosis and diagnosed with HLH. The case, published in Mount Sinai's Division of Nephrology publication earlier this year, indicated CytoSorb was used as a last resort when other therapies failed – the ICU team obtained IRB approval to use CytoSorb, following which the "patient's clinical improvement was immediate and significant, with hemodynamic stabilization during the first treatment, followed by enhanced liver function and mental status."

The latest update relative to the potential use of CytoSorb for CRS/HLH came on the most recent earnings calls with management noting that they are seeing strong interest in both the U.S. and, following approval of Yescarta and Kymriah in Europe, now also in that part of the world. Interest, per their comments, is coming from KOL's in the immunotherapy space and CTSO has been in close contact with the medical centers that were involved with the approval of these two cancer therapies in Europe. Particularly noteworthy, in our opinion, was management mentioning that there is strong interest to evaluate CytoSorb among the hospitals that are authorized to administer these therapies. In addition, CTSO noted that there is interest to collaborate with the company on clinical studies, particularly as a rescue therapy in cases where patients with CRS/HLH fail first line therapies such as tocilizumab and steroids. Further progress on this front – potentially including an announced formal clinical study or partnership with an authorized Kymriah or Yescarta center, could be a value inflection event, in our opinion.

Near-term Outlook
We continue to see no reason why product sales do not continue to set new regular records, particularly given some recent catalysts that came online. These include;

- opportunity in COVID-19: CytoSorb has been used in more than 750 patients infected with COVID-19 and has shown a marked reduction in cytokine storm and inflammation, improved lung function, weaning from mechanical ventilation, and a reversal of shock.
- **dedicated reimbursement in Switzerland**: Dedicated reimbursement went into effect Jan 1, 2019 in Switzerland (another direct-sales territory), which could provide another potentially substantive boost to product sales once a reimbursement amount is assigned.
- expanded indications: Removal of anti-thrombotic agents came in Q1 2020, should provide some level of market expansion and potentially provide strategic optionality. We also think it may be a harbinger of more approvals to come - clearly CTSO has already parlayed validation from grant-funded studies into broadening the commercial market for CytoSorb - that may be a strategy that they continue to employ

- demand-pull: management noted that awareness of CytoSorb over the last few years has reached a point where education in sales process has become easier. That trend, as we have noted in the past, will undoubtedly continue and benefit from continued increase in utilization

- **accelerating adoption in Germany**, the largest (yet still barely tapped) medical device market in Europe. At least one hospital in Germany already generates over $1M in product sales for CTSO. With over 400 mid-to-large hospitals in the country and strong support from KOLs, we think there is considerable near-term upside from that market

- **Fresenius**: expect the roll-out in Mexico in the near-term and continued expansion in other territories over time.

- **Terumo** (cardiac channel): launch began December 2016. We think Terumo could also be key in eventually accessing (very substantial) Japanese market

- **Biocon**: CTSO's large distributor in India recently reorganized CytoSorb into a separate division. Biocon has been a key partner and this restructuring is an indication they are putting even more resources behind CytoSorb. In February 2018 CTSO announced that Biocon will also handle distribution in Malaysia. Biocon could be key in driving additional adoption and use in investigator-initiated studies

- **direct sales territories**: growth the number of direct sales territories. Direct sales account for over 80% of total product sales and come at a relatively high margin. Therefore, expanding their direct sales footprint could have an outsized impact on sales and margin growth. Currently, CTSO has a total of ten direct sales territories.

- **distribution/geographic expansion**: distribution now secured in 58 countries and we expect additional territories and distribution agreements will continue to come online on a regular basis. S. Korea could be a near-term catalyst in this regard.

- **clinical data / validation**: has been and continues to be the driving force behind adoption. In addition to REFRESH and REMOVE, a fairly regular flow of clinical data from case studies and investigator-initiated trials should continue. FDA IDE approval can sometimes have somewhat of a halo effect – prompting use in the related indication overseas. CytoSorb has now been used in more than 88k human treatments – up from 61k ~12 months ago

- **increasing use in a number of critical care applications** where CytoSorb has been associated with positive patient outcomes including sepsis. Management has indicated that sepsis remains on their radar

- **ECMO kit launch**: provides seamless and rapid connection of CytoSorb to extracorporeal membrane oxygenation

- **HemoDefend**: with an IDE filing expected by year-end and pivotal study commencing shortly thereafter, HemoDefend could be meaningful contributor relatively soon. This addresses significant markets and could prove to be a bigger catalyst than might be currently expected

Valuation

We expect to see continued strength in product sales growth through 2020. We see several catalysts that begin to make an initial impact such as new product launches, product label expansion (including recently for S use in anti-thrombotic agent removal), Switzerland dedicated reimbursement, launch in new direct sales and FMC co-marketing territories, and potential new partnerships and government grants. The greater impact over the next 12 - 18 months could come from accelerating adoption in Germany, greater contribution from Fresenius (including from co-marketing agreement), maturation of existing distribution relationships and expansion of the overall sales footprint, and the release of additional clinical data supporting the utility of CytoSorb in a several indications.

We assume increased awareness and visibility of CytoSorb results in a greater rate of burgeoning interest materializing during the year. Assuming positive results from company-sponsored and investigator-led studies as well as supportive feedback from hospitals and critical care professionals, we think 2020 could mark the beginning of a significantly greater ramp in commercial sales. Given the steeper than anticipated growth rate and several new catalysts coming online, we have made upward revisions to our financial forecasts.

We show CTSO nearly reaching GAAP full-year operating profitability in our out-year (2021). Based on our updates to our 10-year DCF model, which uses a 10% discount rate and a 2% terminal growth rate, the shares are valued at approximately $15. Our model and assumptions will be updated commensurate with news flow which could also influence the valuation. As it is now, we value the company at $15/share, implying upside to the current share price.

FINANCIAL MODEL

CytoSorbents Inc.

CTSO	2019 A	Q1A	Q2E	Q3E	Q4E	2020 E	2021 E	2022 E
CytoSorb Sales	$22,765.9	$8,156.0	$8,936.0	$7,615.2	$8,018.4	$32,725.6	$44,520.2	$55,128.3
y-o-y growth	*12.4%*	*78.2%*	*52.7%*	*34.8%*	*19.8%*	*43.7%*	*36.0%*	*23.8%*
Total Royalties/ Grants/ Other	$2,183.6	$551.3	$412.3	$437.3	$465.1	$1,896.0	$2,271.0	$2,272.0
y-o-y growth	*-3.0%*	*-10.4%*	*7.9%*	*-2.1%*	*-37.1%*	*-13.2%*	*19.8%*	*0.0%*
Revenue	$24,949.5	$8,707.3	$9,348.3	$8,052.5	$8,483.5	$34,621.6	$46,791.2	$57,400.3
YOY Growth	*10.9%*	*67.7%*	*50.0%*	*32.1%*	*14.2%*	*38.8%*	*35.2%*	*22.7%*
Cost of Goods Sold	$7,363.9	$2,384.8	$2,168.8	$1,731.3	$1,764.6	$8,049.5	$10,643.1	$12,454.1
Gross Income	$17,585.6	$6,322.5	$7,179.5	$6,321.2	$6,718.9	$26,572.1	$36,148.1	$44,946.2
Gross Margin	*70.5%*	*72.6%*	*76.8%*	*78.5%*	*79.2%*	*76.8%*	*77.3%*	*78.3%*
SG&A	$24,467.8	$6,836.0	$6,998.3	$6,321.0	$5,483.5	$25,638.8	$29,237.4	$31,028.4
SG&A % of Prod Sales	*107.5%*	*78.5%*	*74.9%*	*78.5%*	*64.6%*	*74.1%*	*62.5%*	*54.1%*
R&D	$12,091.8	$1,965.3	$2,000.0	$2,946.5	$3,300.8	$10,212.6	$9,844.6	$9,345.6
R&D % Tot Sales	*48.5%*	*22.6%*	*21.4%*	*36.6%*	*38.9%*	*29.5%*	*21.0%*	*16.3%*
Operating Income	($18,974.1)	($2,478.8)	($1,818.8)	($2,946.3)	($2,065.4)	($9,279.3)	($2,933.9)	$4,572.2
Operating Margin	-					-	*-6.3%*	*8.0%*
Total Other Expense	$1,384.0	$974.0	$310.0	$345.0	$341.3	$1,975.3	$568.7	$1.0
Pre-Tax Income	($20,358.1)	($3,452.8)	($2,128.8)	($3,291.3)	($2,406.7)	($11,254.6)	($3,502.6)	$4,571.2
Taxes (benefit)	$1,092.4	$0.0	$0.0	$1.0	$2.0	$0.0	$0.0	$1.0
Tax Rate	*-5.4%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*
Preferred/ Othr Dividend	$0.0	$0.0	$0.0	$1.0	$2.0	$0.0	$0.0	$1.0
Net Income	($19,265.6)	($3,452.8)	($2,128.8)	($3,293.3)	($2,410.7)	($11,254.6)	($3,502.6)	$4,569.2
Net Margin	*-77.2%*	*-39.7%*	*-22.8%*	*-40.9%*	*-28.4%*	*-32.5%*	*-7.5%*	*8.0%*
EPS	($0.60)	($0.10)	($0.06)	($0.09)	($0.07)	($0.31)	($0.09)	$0.11
Diluted Shares O/ S	32,255	33,981	34,385	34,879	35,145	36,500	39,500	42,500

Anita Dushyanth, PhD

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Appendix: Summary of Recent Clinical Studies in Various Indications

Condition / Indication: ***Acute Kidney Injury***

REFRESH I Refresher

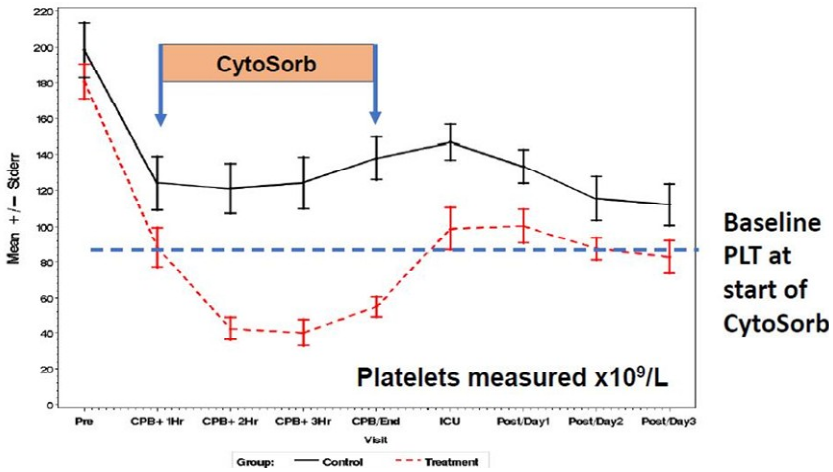
As a reminder, REFRESH I was a multi-site 40+-patient randomized study comparing CytoSorb plus standard-of-care (SOC) to SOC alone (1:1) in the reduction of free hemoglobin in patients undergoing elective complex cardiac surgery requiring cardiopulmonary bypass with anticipated duration of more than 180 minutes. 46 patients (23 each arm) were assessed in the safety population while 38 (18 CytoSorb, 20 control) were assessed in the efficacy population.

In October 2016 CTSO announced positive **safety-related information** and released additional information on the Q1 call. Both the number of total adverse events as well as number of serious adverse events was similar between the treatment and control arms. While there were two deaths in the CytoSorb group (8.7%), this was not statistically different than the one (4.3%) in the control group. Of the 121 adverse events in the CytoSorb arm, two were related to the device – with both related to a drop in platelets.

	Control (N = 23)	CytoSorb (N = 23)
Total Number AEs	137	121
Total Number SAEs	43	44
Mortality	1 (4.3%)	2 (8.7%)
Device Related AEs		2

SOURCE CytoSorbents

Of the 121 adverse events in the CytoSorb arm, two were related to the device – with both related to a drop in platelets. A decrease in platelets (i.e. cells that help blood clot) is not unexpected given that patients undergoing these procedures must be highly anticoagulated and CPB in itself causes a drop in platelets. The chart below illustrates a drop in platelets in both cohorts even prior to introduction of the CytoSorb therapy in the treatment group. Nonetheless, the platelet level in the CytoSorb arm continues to drop with introduction of that therapy while the control group exhibits more of a leveling off. While the decrease in platelets, per management, was not associated with any serious device-related events and post-op coagulation and bleeding parameters as well as transfusions were not different between the two groups, the greater decrease in platelets among the treatment cohort is something that investigators will look at in more detail.



SOURCE CytoSorbents

REFRESH I Efficacy: CytoSorb More Effectively Reduces PfHB Which Is Associated With Kidney Injury….

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A clinical study by Windsant, et al. indicated that hemolysis (including plasma free hemoglobin) during cardiac surgery is a contributor to postoperative kidney injury.[1] Plasma free hemoglobin can be dangerous, particularly at relatively high levels. While levels at or below 60 mg/dL have been found to be generally safe, levels over 120 mg/dL have been associated with acute kidney injury (AKI). As it relates to efficacy, there appears to be an association between the type of cardiac surgery and how much plasma free hemoglobin is generated. Specifically, valve replacement surgery (either in isolation or in combination with other cardiac surgery procedures) appears to be associated with higher levels of plasma free hemoglobin.

The average peak plasma free hemoglobin level of the nine patients in the control group (efficacy population) in REFRESH I that underwent valve replacement surgery was 121 mg/dL (median was 123 mg/dL) – or, at potentially dangerously-high levels.

Control group only: Peak PfHb in Different Surgical Procedures (mg/dL)

Procedure	N	Mean	Std	Median	Min	Max
All	20	104.0	58.54	101	23	245
Valve Replacement	9	121.0	46.57	123	57	204
Non-valve Replacement	11	90.1	65.60	61	23	246

CPB Length (median control): 2.8h (Valve) vs 4.0h (Non-valve), p=0.03

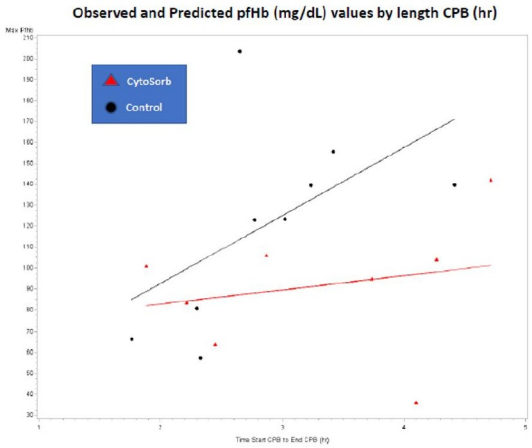
SOURCE CytoSorbents

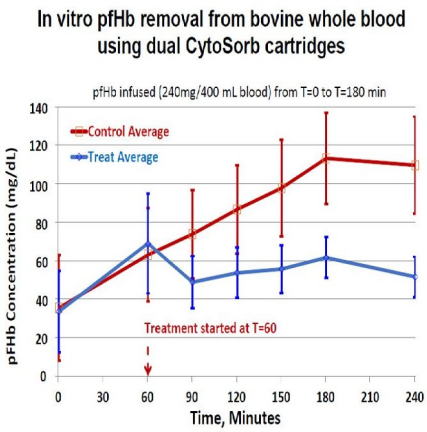
Valve replacement patients in the CytoSorb group fared better as it relates to PfHb levels. Among those patients in REFRESH I that underwent valve replacement surgery that lasted between 3 and 4.5 hours, CytoSorb demonstrated a statistically significant reduction in plasma free hemoglobin as compared to control.

CPB Length	Mean Reduction of pfHb (mg/dL)	P-value
3.0	35 mg/dL	0.09
3.5	48 mg/dL	0.05
4.0	61 mg/dL	0.05
4.5	74 mg/dL	0.07

SOURCE CytoSorbents

Interestingly, these findings are similar to an earlier pre-clinical study which found CytoSorb was more effective than standard bypass circuit in reducing free hemoglobin from bovine blood. In fact, the charts from REFRESH (left) and the in vitro bovine-blood study (right) have very similar patterns.





C3a / C5a:
In addition to plasma free hemoglobin, significant reductions in the activated complements C3a and C5a, high levels of which are associated with poor outcomes, were also observed.

[1] Iris C. Vermeulen Windsant, et al. Hemolysis during cardiac surgery is associated with increased intravascular nitric oxide consumption and perioperative kidney and intestinal tissue damage. Front Physiol. 2014; 5: 340. Published online 2014 Sep 8. doi: 10.3389/fphys.2014.00340

In Summary:
Evidence to date has shown;

- high levels of PfHb are generated during cardiac surgery and valve replacement surgery is associated with particularly high levels
- an association between high levels (i.e. > 120 mg/dL) of PfHb and AKI
- CytoSorb's ability to significantly reduce PfHb vs. control in valve replacement procedures (3hr – 4.5hrs)

REFRESH II

REFRESH II design

The multi-center, randomized, controlled U.S. study is expected to enroll up to 400 patients (over two years) which are undergoing elective open heart surgery for valve replacement or aortic reconstruction with hypothermic cardiac arrest. Patients will be randomized to either standard-of-care (i.e. control) or standard-of-care plus dual CytoSorb cartridges (in parallel in a heart-lung bypass circuit). The primary endpoint, reduction of acute kidney injury (AKI), is outcomes-based. AKI will be measured by Kidney Disease Improving Global Outcomes (KDIGO) criteria. Secondary endpoints include time on mechanical ventilation, use of vasopressors, days in ICU, reduction of inflammatory mediators and 30-day mortality.

Relative to the KDGIO criteria primary endpoint, this is what we found based on our own research…published in March 2012, KDIGO guidelines are an international initiative for the evaluation and management of AKI. KDIGO guidelines build on already established AKI measures such as RIFLE (Risk, Injury, Failure, Loss of Kidney Function, and End-stage Kidney Disease) and AKIN (Acute Kidney Injury Network) criteria and measure changes in serum creatinine as well as urine output in staging AKI (i.e. 1 – 3 severity scale). Below is the definition and staging of AKI as per KDIGO guidelines (SOURCE: Kidney International Supplements, KDIGO Clinical Practice Guideline for Acute Kidney Injury. Vol 2, Issue 1, March 2012).

KDIGO Definition of AKI

AKI is defined as any of the following (*Not Graded*):

- Increase in SCr by ⩾0.3 mg/dl (⩾26.5 μmol/l) within 48 hours; or
- Increase in SCr to ⩾1.5 times baseline, which is known or presumed to have occurred within the prior 7 days; or
- Urine volume <0.5 ml/kg/h for 6 hours.

KDIGO AKI Staging

Stage	Serum creatinine	Urine output
1	1.5–1.9 times baseline OR ⩾0.3 mg/dl (⩾26.5 μmol/l) increase	<0.5 ml/kg/h for 6–12 hours
2	2.0–2.9 times baseline	<0.5 ml/kg/h for ⩾12 hours
3	3.0 times baseline OR Increase in serum creatinine to ⩾4.0 mg/dl (⩾353.6 μmol/l) OR Initiation of renal replacement therapy OR, In patients <18 years, decrease in eGFR to <35 ml/min per 1.73 m^2	<0.3 ml/kg/h for ⩾24 hours OR Anuria for ⩾12 hours

Despite the newness of the KDIGO criteria, it appears to be largely widely accepted in the U.S. for defining AKI[2]. In addition, clinical studies[3] have demonstrated a significant positive correlation between KDIGO AKI stage and 30-day mortality, including among subjects undergoing cardiac surgery[4].

Based on feedback and comments from management, REFRESH 2 was designed in such a way to increase odds of reaching statistical significance on the primary endpoint. Specifically, by enriching with a population at already

[2] Palevsky PM, et al. KDOQI US commentary on the 2012 KDIGO clinical practice guideline for acute kidney injury. Am J Kidney Dis. 2013 May;61(5):649-72. doi: 10.1053/j.ajkd.2013.02.349. Epub 2013 Mar 15.
[3] Talito Machado Levi, et al. Comparison of the RIFLE, AKIN and KDIGO criteria to predict mortality in critically ill patients. Rev Bras Ter Intensiva. 2013 Oct-Dec; 25(4): 290–296.
[4] Maurício Nassau Machado, et al. Acute kidney injury based on KDIGO (Kidney Disease Improving Global Outcomes) criteria in patients with elevated baseline serum creatinine undergoing cardiac surgery. Rev Bras Cir Cardiovasc. 2014 Jul-Sep; 29(3): 299–307.

relatively high risk of AKI (i.e. those already predisposed to known risk factors), it heightens odds that valve replacement surgery (which is well documented as a cause of AKI) will result in AKI. Obviously, the goal is to demonstrate significantly fewer CytoSorb patients develop AKI versus control (i.e. SOC). The proposed protocol amendment includes a modification to baseline risk factors - which may mean the patient population is not quite as narrow as initially designed.

And while enriching with a narrower patient population may similarly narrow the label if and when FDA cleared (again, the protocol amendment was designed to increase the defined patient population, which also broadens the indicated-use population, if approved), we think that the main focus should first be on hitting singles – that is, get CytoSorb approved for marketing in the U.S. for a "usable" indication (such as this) and expand the label thereafter. The initial indication would also be another significant step towards demonstrating safety (and build on that from REFRESH I as well as from the 40k+ human uses overseas) – which could help in facilitating off-label use as well as provide support for approval of future FDA studies in other indications (potentially such as for sepsis or infective endocarditis – below). And in the meantime, OUS product sales may immediately benefit as a result of implied or presumed clinical legitimacy associated with FDA approving the IDE – which can sometimes result in a halo effect and prompt use in the related indication.

Condition / Indication: Infective Endocarditis

Infective Endocarditis 30-Patient Case Series Published in Journal of Artificial Organs

A manuscript of a retrospective case series involving 39 patients with infective endocarditis undergoing valve replacement surgery using CytoSorb was published in May 2017 in the International Journal of Artificial Organs. *Hemoadsorption treatment of patients with acute infective endocarditis during surgery with cardiopulmonary bypass - a case series*, was the largest study to-date using CytoSorb for this patient population in valve replacement surgery.

Infective endocarditis, as the name implies, is an infection of the endocardial surface of the heart – which includes one or more heart valves. Rates of infective endocarditis have been on the rise as a result of the recent dramatic growth of intravenous (i.e. dirty needles) heroin use in the U.S. These infections, from certain bacteria and other pathogens that enter the bloodstream, can be highly and rapidly destructive to heart valves and spread to systemic sepsis and septic shock. In the absence of antibiotic therapy or surgical intervention, infective endocarditis is almost always fatal.

Besides the often-rapid deterioration of the heart (and, possibly, other organs), an additional difficulty in managing these patients during surgery is the complex nature and length of the procedure. As was evidenced by results of REFRESH I, procedural length and relative complexity are positively correlated to higher levels of (toxic) plasma free hemoglobin (PfHb). Evidence also indicates that hemolysis (including plasma free hemoglobin) during cardiac surgery is a contributor to postoperative kidney injury. Results of REFRESH I showed that among those patients that underwent valve replacement surgery that lasted between 3 and 4.5 hours (i.e. procedures that were relatively long in duration), there was a statistically significant reduction in plasma free hemoglobin when CytoSorb was used as compared to control (i.e. patients in which CytoSorb was not used).

Relative to this 39-patient case series….many of these patients were in very poor condition; 59% (n=23) were considered 'medical emergencies', while the remaining 41% (n=16) were characterized as 'urgent'. Median and mean EuroSCORE II (European System for Cardiac Operative Risk Evaluation II) of the entire cohort was 12.8 and 26.0, respectively. Higher EuroSCORE II scores are associated with higher risk of mortality, with EuroSCORE II scores of 20 to 40 considered to be at very high risk of death. Among these patients evaluated to be at very high risk of death, only one of the six (17%) died. Meanwhile, among the larger cohort with EuroSCORE II $\leq$ 40, 7% (3 of 29) died.

These mortality rates were compared to a (unrelated) case study involving 149 patients with infective endocarditis undergoing valve replacement surgery. These patients were in relatively better health than those in the CytoSorb cases – with 34% considered 'medical emergencies' (vs. 59% with CytoSorb), 42% 'urgent' (vs. 41% with CytoSorb) and 24% 'elective' (vs. 0% with CytoSorb). Median and mean EuroSCORE II scores were 9.8 (vs. 12.8 with CytoSorb) and 15.8 (vs. 26.0 with CytoSorb). But, despite the predicted lower mortality, 42.9% of EuroSCORE II 20 – 40 patients died, compared to 17% with CytoSorb, and 18.0% of EuroSCORE II $\leq$ 40 patients died, versus 7% with CytoSorb.

The lead investigator of the CytoSorb case series noted meaningful reductions in certain inflammatory mediators, including IL-6 and IL-8, as well as "normalization of lactate and base excess back to preoperative baseline levels within 3 days and hemodynamic stability before, during, and after the operation accompanied by a rapid decrease in need for vasopressors." This (i.e. reduction vasopressor requirements and levels of inflammatory and other risk-related markers) is similar to what was observed in the (unrelated) refractory septic shock study. Interestingly, septic shock is one of the factors most closely associated with risk of mortality in patients with infective endocarditis.[5]

REMOVE Study

CTSO hopes to further validate use of CytoSorb in this patient population and in December 2017 announced that a new, large, randomized clinical study, conducted in Germany, is aimed at doing just that. The multi-center study, dubbed **REMOVE (REvealing Mechanisms and Investigating Efficacy Of Hemoadsorption for Prevention of Vasodilatory Shock in Cardiac Surgery Patients With Infective Endocarditis) has already enrolled 130 patients (of an expected 250 total).**

As planned, the Data Safety Monitoring Board overseeing the study did an evaluation of the first 50 patients. CytoSorbents announced in early February that the DSMB recommended that it continue. Their assessment, which included 28 patients in the CytoSorb cohort and 22 in the control group, analyzed cytokine and vasoactive mediator levels as "an indicator of the mechanistic mode of action" and found no device-associated adverse events in the CytoSorb group. Given that continuance of the study was contingent on a positive recommendation, this DSMB outcome was of obvious critical importance.

REMOVE is evaluating safety and efficacy of CytoSorb in patients with infective endocarditis undergoing valve replacement surgery. Primary endpoint is the difference in mean SOFA (Sequential Organ Failure Assessment) scores between experimental and control arms. Secondary endpoints include 30-day mortality, changes in cytokine levels, need for supportive care therapies such as vasopressors, mechanical ventilation, and dialysis, incidence of stroke, and the length of intensive care unit and in-hospital stay.

This study could be a win-win for CytoSorbents – potentially providing robust evidence of CytoSorb's utility in a large and growing patient population – and doing so at little or no cost to the company as the study is being fully funded by the German government. Jena University Hospital is primary sponsor - Jena has been an important partner of CTSO's over the years and manages the company's International CytoSorb registry. B.R.A.H.M.S. (a division of Thermo Fisher Scientific) and the Fraunhofer Institute for Interfacial Engineering and Biotechnology are co-collaborators.

REMOVE incorporates inclusion criteria of EuroSCORE II > 4. Higher EuroSCORE II (European System for Cardiac Operative Risk Evaluation II) scores are associated with higher risk of mortality. For reference, mean and median EuroSCORE II scores among the 39 patients from the earlier case study was 12.8 and 26.0, respectively, - so those were relatively very sick individuals. While a specific organ function-related measure was not part of that case study, certain parameters associated with organ function and clinical outcomes, were. The case study showed that CytoSorb-treated patients experienced marked reduction in IL-6 and IL-8, "normalization of lactate and base excess back to preoperative baseline levels within 3 days and hemodynamic stability before, during, and after the operation accompanied by a rapid decrease in need for vasopressors."

Primary endpoint of REMOVE is change in SOFA score – which is a widely accepted clinical measure of organ function as well as of mortality. SOFA is based on six different measures; respiratory, cardiovascular, hepatic, coagulation, renal and neurological – many of which were assessed (with favorable results) in the 39-patient case study (see Appendix). Mortality was also much lower than predicted in the 39-patient case series – also suggesting a CytoSorb-related mortality benefit. We also note that another recently published study ("Extracorporeal cytokine elimination as rescue therapy in refractory septic shock: a prospective single-center study", *Journal of Artificial Organs*, Sept 2017) also showed that CytoSorb treatment was associated with significant reduction in vasopressor requirements, hemodynamic stability, pro-inflammatory mediators and mortality. We provide this as background as we think it offers context in terms of the potential for eventual success of REMOVE.

REMOVE is being conducted in parallel with REFRESH II, which specifically excludes subjects with infective endocarditis. As such and assuming success of both studies, CytoSorbents envisions that their device could one day be considered standard of care for the majority of open heart valve replacement surgeries ("hundreds of thousands of procedures worldwide"). Management recently noted that, given the robustness of the trial design,

[5] Olmos C., et al. Contemporary epidemiology and prognosis of septic shock in infective endocarditis. European Heart Journal (2013) 34, 1999–2006

that it might be possible to use it as primary support (assuming positive results) for a future FDA filing for an infective endocarditis indication.

While it is way too early to guess the chances of that happening, positive results from this German study would certainly lend significant veracity to the likelihood of an eventual FDA approval for a similar indication – whether it requires a U.S study or not. But, it's probably no coincidence that the anticipated timelines for REMOVE and REFRESH II are somewhat similar.

Condition / Indication: ***Sepsis***

Refractory Septic Shock Study

Published in September 2017 in the Journal of Artificial Organs, *Extracorporeal cytokine elimination as rescue therapy in refractory septic shock: a prospective single-center study*[6] (Germany) evaluated the use of CytoSorb treatment in 20 patients with refractory septic shock. The study assessed the ability of CytoSorb to reduce vasopressor requirements (i.e. life-saving drugs) and improve outcomes (based on organ function, reversal of shock and lower mortality) among a group of critically-ill patients.

Septic shock occurs when infection leads to critically low blood pressure and organ failure. It often results in death. Vasopressors, such as noradrenaline (norepinephrine), dopamine, vasopressin and epinephrine are used to increase blood pressure through methods such as increasing the heart rate and vasoconstriction. Refractory (i.e. critically-ill) septic shock is characterized as persistently-low blood pressure despite vasopressor therapy and adequate fluid resuscitation. As persistently-low blood pressure can lead to multiple organ failure, refractory septic shock patients are at particularly high risk of death.

Patients with refractory shock after six hours of standard treatment were included in the study to receive CytoSorb therapy. Certain criteria related to venous oxygen saturation, fluid administration, cardiac output and organ function were used to determine when standard therapy was no longer effective (at which point CytoSorb therapy was introduced). Patients that received CytoSorb therapy were critically ill, all of which had kidney failure, little or no urine output, respiratory failure (requiring mechanical ventilation) and were on high doses of vasopressors. Based on high severity of organ dysfunction and overall severity of disease (based on SAPS II score), predicted mortality among this cohort was greater than 80%.

Prior to the start of CytoSorb therapy;

- lactate clearance in all patients was very low (<25%) and was zero or negative in 16 of the 20. Lactate level is a marker for cellular hypoxia (increasing clearance indicates increasing oxygen saturation) and is positively correlated to the risk of mortality. Studies have shown that lactate clearance is an independent predictor of death[7] in sepsis patients and lactate clearance of less than 33% over 12 hours is associated with a mortality rate of 97%
- average Simplified Acute Physiology Score (SAPS II) implied risk of death of at least 80%
- vasopressor (noradrenaline) demand was increasing in all 20 patients in the two hours prior to commencement of CytoSorb therapy
- IL-6 levels were very high. Average IL-6 among all patients was 25,523 pg/mL, indicative of cytokine storm

Primary endpoint was the change in noradrenaline requirement after six hours and after twelve hours of CytoSorb treatment as compared to baseline (i.e. just prior to the introduction of CytoSorb therapy). Secondary endpoints included resolution of shock and lactate clearance. Change in IL-6 was used as the determinant as to whether CytoSorb would be discontinued. If no further change in IL-6 was expected, then CytoSorb treatment was ended.

Results;

- Primary endpoint: noradrenaline requirements were significantly reduced after both six (p=0.03) and twelve (p=0.001) hours of CytoSorb treatment versus baseline. The decrease continued after 24 (p<0.001) and 36 hours (p<0.001). (see chart below)
- Secondary endpoints:
    - as compared to the six hours prior to the commencement of CytoSorb treatment, lactate clearance increased significantly with CytoSorb treatment during three (i.e. hour 6–12, hour 12-18 and hour 18-24) of the four (hour 0-6 was also measured but not statistically significant) timepoints measured (see chart below)

[6] Friesecke S. et al. Extracorporeal cytokine elimination as rescue therapy in refractory septic shock: a prospective single-center study. J Artif Organs DOI 10.1007/s10047-017-0967-4
[7] Philippe M. et al. Lactate clearance for death prediction in severe sepsis or septic shock patients during the first 24 hours in Intensive Care Unit: an observational study. Ann Intensive Care. 2013; 3: 3.

- shock reversal was achieved in 13 patients, although four of these patients died later of other causes. Nine patients survived 28 days (i.e. standard, accepted primary endpoint in pivotal sepsis studies). This 45% survival compares very favorably to the 20% or less survival rate as predicted by SOFA, SAPS III and lactate clearance metrics of the patients prior to the start of CytoSorb therapy

- In fourteen patients IL-6 levels were either reduced by 90% (or more) or IL-6 concentration was reduced to less than 500 pg/ml

Primary Endpoint: Significant Reduction in Vasopressors

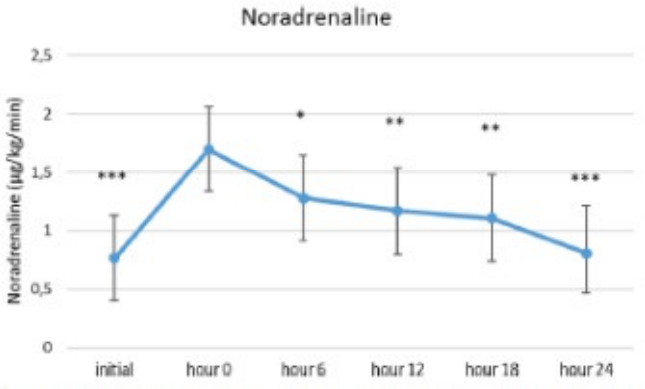


Fig. 1 Noradrenaline dose before and during treatment with CytoSorb®. Values are shown as means with 95% CIs. Difference vs. "hour 0" (CytoSorb® start): $*p < 0.05$, $**p < 0.01$, $***p < 0.001$. Initial and start $n = 20$, hour 6, 12 and 18 $n = 19$, hour 24 $n = 18$

SOURCE: Frisecke S., et al

Secondary Endpt: Significant Increase in Lactate Clearance

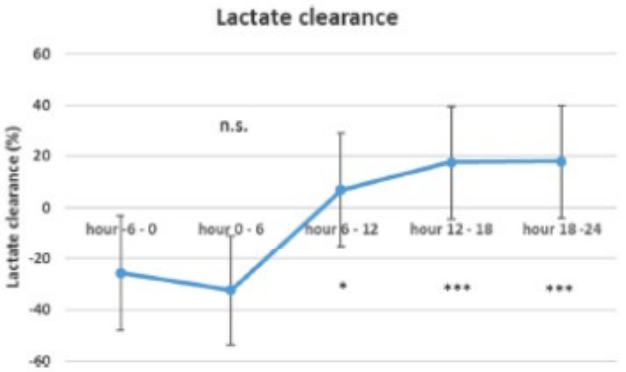


Fig. 2 Lactate clearance before and during treatment with CytoSorb®. Values are shown as means with 95% CIs. Difference vs. "hour -6 - 0" (6 h before CytoSorb® start): $*p < 0.05$, $***p < 0.001$, *n.s.* not significant

SOURCE: Frisecke S., et al.

While this study is too small and not designed or powered to evaluate efficacy on clinical outcomes, we do think it adds to the growing evidence supporting the relationship between the reduction of certain inflammatory mediators, such as IL-6, and improved biological functioning. The study further supports the association between controlling cytokine levels and pared risk of cellular hypoxia, organ failure, hypotension and other signs of hemodynamic instability associated with sepsis and mortality. But it takes this relationship another important step forward, demonstrating that cytokine elimination (via CytoSorb) may provide significant incremental benefit to outcomes and survival in patients with refractory septic shock in which the benefits of vasopressor therapy have been exhausted and predicted mortality may otherwise be near 100%.

Sepsis is a complex condition, the pathogenesis of which is influenced by a number of factors but is still not fully understood. Compounding the difficulty in treating the condition is that even slight patient-to-patient differences (age, health, co-morbidities, etc) may play a significant role in the body's response and in clinical outcomes. This heterogeneity makes trial design a major challenge and means pursuit of a sepsis indication is a risky endeavor (as evidenced by the high failure rate of various other sepsis therapy candidates) and possibly a costly mistake.

Given these challenges, CytoSorbents has been methodical in evaluating possible options as it relates to designing a clinical program around sepsis. Chipping away at the heterogeneity through narrowing of patient and/or condition-related differences and which will help power response to CytoSorb therapy is clearly a goal and one that should improve the chances of success (or at least reduce risk of failure). Results of this refractory sepsis study, like ones that came before and others that will certainly come in the future, should help the company in making informed decisions relative to how best to proceed relative to a pivotal sepsis clinical program.

Condition / Indication: ***Hemophagocytic Lymphohistiocytosis (HLH) / Cytokine Release Syndrome (CRS)***

Cytokine Release Syndrome Associated With CAR-T Cell Cancer Therapies

The feasibility of CytoSorb as a treatment for cytokine release syndrome (CRS) could soon become more clear given the recent FDA and European Union approvals of two CAR-T immunotherapies; Novartis' Kymriah (tisagenlecleucel-T) and Gilead/Kite's Yescarta (axicabtagene ciloleucel). These novel CAR-T therapies have shown extraordinary efficacy in the treatment of certain cancers but have also been associated with certain severe

side effects in some patients. Specifically, clinical studies have shown that severe CRS (i.e. severe inflammatory response with excessive and harmful levels of cytokines) effects about 47% of patients treated with these therapies. CRS can result in serious complications and lead to organ failure and death.

While corticosteroids and tocilizumab have been used with some success in controlling CRS, there are drawbacks. This includes that corticosteroids are suspected of potentially comprising immunotherapy efficacy. Relative to tocilizumab, researchers have noted that its use should be avoided if macrophage activating syndrome (MAS) is suspected.[8] Interestingly, CytoSorb has been used successfully in several patients with a condition called hemophagocytic lymphohistiocytosis (HLH) - one of these was the subject of a case report published in early March 2017 in the Journal of Clinical Immunology. Studies have shown that subjects with secondary HLH, which is often caused by virologic infection and characterized by a strong and sometimes uncontrollable immune response including CRS, can exhibit responses similar to cancer patients treated with certain immunotherapies. The similarity in CRS response in HLH and cancer patients treated with immunotherapies and CytoSorb's early success in treating HLH patients (via reduction in inflammatory markers) is encouraging, particularly as it may relate to mitigating the toxicity of CAR-T therapies.

In 2017 CTSO announced that Dr. Carl June joined their scientific advisory board for the purpose of guiding their strategy in oncology. Dr. June is considered the pioneer of cancer immunotherapy and guided Novartis' Kymriah program. In March 2017 CTSO disclosed that "we have confirmed the interest in the therapy [CytoSorb], once available, as an adjunct to tocilizumab, and before high dose steroids are administered. We plan to continue to pursue applications of our therapy in the treatment of CRS in the United States, Europe, and elsewhere, as cancer immunotherapies continue to expand worldwide."

As we noted in early 2017, the similarity in CRS response in HLH and cancer patients treated with immunotherapies and CytoSorb's apparent early success in treating HLH patients (via reduction in inflammatory markers) was encouraging, particularly as it may relate to the leveraging the massive interest in and growth of the immunotherapy segment. Activity has clearly continued as evidenced by a recent case at Mount Sinai Beth Israel where CytoSorb was successfully used on a patient with poor prognosis and diagnosed with HLH. The case, published in Mount Sinai's Division of Nephrology publication earlier this year, indicated CytoSorb was used as a last resort when other therapies failed – the ICU team obtained IRB approval to use CytoSorb, following which the "patient's clinical improvement was immediate and significant, with hemodynamic stabilization during the first treatment, followed by enhanced liver function and mental status."

The latest update relative to the potential use of CytoSorb for CRS/HLH came on the Q4'18 call (March 2019) with management noting that they are seeing strong interest in both the U.S. and, following approval of Yescarta and Kymriah in Europe, now also in that part of the world. Interest, per their comments, is coming from KOL's in the immunotherapy space and CTSO has been in close contact with the medical centers that were involved with the approval of these two cancer therapies in Europe. Particularly noteworthy, in our opinion, was management mentioning that there is strong interest to evaluate CytoSorb among the hospitals that are authorized to administer these therapies. In addition, CTSO noted that there is interest to collaborate with the company on clinical studies, particularly as a rescue therapy in cases where patients with CRS/HLH fail first line therapies such as tocilizumab and steroids. Further progress on this front – potentially including an announced formal clinical study or partnership with an authorized Kymriah or Yescarta center, could be a value inflection event, in our opinion.

[8] Shannon L. Maude, MD, PhD,* David Barrett, MD, PhD,* David T. Teachey, MD,* and Stephan A. Grupp, MD, PhD. Managing Cytokine Release Syndrome Associated With Novel T Cell-Engaging Therapies. Cancer J. 2014 Mar-Apr; 20(2): 119 122.

HemoDefend Closer to Commercialization with New $3M, 3-Year NHLBI Award: "Back on track"…
With CytoSorb consuming most of the investor interest in CTSO, the potential incremental value of HemoDefend may be under-realized. This is despite successful progression through a phase 1 program (*Elimination of blood contaminants from pRBCs using HemoDefend™ hemocompatible porous polymer beads*) funded by a $204k grant (awarded Sept 2013) from NHLBI and a follow-on $1.5M phase 2 NHLBI award (*pRBCs Contaminant Removal with Porous Polymer Beads*). The final $140k of the ph2 award was recognized by CTSO in Q3'18.



In August another NHLBI award was announced. p*RBC contaminant removal with hemocompatible porous polymer beads* provides up to $1M per year for up to three years (i.e. up to $3M total) and is matched dollar-for-dollar with CTSO's own funds. CTSO expects this will be used to fund a pivotal FDA clinical trial. While the company had hoped that a pivotal study would begin in Q2 2019 (contingent on FDA IDE approval), that timeline was recently pushed back "due to the sale and loss of key technical personnel at our main parts supplier" (per the Q4'18 earnings release). CTSO noted on the Q4 call that they were working with their supplier and, if all goes well, hope to have a pivotal study for HemoDefend underway by the end of this year.

Progress appears to have been made as on the Q1'19 call (in early May) management noted that they are "back on track" and are aiming to make an IDE submission to FDA in the second half of this year. Management reiterated that timeline on the Q2 call, noting that they anticipate making the IDE filing in Q4, subsequent to successful bench testing – which simply requires demonstration that HemoDefend can remove targeted substances from blood. They further noted that they are assembling devices to be used in the clinical trial and have selected a CRO to conduct site selection and oversee the study.

Assuming no hiccups, CTSO hopes to have the clinical study started in Q1'20 and completed around the middle of next year. **The pivotal study** is designed as a post-transfusion recovery and survival assay for autologous blood – in essence, (healthy donor donated) blood will be aged and then filtered through HemoDefend – a (standard) assay will then assess survivability of the blood after it is transfused back into the donor. CTSO noted on the Q2 call that the trial will require a very small number of patients (i.e. 25 or less healthy volunteers to donate blood) and that it should only require three to six months to complete. If all goes smoothly, CTSO believes they could have HemoDefend on the U.S. market by the end of next year.

The potential market for HemoDefend could be fairly enormous. An estimated 80M – 100M blood donations happen each year worldwide with each donation generating multiple blood transfusion products such as packed red blood cells (pRBCs), platelets, fresh frozen plasma, and cryoprecipitate. Every year more than 100M RBC units are transfused, including ~30M in the U.S. Blood can become contaminated either from the donor or during storage as the blood ages. If not removed, contaminants can cause health risks, which can range from mild fever and itching, to potentially life-threatening and lethal reactions. The NHLBI-funded development of HemoDefend focuses on use as an RBC filter for removal of contaminants such as antibodies, free hemoglobin, cytokines, and bioactive lipids in packed red blood cells.

Practical and effective ways to purify contaminated blood and reduce risk of transfusion-related adverse reactions is an objective of NHLBI (100+ related projects are listed in NIH's Project Information database) as well as the U.S. military and represents a significant current unmet need. As such, the significance of continued development progress of HemoDefend and success under these NHBLI-funded programs should not be underestimated. And certain tangible milestones, such as eventual commencement of a pivotal FDA study, if that happens, should be a wake-up call for investors to pay much more attention to HemoDefend – as we think this program has the potential to create meaningful incremental shareholder value.

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