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CytoSorbents Corporation (CTSO-NASDAQ)

Q2'19: Product Sales Rebound to Record High Despite Distributor Hangover. Value-Inflection Opportunities Abound…

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 $13.75.

Current Price (08/21/19)	$4.83
Valuation	**$13.75**

OUTLOOK

Not only did product sales strongly rebound from the relative weakness in Q1 to set a new record high (of $5.85M, +12% yoy, +28% qoq) but did so despite continued lack of significant ordering from three of the company's most important distributors. Mgmt noted on the call that while one of the three resumed purchasing in Q2, that had they not, product sales would have still been a record. We think this is at least partially attributable to the company's incremental shift towards 'owning' a greater portion of the sales channels, which can have several benefits including higher margins. Importantly, the company continues to expect the other two distributors (inc Fresenius) to resume ordering before year end. We continue to see other catalysts either having an initial influence on sales or making a more significant impact. This includes Fresenius entering Mexico, S. Korea and the Czech Republic, 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, 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	**$14.95**
52-Week Low	**$3.68**
One-Year Return (%)	**-59.92**
Beta	**1.74**
Average Daily Volume (sh)	**158,280**
Shares Outstanding (mil)	**32**
Market Capitalization ($mil)	**$156**
Short Interest Ratio (days)	**N/A**
Institutional Ownership (%)	**27**
Insider Ownership (%)	**10**
Annual Cash Dividend	**$0.00**
Dividend Yield (%)	**0.00**
5-Yr. Historical Growth Rates	
Sales (%)	**57.2**
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)
2018	4925 A	5755 A	5743 A	6081 A	22504 A
2019	5192 A	6233 A	6637 E	7678 E	25740 E
2020					36173 E
2021					50045 E

Earnings per Share

	Q1 (Mar)	Q2 (Jun)	Q3 (Sep)	Q4 (Dec)	Year (Dec)
2018	-0.10 A	-0.19 A	-0.10 A	-0.17 A	-0.56 A
2019	-0.15 A	-0.14 A	-0.14 E	-0.14 E	-0.54 E
2020					-0.26 E
2021					-0.01 E

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

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Recent Highlights

- **Record Revenue, Margins**: Q2 set records on Product Revenue, Total Revenue, Direct Sales and Product Margin. And this is despite lack of significant ordering from three key distributors. CTSO expects all three to be back online by year-end (one of which resumed ordering in Q2). Product margins, expected to widen to 80% by Q4, are benefitting from growth in direct sales (proportionally as well as in aggregate) and new, more efficient manufacturing facility
- **CE Mark Renewal**: on August 15th, CytoSorbents announced that they received renewal of its European Union CE Mark through May 2024, ensuring no interruptions to international commercialization
- **REFRESH 2-AKI**: more than 25% enrolled as pace accelerates from 12 to 15 patients per month. Guiding to reach 50% mark (i.e. 200 patients) by Q1'20 and, if all goes to plan, make PMA filing by ~mid-2021. 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 222 patients (of planned 250) through. Guiding for enrollment to complete by year-end. 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
- **Data Published:** volume of published data continues to grow – including REFRESH I data which was recently published in the journal Seminars in Thoracic and Cardiovascular Surgery. We have and continue to believe clinical evidence represents a major catalyst to driving awareness, adoption and utilization of CytoSorb (in a variety of indications)
- **Commercialization Footprint Expanding:** CTSO's footprint continues to grow and now encompasses 58 countries – and counting. Regulatory clearances anticipated in S. Korea and Mexico, both substantial markets. 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 make an IDE filing this year seeking 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

Q2 2019: *Product Sales Rebound to Record High Despite Distributor Hangover. Value-Inflection Opportunities Abound…*

CytoSorbents reported financial results for their second quarter ending June 30th and provided a business update. Encouragingly, not only did product sales strongly rebound from the relative weakness in Q1 to set a record high (of $5.85M, +12% yoy, +28% qoq) but did so despite continued lack of significant ordering from three of the company's most important distributors. As a reminder, while Q1 product sales increased modestly yoy, they were lower than each of the final three quarters of 2018 (including a 16% drop from Q4). That weakness was largely attributed to inventory rebalancing by three of CTSO's distributors, including Fresenius.

Management noted on the earnings call that while one of the three resumed purchasing in Q2, that had they not, product sales would have still been a record high. We think this is at least partially attributable to the company's incremental shift towards 'owning' a greater portion of the sales channels, which can have several benefits including higher margins. This is reflected in the record high of direct (as opposed to third-party) sales in Q2, which increased 13% yoy and 14% qoq to $4.5M, accounting for 78% of total product sales. Importantly, the company continues to expect the other two distributors (which includes Fresenius) to resume ordering before year end. Also noteworthy as it relates to product sales reaching a new record, is that this was achieved despite a meaningful foreign exchange headwind, which took a $357k bite (or ~6% of product sales) off of the topline.

In addition to resumption of ordering from these distributors, we continue to see other catalysts either having an initial influence on sales or making a more significant impact. This includes Fresenius entering Mexico, S. Korea and the Czech Republic (as new exclusive territories), assignment of reimbursement amount in Switzerland (possibly by current year-end), expansion into other countries (including Israel, where CytoSorb was recently granted marketing approval) growing awareness of the potential utility of CytoSorb in various indications 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.

And despite the dip in sales in Q1'19, product revenue through the first half of the year is up nearly 8% to $10.4M. This is just 1% lower than product sales in the second half of 2018 and higher than any other consecutive two-quarter period. And it is not just product sales and total revenue (which, at $6.2M, was also a new high) that were financial highlights as product margin, which came in at 76% in Q2 and averaged 75% through 1H'19, similarly set new highs (on a quarterly and two consecutive quarters bases). Management continues to guide for product margin to reach 80% on a quarterly basis by year end.

And, importantly, CTSO continues to make substantial progress on the operational front. That includes accelerating the pace of enrollment in both their REMOVE (German infective endocarditis) and REFRESH 2-AKI (complex cardiac surgery) studies, the addition of five new direct sales territories (Poland, Sweden, Denmark, Norway and the Netherlands) and three new FMC countries (S. Korea, Mexico and Czech Republic), and assignment of dedicated reimbursement in Switzerland. In addition, management continues to anticipate being in a position to file an IDE to FDA (following successful requisite bench testing) for a pivotal study of HemoDefend by the end of 2019. Given a relatively straightforward FDA pathway, CTSO believes that (assuming all goes well) HemoDefend could launch in the U.S. by late next year. Management talked about the design of the intended U.S. pivotal study for HemoDefend on the Q2 call, which we include below. We reiterate that the potential for HemoDefend should not be underestimated.

As it relates to REMOVE, CytoSorbents announced in early February that the Data Safety Monitoring Board overseeing the study recommended that it continue. Their recommendation was based on an evaluation of the first 50 patients. The 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.

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 a large 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. As we noted in our recent update on CTSO, 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.

REMOVE continues to enroll very rapidly. Current enrollment (i.e. as of August 6th) stands at 222 patients across 15 trial sites. This is up from 180 patients (also across 15 sites) as of May 3rd and from 130 patients (at 13 sites) as of March 7th. While this indicates that the pace of enrollment slowed over the last few months, that may be reflective of the typical summer seasonality in healthcare procedural volumes, which often decline during summer months. Management is guiding for full enrollment (n=250) to complete before current year-end and, given the potential that it accelerates into the Fall, we think it is possible that the final patient runs through by early-to-mid Q4. 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.

REFRESH 2-AKI is also moving along and has accelerated since the protocol amendment was approved in September 2018. The study is now more than 25% completed with 109 patients enrolled (as of August 6th), which is up from 79 as of early May and 56 in early March. There are 24 sites active (up from 23 in May) and others that should come online over the coming months. Rate of enrollment has increased from about 12 per month in the Spring to 15 per month over the last two months – which is particularly encouraging given the typical summer slowdown in elective procedures. 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).

The company continues to guide for hitting the 200-patient mark by Q1 2020 – at that point, which will represent 50% of total expected enrollment, an interim analysis will be completed. Assuming no unexpected issues from that analysis and pace of enrollment reaches ~20/month, CTSO anticipates enrollment will complete by the end of 2020. If all goes to plan, CTSO believes they can have data analysis completed and a PMA application submitted to FDA by ~mid-2021. While we think that timeline leaves little-to-no room for unexpected delays and may be somewhat aggressive (although not unrealistic), if this ends up being pushed back by several months or even quarters from what management is proposing here, it would be largely immaterial from a valuation perspective in our opinion (given the relatively meager estimated cash burn rate at that time, particularly in relation to the commercial upside that would result from U.S. regulatory approval).

CTSO continues to build out their geographic footprint. That includes their direct sales territories, distributor-detailed areas and countries in which they have a presence through their Fresenius co-marketing arrangement. As it relates to their direct territories, CTSO recently added five new countries; Poland, Sweden, Denmark, Norway and the Netherlands, bringing the total number of countries where they detail direct, to ten (which also includes Germany, Austria, Switzerland, Belgium and Luxembourg). These new five countries have aggregate populations roughly equal in size to that of Germany, which currently accounts for approximately 80% and 65% of direct and total product sales, respectively. As sales made through their own sales force come at wider margins, this proportional expansion of their direct-sales footprint should benefit product margins and (at least eventually) overall profitability.

Meanwhile, Fresenius will begin selling in Mexico and South Korea through the co-marketing partnership with CTSO whereby the dialysis giant has exclusive rights to distribute CytoSorb for acute care and other hospital applications. Combined, these two countries have populations of approximately 180M people. Sales will commence following obtainment of regulatory clearance in those countries – which could happen either late this year or early next. Fresenius also has exclusive distribution rights in the Czech Republic and Finland and for all critical care and ICU applications on dialysis or ECMO machines in France.

Financials…
Q2 total revenue was $6.2M, a new record, up 8% yoy and +20% sequentially. Product revenue was $5.9M (+4% vs. $5.7M E), also a record high, up 12% yoy and +28% from Q1'19. As noted, Q2 revenue records were achieved despite continued lack of significant ordering from three of the company's most important distributors. Management noted on the earnings call that while one of the three resumed purchasing in Q2, that had they not, product sales would have still been a record high. Importantly, the company continues to expect the other two distributors (which includes Fresenius) to resume ordering before year end. Also, noteworthy as it relates to product sales reaching a new record, is that this a foreign exchange headwind negatively affected sales by $357k (or ~6% of product sales).

Meanwhile, grant income remains significant and was $382k (vs. $515k E) in Q2. While we expect additional (and near-term) opportunities to score future grants, the yet-to-be billed portion of CTSO's current grant contracts is still substantial. Of the remaining ~$3.1M available under their current roster, we model ~$935k to be billed during the rest of 2019, including $475k in Q3.

Relative to product sales, Germany continues to account for the majority, contributing 63% in Q2 and 65% in 1H'19 (compared to 58% for the full year 2018) and accounting for 78% and 81% of direct sales in those respective periods (compared to 81% in FY2018). Sales from Germany grew 14% yoy and were up 19% on a sequential basis through Q2'19. Q2 also set a record on direct sales, which were $4.5M. Direct sales have climbed as a proportion of total product sales – increasing from 72% in FY2018 to 78% and 82% in Q2'19 and 1H'19, respectively. Total direct sales grew 13% yoy and 14% qoq – slightly less than the growth in Germany and reflecting less robust sales

from the U.S. and other (non-itemized) countries. 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 2019. 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.

Expansion of the geographic and distribution footprint as well as increasing commercial use in a growing number of 'indications' have also benefitted product revenue. The recent addition of the five new direct sales territories and eventual entry into Mexico and South Korea via the Fresenius co-marketing agreement will bring the total distribution footprint to more than 58 countries, compared to 53 one year ago and 44 two years prior. In mid-August CTSO announced the latest additions to their international footprint with their expansion into Brazil, Colombia and Costa Rica which have combined populations of more than 250M people. CytoSorb has been used in a host of conditions throughout much of the world. To-date CytoSorb has been used in more than 67k human treatments, up from 46k a year ago. Current utilization (based on our crude calculations) is now averaging approximately 2,000 per month and we expect that both aggregate and rate of utilization will continue to climb.

The recent indication for removal of bilirubin and myoglobin could have the effect of further expanding 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. Further label expansion for use in additional indications 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.

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. CTSO's most recent grant award, $3M related to further development of HemoDefend, came in August 2018. This is an extension of previous grants and expected to fund a pivotal U.S. study for HemoDefend. 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.

Relative to expenses and margins…product margin was 76% in Q2'19 and 75% in 1H'19, setting records for each respective period and up from 74% in both Q2'18 and 1H'18. Recent activation of the new (more efficient) manufacturing facility and proportionally greater (higher margin) direct sales should further bolster product margins. Management continues to guide for product margins to reach 80% on a quarterly basis this year. We currently model full year 2019 product margin of nearly 77%, or ~300 basis points better than 2018.

Meanwhile operating expenses fell slightly on a yoy basis but increased as compared to Q1'19. Operating expenses, which included about $150k worth of non-cash stock compensation, were $8.0M in Q2'19, compared to $8.2M (including ~$2M in stock comp) in Q2'18 and $7.7M (including ~$230k in stock comp) in Q1'19. An increase in headcount and other 'investments' has contributed to the recent increase in operating expenses. The direct sales force (including support staff) now stands at 63 people, up from 40 one year ago. 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 $3.1M and $7.4M ($3.5M and $7.3M, ex-changes in working capital) in the three and six months ending 6/30/19, compared to $3.3M and $5.5M ($2.3M and $5.0M, ex-changes in w/c) in the comparable prior year periods. Cash balance, pro forma for the July 2019 Term loan 'B' $5M draw, was

approximately $21M at quarter end. The Term loan B draw also had the effect of extending the interest-only period on the total o/s debt facility (which now stands at $15M) from November 1, 2019 (previously) to April 2020 (or later, if they meet certain revenue tests are met). Management anticipates the current cash balance to be sufficient to fund operations "well into 2020."

Operational Update: KOL Interest in CytoSorb Growing, REFRESH 2-AKI and REMOVE Enrollment Accelerating, Clinical Database Growing, HemoDefend FDA Pivotal Study In View…

6th Int'l Users Meeting, ISICEM Indicate Growing KOL Interest in CytoSorb in Various Indications
CytoSorbents' efforts to drive awareness of CytoSorb and build their evidence-based databases of its utility in a variety of indications and applications continues to pay substantive dividends. Attendance and participation at major critical care medical conferences and sponsoring their own International CytoSorb User's Meeting have been key components of this strategy and have undoubtedly played a role in helping to build awareness of the utility of CytoSorb among KOLs in Europe and elsewhere.

This includes CTSOs' 6th International CytoSorb Users' Meeting, which was held at the beginning of the 39th International Symposium on Intensive Care and Emergency Medicine (ISICEM) in Brussels, Belgium. CTSO also conducted a two-day live presentation during the 8th Annual EuroELSO 2019 Conference in Barcelona, Spain. These conferences and meetings provide them with access to hundreds of thought leaders in specialties including nephrology, critical care, cardiology, organ transplantation, anesthesia and more.

These recent events included presentations from various medical experts in a variety of specialties discussing successful use of CytoSorb in addressing sepsis, necrotizing fasciitis, organ function, liver failure, Rhabdomyolysis and other applications. Among the presentations was an update to the International CytoSorb Registry which showed use of CytoSorb among nearly 350 sepsis patients appears to be associated with lower mortality/higher survival than what historical data would suggest would be the case. This is just one of many data points supporting the case for CytoSorb use in sepsis.

A speech by Dr. Robert Bartlett, CTSO's prior CMO and the pioneer of ECMO, provided additional encouragement as to the potential future of CytoSorb noting, "The combination of ECMO and systemic inflammatory mediator reduction with CytoSorb has the potential to be an exciting new innovation in treating lung injury, shock and other complications. The data combining the two therapies are very encouraging, especially in sepsis. I look forward to seeing the story strengthen as we gain greater clinical experience."

This is the type of KOL support which we think can result in growing awareness of CytoSorb amongst the medical community and, potentially, help in driving adoption and use of the device (for various indications).


Source: CytoSorbents

Published Database Continues to Grow, Is Key to Driving Awareness and Adoption
The database of evidence supporting the utility of CytoSorb continues to rapidly grow which, as we have noted in the past, is what we believe has been and will continue to be a key catalyst in driving awareness, adoption and utilization of CytoSorb. Recently this included publication of the REFRESH I study (*Hemoadsorption to Reduce*

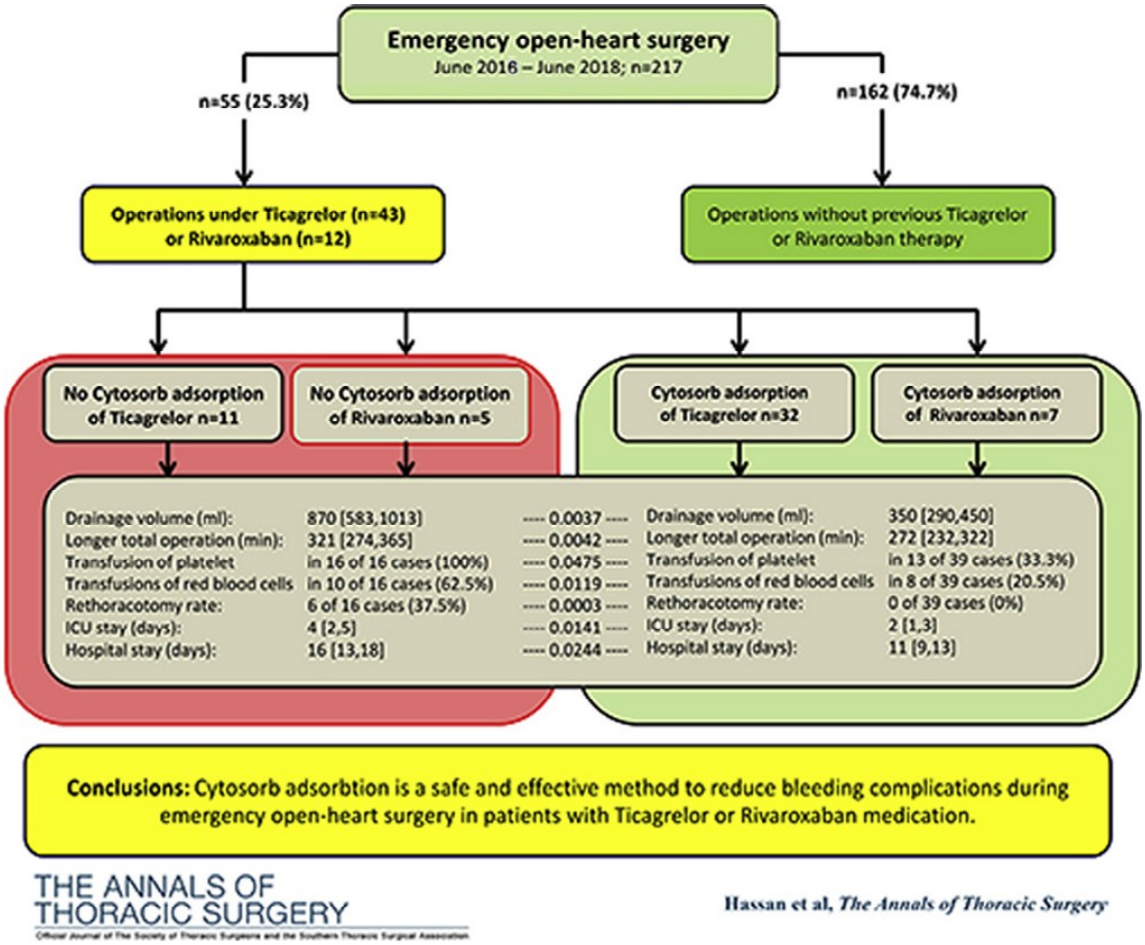
Plasma-Free Hemoglobin During Cardiac Surgery: Results of REFRESH I Pilot Study) in the journal Seminars in Thoracic and Cardiovascular Surgery (from the American Association of Thoracic Surgery).

Cytosorb Adsorption During Emergency Cardiac Operations in Patients at High Risk of Bleeding is another recently published study that demonstrated the safety and effectiveness of CytoSorb (and provides further evidence of the diversity of applications and indications in which CytoSorb can be used to improve outcomes). Published in July 2019 in The Annals of Thoracic, this was the first formal study evaluating the use of CytoSorb in patients undergoing open heart surgery and at high risk of bleeding due to the use of anticoagulants. CytoSorb was used with 39 of the 55 patients, all of which received either ticagrelor or rivaroxaban (both common anticoagulants used during these types of procedures). Bleeding complications during and after surgery were the outcome of interest.

The study found that, among patients where CytoSorb was used, no rethoracotomies had to be performed, drainage volumes were significantly lower (compared to the non-CytoSorb group) and, in most patients, blood transfusions were not required. By contrast, for those patients where CytoSorb was not used, multiple bleeding complications occurred, total operation time was significantly longer, drainage volumes were significantly higher, transfusion rates (of red blood cells and platelets) were significantly greater, there were significantly more rethoracotomies and stay in the ICU was significantly longer.

Per the investigators' conclusions…"The intraoperative use of Cytosorb adsorption of ticagrelor and rivaroxaban in emergency open heart operations is reported for the first time. The data show that the strategy is safe and is an effective method to reduce bleeding complications. We recommend the use for safety in patients with ticagrelor or rivaroxaban undergoing emergency cardiac surgery."[1]

July 2019 in Annals of Thoracic Surgery: Cytosorb Safe/Effective to Reduce Bleeding During Cardiac Surgery



Source: Hassan K et al. Ann Thorac Surg. 2019 Jul;108(1):45-51.

[1] Hassan K. et al. Cytosorb Adsorption During Emergency Cardiac Operations in Patients at High Risk of Bleeding. Ann Thorac Surg. 2019 Jul;108(1):45-51.

REFRESH 2-AKI Enrollment Accelerating
In early September 2018 CTSO announced that FDA approved the protocol amendment for their REFRESH 2-AKI trial. As a reminder, CTSO mentioned prior to that that their clinical advisors recommended the protocol amendment as it would "expand the inclusion criteria, improve operational aspects of the patient screening process, enhance the rate of enrollment, and ultimately increase the applicable market that CytoSorb could address if approved."

Specifically, the amendment modified the age and weight patient eligibility criteria, removing the age cap and eliminating a weight restriction. Initial protocol restricted eligibility to only people 18 to 80 years old and of weight 100 to 382 pounds. The amendment removed the 80 year-old cap and completely eliminates any weight restriction. Given that age and obesity are correlated to and risk factors for acute kidney injury, these eligibility tweaks open up the study to a broader population. Management has noted that this has helped facilitate enrollment, which began in April 2018 and had been lagging up to that point.

Since the amendment approval, 89 patients have enrolled. This includes 30 over the last two months, or ~3.5/week – this pace is significantly faster than the ~2.0/week enrollment rate during the previous four months. Total enrollment currently stands at 109. Currently 24 sites have been initiated – up from 23 in early May and from 14 sites in early November 2018. Additional sites are expected to come online on the coming months with a total 30 to 35 anticipated to eventually be active. As some of these new sites come onboard, we could see the pace of enrollment pick up further. CTSO believes that with all targeted sites active that the pace of enrollment should increase to about 20 patients per month (up from 15/month currently but inline with the current patient per-site pace). Their most recent guidance (on the Q2'19 call in early August 2019) is to have a total of 200 patients enrolled by the end of Q1'20 – which, based on the current enrollment pace, appears very reasonable. We also think their guidance of full enrollment (n=400) by late-2020 is doable.

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.

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;

- **dedicated reimbursement in Germany** which became effective Jan 1, 2017. While the new code may have actually been an impediment to sales in early 2017, indications (including rates increasing by as much as 100% in some locations as well as feedback from some of CTSO's key German accounts) are that the reimbursement issue is proving to be just a short-term hiccup. Certainly the fact that product revenue grew 51% in 2018 and sales in Germany are up ~15% through 1H'29 also supports that theme. 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 bilirubin and myoglobin came in May 2018. 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 they are seeing demand-pull from the market - indicating 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**: roll-out began in Q2 2016, expect this to continue to expand over time. In addition, co-marketing agreement, which began initial roll-out in Q3 2017 continues to expand – most recently (announced January 2019), this was expanded to South Korea and Mexico

- **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. In March 2019 CTSO announced the addition of five new direct sales territories (Poland, Sweden, Denmark, Norway and the Netherlands), bringing the total to ten

- **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 and Mexico could be near-term catalysts in this regard. Two of three (including Fresenius) key distributors expected to resume ordering later this year

- **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 67k human treatments – up from 46k ~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

- **increased capacity**: a new manufacturing facility, which is expected to increase capacity to support up to $80M in sales, is now online and is already benefitting margins

- **HemoDefend**: with an IDE filing expected by year-end and pivotal study completing potentially by mid-2020, 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 2019, as well as more strides on the operational front. We see several catalysts that begin to make either an initial or a greater impact over the next 18 - 24 months. Among the former are new product launches, such as HemoDefend, label expansion (including recently for OUS use in bilirubin and myoglobin removal), Switzerland dedicated reimbursement, launch in new direct sales and FMC co-marketing territories, and potential new partnerships and government grants. Among the latter are dedicated reimbursement in Germany and accelerating adoption in that country, greater contribution from Fresenius (including from co-marketing agreement) as well as from Terumo (which came online in December 2016), 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 now look for 2019 product and total revenue of $23.8M (+18%) / $25.7M (+14%). We show CTSO nearly reaching GAAP full-year operating profitability in our out-year (2021).

Our DCF-based methodology values CTSO at $13.75/share.

FINANCIAL MODEL

CytoSorbents Inc.

	2018 A	Q1A	Q2A	Q3E	Q4E	2019 E	2020 E	2021 E
CytoSorb Sales	$20,252.4	$4,576.6	$5,850.4	$6,162.1	$7,218.2	$23,807.3	$34,276.5	$47,773.5
y-o-y growth	51.3%	3.2%	11.5%	20.8%	31.9%	17.6%	44.0%	39.4%
Total Royalties/Grants/Other	$2,251.5	$615.1	$382.1	$475.0	$460.0	$1,932.2	$1,896.0	$2,271.0
y-o-y growth	27.2%	25.2%	-25.1%	-25.8%	-24.6%	-14.2%	-1.9%	19.8%
Revenue	$22,503.9	$5,191.6	$6,232.5	$6,637.1	$7,678.2	$25,739.5	$36,172.5	$50,044.5
YOY Growth	48.5%	5.4%	8.3%	15.6%	26.3%	14.4%	40.5%	38.3%
Cost of Goods Sold	$7,489.4	$1,738.6	$1,834.4	$1,892.3	$1,900.6	$7,365.9	$8,390.3	$10,643.1
Gross Income	$15,014.5	$3,453.0	$4,398.2	$4,744.8	$5,777.6	$18,373.6	$27,782.2	$39,401.4
Gross Margin	66.7%	66.5%	70.6%	71.5%	75.2%	71.4%	76.8%	78.7%
SG&A	$22,876.5	$5,319.6	$5,098.6	$6,099.4	$7,155.7	$23,673.2	$25,638.8	$29,237.4
SG&A % of Prod Sales	113.0%	116.2%	87.1%	99.0%	99.1%	99.4%	74.8%	61.2%
R&D	$7,723.0	$2,418.6	$2,929.6	$2,781.5	$2,912.9	$11,042.6	$10,212.6	$9,844.6
R&D % Tot Sales	34.3%	46.6%	47.0%	41.9%	37.9%	42.9%	28.2%	19.7%
Operating Income	($15,585.0)	($4,285.2)	($3,630.0)	($4,136.1)	($4,290.9)	($16,342.2)	($8,069.2)	$319.4
Operating Margin	-	-	-	-	-	-	-	
Total Other Expense	$2,245.7	$598.6	($82.6)	$303.3	$341.2	$1,160.6	$1,306.8	$568.7
Pre-Tax Income	($17,830.7)	($4,883.8)	($3,547.4)	($4,439.4)	($4,632.2)	($17,502.8)	($9,376.0)	($249.4)
Taxes (benefit)	($619.5)	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0
Tax Rate	3.5%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
Preferred/Othr Dividend	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0
Net Income	($17,211.2)	($4,883.8)	($3,547.4)	($4,439.4)	($4,632.2)	($17,502.8)	($9,376.0)	($249.4)
Net Margin	-76.5%	-94.1%	-56.9%	-66.9%	-60.3%	-68.0%	-25.9%	-0.5%
EPS	($0.56)	($0.15)	($0.11)	($0.14)	($0.14)	($0.54)	($0.26)	($0.01)
YOY Growth		-	-	-	-			
Diluted Shares O/S	30,719	31,931	32,267	32,300	33,200	32,425	36,500	39,500

Brian Marckx, CFA

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Appendix: Summary of Recent Clinical Studies in Various Indications

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

REFRESH I Refresher

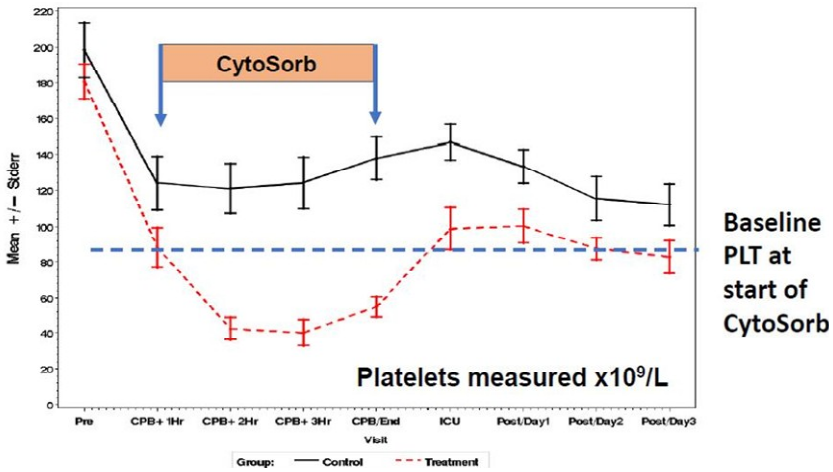
As a reminder, REFRESH I was a multi-site 40+-patient randomized study comparing CytoSorb plus standard-of-care (SOC) to SOC alone (1:1) in the reduction of free hemoglobin in patients undergoing elective complex cardiac surgery requiring cardiopulmonary bypass with anticipated duration of more than 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.[2] 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

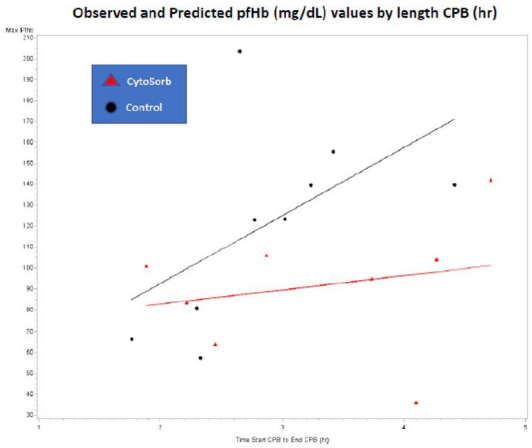
SOURCE CytoSorbents

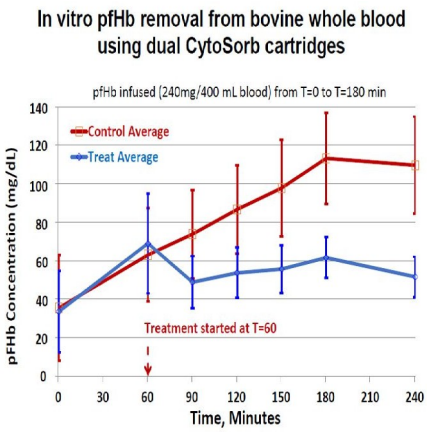
Valve replacement patients in the CytoSorb group fared better as it relates to PfHb levels. Among those patients in REFRESH I that underwent valve replacement surgery that lasted between 3 and 4.5 hours, CytoSorb demonstrated a statistically significant reduction in plasma free hemoglobin as compared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

[2] 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[3]. In addition, clinical studies[4] have demonstrated a significant positive correlation between KDIGO AKI stage and 30-day mortality, including among subjects undergoing cardiac surgery[5].

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

[3] 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.
[4] 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.
[5] 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.[6]

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,

[6] 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*[7] (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[8] 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)

[7] 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
[8] 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

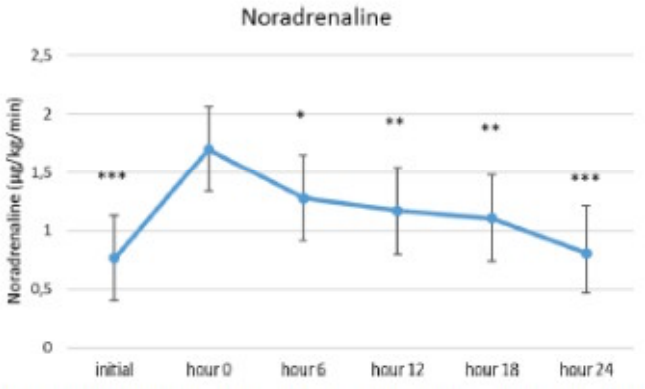


Fig. 1 Noradrenaline dose before and during treatment with CytoSorb®. Values are shown as means with 95% CIs. Difference vs. "hour 0" (CytoSorb® start): $*p < 0.05$, $**p < 0.01$, $***p < 0.001$. Initial and start $n = 20$, hour 6, 12 and 18 $n = 19$, hour 24 $n = 18$

SOURCE: Frisecke S., et al

Secondary Endpt: Significant Increase in Lactate Clearance

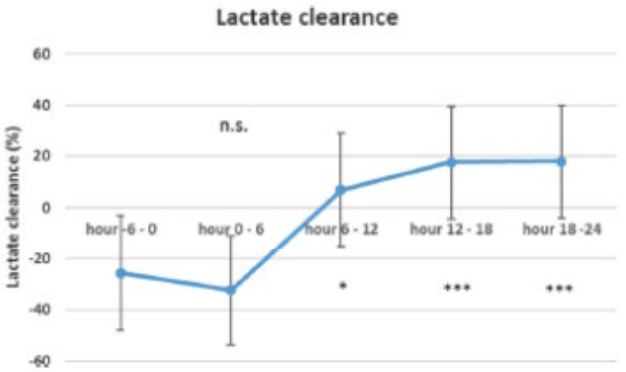


Fig. 2 Lactate clearance before and during treatment with CytoSorb®. Values are shown as means with 95% CIs. Difference vs. "hour -6 - 0" (6 h before CytoSorb® start): $*p < 0.05$, $***p < 0.001$, *n.s.* not significant

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.[9] 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.

[9] 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.

HISTORICAL STOCK PRICE



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