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Zacks Small-Cap Research

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Brian Marckx, CFA
bmarckx@zacks.com
Ph (312) 265-9474

scr.zacks.com
10 S. Riverside Plaza, Chicago, IL 60606

CytoSorbents Corporation (CTSO-NASDAQ)

Q4 2018: Product Sales +27%, Expenses Jump In Part Due to Investments Aimed at Further Accelerating Growth…

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.

Current Price (03/11/19)	$7.46
Valuation	**$15.00**

OUTLOOK

CytoSorbents reported financial results for their fourth quarter and fiscal year ending December 31st and provided a business update. Product and total sales continue their rather consistent climb higher with each setting new all-time highs and benefitting from both new and repeat orders of CytoSorb. Product revenue was driven by strong gains in both direct and distributor sales, the geographic footprints of both of which continue to expand. Meanwhile, product and total gross margin also continue to impress, both widening by several-hundred basis points and reaching new highs in both Q4 and the FY2018. Unfortunately, much of the revenue and margin growth did not flow through the income statement in Q4 as new investments, aimed at further steepening the topline growth, resulted in the largest operating loss in company history. These added expenses and investments, however, are expected to result in positive ROI. Our updated model now shows positive GAAP operating income in our new out-year (i.e. 2021).

SUMMARY DATA

52-Week High	**$14.95**
52-Week Low	**$6.67**
One-Year Return (%)	**-9.43**
Beta	**1.37**
Average Daily Volume (sh)	**180,274**
Shares Outstanding (mil)	**32**
Market Capitalization ($mil)	**$238**
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 (%)	**56.5**
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	6245 E	6737 E	7679 E	8319 E	29980 E
2020					41866 E
2021					57054 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 E	-0.14 E	-0.11 E	-0.11 E	-0.51 E
2020					-0.17 E
2021					0.06 E

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

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Q4 2018 Update: *Product Sales +27%, Expenses Jump In Part Due to Investments Aimed at Further Accelerating Growth…*

CytoSorbents reported financial results for their fourth quarter and fiscal year ending December 31st and provided a business update. Product and total sales continue their rather consistent climb higher with each setting new all-time highs and benefitting from both new and repeat orders of CytoSorb. Product revenue was driven by strong gains in both direct and distributor sales, the geographic footprints of both of which continue to expand. Meanwhile, product and total gross margin also continue to impress, both widening by several-hundred basis points and reaching new highs in both Q4 and the FY2018. Unfortunately, much of the revenue and margin growth did not flow through the income statement in Q4 as new investments, aimed at further steepening the topline growth, resulted in the largest operating loss in company history. These added expenses and investments, however, are expected to result in positive ROI. Our updated model now shows positive GAAP operating income in our new out-year (i.e. 2021).

The highlights on the operating front in just the last several months include a positive DSMB review (Feb 4th) of REMOVE (Germany-based RCT in infective endocarditis) at the 50-patient enrollment mark, pace of enrollment accelerating in both REMOVE and REFRESH 2-AKI (U.S. RCT in complex cardiac surgery), the addition of five new direct sales territories (Poland, Sweden, Denmark, Norway and the Netherlands) and two new FMC-partnership countries (S. Korea and Mexico), and assignment of dedicated reimbursement in Switzerland.

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.

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 is enrolling very rapidly. As of the Q4'18 earnings call on March 7th, 130 patients had been brought into the study across a total 13 sites. This is more than double the 63 that had enrolled as of the company's Q3'18 call on November 6th and implies an average rate of 16 to 17 patients per month. Assuming that pace holds, total enrollment of 250 could happen by mid-Q4 of this year.

REFRESH 2-AKI is also moving along, although not nearly at the same pace as REMOVE. Part of the reason was the protocol amendment, the wait for approval of which all but stunted patient screening. But, with the amendment approved in September, enrollment appears to have picked up and currently stands at 56, up from 20 four months prior. The number of trial sites has similarly increased, up from 14 in November to 21 today. Another eight are on-deck and expected to come online in the near-term. Back-of-the-envelope says enrollment has averaged about one

patient per site every two months (or, 0.5 patients/site/month) over the last several months. CTSO hopes to have a total of 200 patients through the study within the next 12 months – which, based on the current enrollment pace, appears very reasonable (implying a pace of less than 0.6 p/s/m).

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 81% and 58% 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. Management noted on the Q4 call that they are fully staffed in each of these new territories with the exception of Poland, where they expect to have a full sales team in place by next month.

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.

Financials…
Q4 total revenue was $6.1M, up 31% yoy and +12% sequentially. Product revenue was $5.5M (vs. $5.5M E), up 27% yoy and up 7% from Q3'18. Grant income remains robust and was $610k (vs. $493k E) in Q4. 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 significant. Of the remaining ~$4.1M available under their current roster, we model ~$2.0M to be billed in 2019, including $606k in Q1.

Relative to product sales, Germany continues to account for the majority, contributing 56% and 58% in Q4 and the full-year 2018, respectively and accounting for 81% of direct sales in both periods. This is largely consistent with that country's proportional contribution in the prior year periods. Sales from Germany grew 48%, from $7.9M the prior year to $11.8M in 2018 – which is actually slightly below the total product sales growth rate of 51% over the same period.

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. **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 entry into Mexico and South Korea via the Fresenius co-marketing agreement brings the total distribution footprint to 55 countries, compared to 45 one year ago and 32 two years prior. CytoSorb has been used in a host of conditions throughout much of the world. To-date CytoSorb has been used in more than 56k human treatments, up from 35k a year ago. 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.

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). The recent label expansion of CytoSorb for the removal of myoglobin, for example, appears to be a direct extension of the rhabdomyolysis clinical study funded by a grant from the USAF. 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 75% and 74% in Q4 and the full year 2018, up from 72% and 71% in the prior year periods. Activation of the new (more efficient) manufacturing facility and increasing (higher margin) direct sales should further bolster product margins. Management is guiding for product margins to reach 80% on a quarterly basis in 2019. We currently model full year 2019 product margin of nearly 78%, or ~400 basis points better than 2018.

Meanwhile operating expenses jumped significantly in Q4, increasing by almost 50% as compared to Q3'18. Stock and other non-cash compensation accounted for about 56% of the $3.2M sequential increase in expenses. An increase in headcount and other 'investments' also contributed to the record spend in Q4, although these are expected to result in steepening of the revenue and, eventual, earnings curve.

Cash used in operating activities was $2.7M and $10.8M ($3.2M and $9.9M, ex-changes in working capital) in the three and twelve months ending 12/31/18, compared to $410k and $6.5M ($1.4M and $5.6M, ex-changes in working capital) in the comparable prior-year periods. Cash balance stood at $22.4M at year-end. Debt maturities within one-year are just $667k. Management expects the current cash balance will be sufficient to fund operations into 2020.

Operational Update: REFRESH II Enrollment Accelerates Following Amendment Approval, HemoDefend $3M Grant and FDA Program, New Liver Disease Indication, REMOVE Positive DSMB Rec…

(See our Appendix for background on REFRESH studies, REMOVE study in infective endocarditis and other CytoSorb related programs and indications)

REFRESH II Enrollment Accelerates Following FDA Approval of Protocol Amendment in Sept 2018
In early September 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, 48 patients have enrolled. This includes 28, or more than 1.5/week, during the last four months. Total enrollment currently stands at 48. Currently 21 sites have been initiated – up from 14 sites in early November, and another 8 are undergoing start-up activities. As some of these new sites come onboard, we could see the pace of enrollment pick up further. On a per site basis, enrollment has averaged about one patient per site every two months. CTSO has said previously that with all targeted sites active that the pace of enrollment is anticipated to be approximately one patient per site per month. Their most recent guidance (on the Q4'18 call in early March 2019) is to have a total of 200 patients enrolled within the next 12 months – which, based on the current enrollment pace, appears very reasonable (implying a pace of less than 0.6 p/s/m). At this rate, and assuming all eight on-deck sites are activated by mid-2019, full enrollment (n=400) could happen by late-2020 or early 2021.

HemoDefend Closer to Commercialization with New $3M, 3-Year NHLBI Award
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 has since been 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 that they are working with their supplier and, if all goes well, hope to have a pivotal study for HemoDefend underway by the end of this year. We expect we'll hear updates on the progress of this on future calls.

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 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.

European Approval for Treatment of Liver Disease and Trauma

Organ failure has recently become a significant focus for CTSO and new indications are directly aligned with that goal. In May 2018 CTSO announced CytoSorb received European approval for use in the reduction from the blood of elevated bilirubin and myoglobin. Elevated bilirubin is associated with chronic liver disease and failure, while elevated myoglobin, which is a symptom of severe trauma, can lead to kidney failure. While CE Mark has always meant that (at least in theory) clinicians (in areas of the world where CE Mark is accepted) had wide discretion to use CytoSorb as they saw fit (mostly for conditions in which cytokines are elevated), we think that this recent approval likely does expand the overall market for the device.

Bilirubin is a by-product from the breakdown of hemoglobin. Normally, bilirubin is conjugated (i.e. processed) by the liver and then excreted. But, in people with liver disease, the liver has difficulty processing bilirubin, resulting in a toxic build-up of the substance. Elevated bilirubin is common among people with hepatitis A, alcoholism and non-alcoholic fatty liver disease (NASH) - a global market estimated at approximately 50M people.

Myoglobin, found in heart and skeletal muscles, is tasked with capturing oxygen which muscles then use for energy. But, when the body experiences trauma, myoglobin (and other substances) is released into the blood and can become elevated (i.e. rhabdomyolysis). High levels of myoglobin can be toxic - it is the kidney's job to remove it from the blood so it can be excreted in the urine. Typical treatment consists of intravenous fluids and extracorporeal therapy (i.e. dialysis). As a reminder, CytoSorb was evaluated in a clinical study funded by a grant from the U.S. military for the removal of myoglobin in patients with rhabdomyolysis. It has also been the subject of case studies for rhabdomyolysis.

These new indications mean that clinicians can use CytoSorb on-label for conditions associated with elevated cytokines, myoglobin and bilirubin. 'On-label' potentially opens up use in instances where institutional policies forbid off-label use and, per management's comments on the call, may provide reimbursement benefits. And while not mentioned specifically by CTSO, we think that having approval may also open the door to one or more commercialization partnerships focused on these indications (perhaps similar to CTSO's deal with Fresenius).

CytoSorbents believes these new indications have the potential to significantly increase the total worldwide market for their device - while we think it is too early to estimate the significance of these approvals, we think they likely do broaden the market for CytoSorb (for the reasons stated) and, perhaps more importantly, provide additional strategic options. 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.

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 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

- 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 70% 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 55 countries and we expect additional territories and distribution agreements will continue to come online on a regular basis

- **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 56k human treatments – up from 35k ~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 should immediately benefit margins

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 $27.0M (+33%) / $29.0M (+29%). We show CTSO reaching GAAP full-year operating profitability in our new out-year (2021). While management was not able to achieve reaching their guidance to be at a level of break-even operating profitability (excluding clinical trial-related and non-cash expenses) on a quarterly basis in 2018, they expect new investments (which showed up in opex in Q4'18) to steepen their growth curve.

Our DCF-based methodology continues to value CTSO at $15/share.

FINANCIAL MODEL

CytoSorbents Inc.

	2018 A	Q1E	Q2E	Q3E	Q4E	2019 E	2020 E	2021 E
CytoSorb Sales	$20,252.4	$5,639.3	$6,221.7	$7,258.9	$7,874.2	$26,994.1	$40,036.0	$54,772.0
y-o-y growth	*51.3%*	*27.2%*	*18.6%*	*42.3%*	*43.9%*	*33.3%*	*48.3%*	*36.8%*
Total Royalties/Grants/Other	$2,251.5	$606.0	$515.0	$420.0	$445.0	$1,986.0	$1,830.0	$2,282.0
y-o-y growth	*27.2%*	*23.3%*	*1.0%*	*-34.4%*	*-27.1%*	*-11.8%*	*-7.9%*	*24.7%*
Revenue	$22,503.9	$6,245.3	$6,736.7	$7,678.9	$8,319.2	$28,980.1	$41,866.0	$57,054.0
YOY Growth	*48.5%*	*26.8%*	*17.0%*	*33.7%*	*36.8%*	*28.8%*	*44.5%*	*36.3%*
Cost of Goods Sold	$7,489.4	$1,900.0	$1,897.6	$2,017.6	$1,982.0	$7,797.2	$9,053.7	$11,912.8
Gross Income	$15,014.5	$4,345.2	$4,839.1	$5,661.3	$6,337.2	$21,182.9	$32,812.3	$45,141.2
Gross Margin	*66.7%*	*69.6%*	*71.8%*	*73.7%*	*76.2%*	*73.1%*	*78.4%*	*79.1%*
SG&A	$22,876.5	$6,312.1	$6,741.2	$6,558.7	$7,395.4	$27,007.4	$28,305.5	$31,986.8
SG&A % of Prod Sales	*113.0%*	*111.9%*	*108.3%*	*90.4%*	*93.9%*	*100.0%*	*70.7%*	*58.4%*
R&D	$7,723.0	$2,322.2	$2,399.7	$2,451.7	$2,587.9	$9,761.5	$9,541.2	$9,687.5
R&D % Tot Sales	*34.3%*	*37.2%*	*35.6%*	*31.9%*	*31.1%*	*33.7%*	*22.8%*	*17.0%*
Operating Income	($15,585.0)	($4,289.1)	($4,301.8)	($3,349.1)	($3,646.1)	($15,586.0)	($5,034.3)	$3,466.9
Operating Margin	-	-	-	-	-	-	-	
Total Other Expense	$2,245.7	$375.3	$359.7	$312.8	$288.5	$1,336.2	$1,318.6	$1,010.2
Pre-Tax Income	($17,830.7)	($4,664.4)	($4,661.4)	($3,661.8)	($3,934.6)	($16,922.2)	($6,352.9)	$2,456.7
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)	($4,664.4)	($4,661.4)	($3,661.8)	($3,934.6)	($16,922.2)	($6,352.9)	$2,456.7
Net Margin	*-76.5%*	*-74.7%*	*-69.2%*	*-47.7%*	*-47.3%*	*-58.4%*	*-15.2%*	*4.3%*
EPS	($0.56)	($0.15)	($0.14)	($0.11)	($0.11)	($0.51)	($0.17)	$0.06
YOY Growth		-	-	-	-			
Diluted Shares O/S	30,719	31,850	32,400	33,500	34,250	33,000	37,200	39,800

Brian Marckx, CFA

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Appendix: Summary of Recent Clinical Studies in Various Indications

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

REFRESH I Refresher

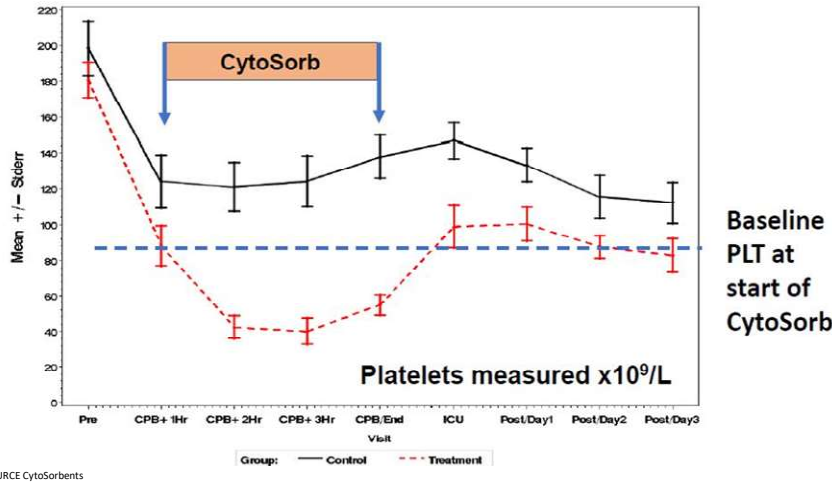
As a reminder, REFRESH I was a multi-site 40+-patient randomized study comparing CytoSorb plus standard-of-care (SOC) to SOC alone (1:1) in the reduction of free hemoglobin in patients undergoing elective complex cardiac surgery requiring cardiopulmonary bypass with anticipated duration of more than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

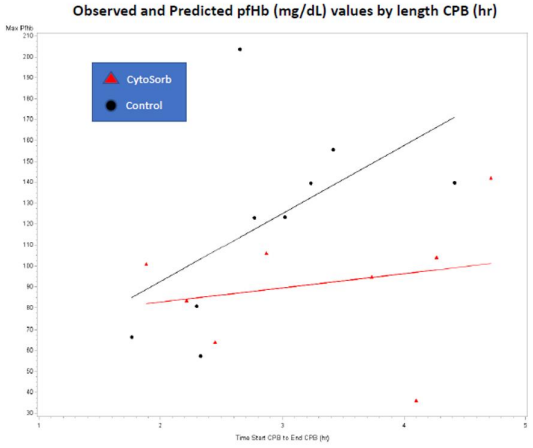
SOURCE CytoSorbents

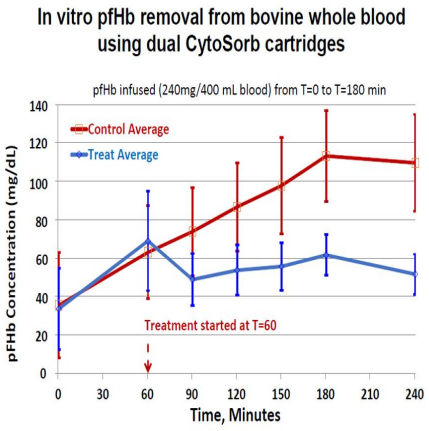
Valve replacement patients in the CytoSorb group fared better as it relates to PfHb levels. Among those patients in REFRESH I that underwent valve replacement surgery that lasted between 3 and 4.5 hours, CytoSorb demonstrated a statistically significant reduction in plasma free hemoglobin as compared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

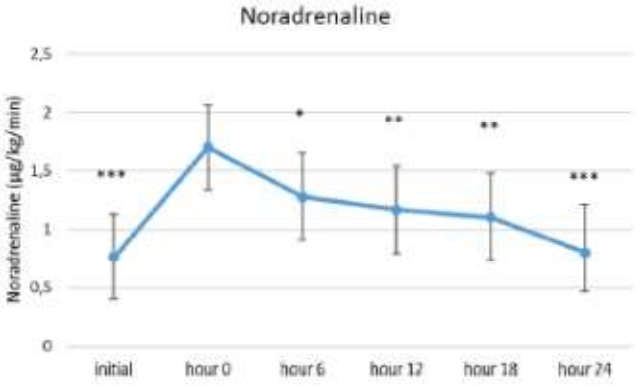


Fig. 1 Noradrenaline dose before and during treatment with CytoSorb®. Values are shown as means with 95% CIs. Difference vs. "hour 0" (CytoSorb® start): $*p < 0.05$, $**p < 0.01$, $***p < 0.001$. Initial and start $n = 20$, hour 6, 12 and 18 $n = 19$, hour 24 $n = 18$

SOURCE: Frisecke S., et al

Secondary Endpt: Significant Increase in Lactate Clearance

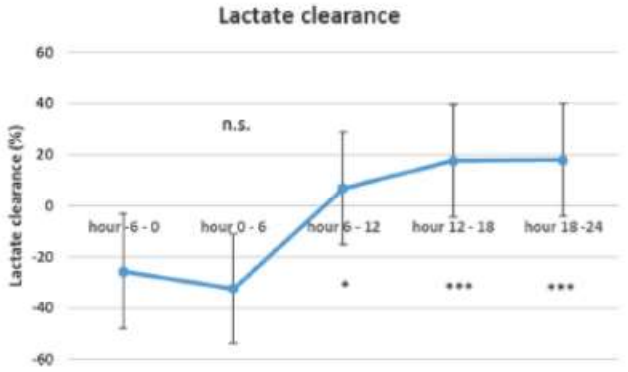


Fig. 2 Lactate clearance before and during treatment with CytoSorb®. Values are shown as means with 95% CIs. Difference vs. "hour -6 - 0" (6 h before CytoSorb® start): $*p < 0.05$, $***p < 0.001$, *n.s.* not significant

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.

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