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Zacks Small-Cap Research

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CytoSorbents Corporation (CTSO-NASDAQ)

CTSO: Germany Reimbursement Rebounds, Drives Strong Record Product

Based on our 10-year DCF model, which uses a 13% discount rate to account for certain risks and uncertainties that CytoSorbents faces, and a 2% terminal growth rate, the shares are valued at approximately $12.

Current Price (08/11/17)	$6.48
Valuation	**$12.00**

OUTLOOK

Product sales returned to growth – on both a yoy and sequential basis and set a new record high, eclipsing the previous best by 13%. The recent inflection in product sales is encouraging given that they edged down from Q4 '16 to Q1 '17 – which was attributed to a change in reimbursement in Germany. At that time, management indicated that they expected the issue would dissipate with availability of the new (i.e. higher) payment rates in that country. Indications, including results of a survey (about reimbursement) of some of CTSO's key German accounts as well as an increase in rates by as much as 100% in some locations, suggest that is what has happened. Certainly, the sequential revenue growth also supports that same theme - product revenue grew 17% from Q1 to Q2 and another 13% from Q2 to Q3.

There was not much in the way of an update related to the REFRESH studies on the last two earnings calls although Dr. Chan did note on the Q3 call that they have met with FDA to discuss REFRESH II's proposed trial design and that they will make an announcement when more information becomes available. CTSO still hopes to kick-off REFRESH II this year.

SUMMARY DATA

52-Week High	**$6.70**
52-Week Low	**$3.30**
One-Year Return (%)	**20.19**
Beta	**-0.59**
Average Daily Volume (sh)	**196,924**
Shares Outstanding (mil)	**29**
Market Capitalization ($mil)	**$185**
Short Interest Ratio (days)	**N/A**
Institutional Ownership (%)	**6**
Insider Ownership (%)	**6**
Annual Cash Dividend	**$0.00**
Dividend Yield (%)	**0.00**
5-Yr. Historical Growth Rates	
Sales (%)	**55.1**
Earnings Per Share (%)	**N/A**
Dividend (%)	**N/A**
P/E using TTM EPS	**N/A**
P/E using 2017 Estimate	**N/A**
P/E using 2018 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)
2016	1810 A	2222 A	2412 A	3083 A	9528 A
2017	3114 A	3566 A	3824 A	3850 E	14354 E
2018					21253 E
2019					30676 E

Earnings per Share

	Q1 (Mar)	Q2 (Jun)	Q3 (Sep)	Q4 (Dec)	Year (Dec)
2016	-0.08 A	-0.12 A	-0.11 A	-0.17 A	-0.47 A
2017	-0.05 A	-0.04 A	-0.07 A	-0.09 E	-0.26 E
2018					-0.36 E
2019					-0.19 E

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

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Q3 Financials / Operating Update: *Germany Reimbursement Rebounds, Drives Strong Record Product Sales…*

CytoSorbents reported financial results for their third quarter ending September 30th and provided a business update. Product sales returned to growth – on both a yoy and sequential basis and set a new record high, eclipsing the previous best (Q2 2017) by 13% and beating our estimate by a healthy 10%. The recent inflection in product sales is encouraging given that they edged down from Q4 '16 to Q1 '17 – which was attributed to a change in reimbursement in Germany. At that time, management indicated that they expected the issue would dissipate with availability of the new (i.e. higher) payment rates in that country.

Indications, including results of a survey (about reimbursement) of some of CTSO's key German accounts as well as an increase in rates by as much as 100% in some locations, suggest that is what has happened. Certainly, the sequential revenue growth also supports that same theme - product revenue grew 17% from Q1 to Q2 and another 13% from Q2 to Q3.

While we think the potential for qoq volatility in product sales remains, we also continue to believe product sales will trend higher given several catalysts which we have discussed in prior updates. These include the improved reimbursement picture in Germany, continued robust product sales growth from existing distributors OG (i.e. outside of Germany), recently established distribution in new territories and initial roll-out of the Fresenius co-marketing agreement. Additionally, new product launches, such as the recently-introduced ECMO kit could provide incremental upside. And, with ~60 investigator initiated studies either ongoing or planned as well as potential near-term publication of the REFRESH I data, there should be a regular flow of additional clinical and outcomes data to help further enhance the marketing message.

Financials…

Total revenue was $3.8M, up 59% yoy, up 7% sequentially and 4% higher than our $3.7M estimate. Product revenue came in at $3.5M, up 61% yoy and 13% sequentially. Grant income was $376k.

While most of the revenue-related focus is and should be on product sales, we think it's relevant to point to a trend related to grants. Not only has grant income been robust as of late, it continues to trend higher. Through the first nine months of 2017 CTSO recorded $1.4M in grant-related revenue – which is more than any prior full-year period. Perhaps, even more significant is that the company currently has ongoing contracts with more than $2.7M of funding remaining. Beyond subsidizing R&D, we think the fact that the list of contracts from U.S. government agencies continues to grow provides additional validation of the potential of CTSO's technology. These also may presumably result in new technology that could provide some optionality in terms of commercial programs that CTSO could pursue.

The last three most recent grant awards are funded by the United States Army Medical Research Acquisition Activity (USAMRAA), including two in May and one in September. This includes funding of up to $999k over two years for a phase II contract related to the development of HemoDefend in enabling universal plasma. The other one awarded in May is a phase I contract which will pay up to $719k over four years and relates to novel hemoadsorptive therapies for severe burn injuries. Then in September a phase II SBIR contract worth up to $1M was awarded – this relates to the development of potassium binding sorbents to be used in the treatment of traumatic injury and acute kidney injury – this contract follows the related phase I grant that CTSO scored in July 2016.

Relative to product sales, much of the growth has been attributed to improved reimbursement in Germany. 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. 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.

As we explained in our Q1 update, we felt that since we viewed Germany as CTSO's most important territory relative to both near-term sales as well as opportunity for growth, that it was important that any reimbursement-related headwind be rectified so as to not create a long-term hangover. Management's comments on both the Q2 and Q3 calls indicating that reimbursement in that country has significantly increased from earlier in 2017, and may further broaden throughout additional hospitals, and coupled with the strong sequential product revenue growth, is highly encouraging in that regard.

Product margin, at 69%, was also a highlight. In fact, we looked back through our historical models and it appears that this is the highest in recent history and second highest of all time (Q3 2013 hit 71%). Management again cited the mix of direct versus distributor sales as the main influence to product margin. This compares to 65% in Q2 2017 and 68% in Q3 2016. With a new manufacturing facility slated to come online in early 2018, management expects efficiencies to result in further improvement in product margin – they are guiding for gross margin to grow to 70% or better in 2018 and have additional future upside from there.

Operating expenses were $4.5M, roughly flat from Q2 although up about $1M from the prior-year comparable period. Similar to Q2 of this year, the increase from the prior year period relates almost entirely to higher (non-cash) stock compensation. Excluding the increase in stock comp, operating expenses were actually about $500k lower than our estimate.

While R&D expenses, which have averaged ~$500k per quarter through the first three quarters of 2017, remains relatively low (as a result of the conclusion of REFRESH I), we expect these expenses to climb with commencement of REFRESH II (which could potentially happen prior to current year-end). As it relates to SG&A – we continue to model this line to grow at a lower than historical rate as compared to revenue given leverage of certain fixed costs which should also help to improve profitability.

Cash used in operating activities was $2.2M and $6.1M ($1.4M and $4.5M, ex-changes in working capital) in the three and nine months ending 9/30/2017, respectively. Cash balance, recently bolstered by $1.5M raise from the sale of common equity (via ATM), was $15.4M at quarter-end. Subsequently, another $1.1M was raised via the ATM. CTSO expects current cash balance to fund operations into 2019.

Operational Update: REFRESH II Could Start By Year-End, Add'l Evidence of CytoSorb's Efficacy…

REFRESH: On June 1st, Dr. Eric Mortensen, MD, PhD joined CTSO as their new Chief Medical Officer. He is now in charge of leading the clinical programs including the U.S. cardiac surgery studies. There was not much in the way of an update related to the REFRESH studies on the last two earnings calls although Dr. Chan did note on the Q3 call that they have met with FDA to discuss REFRESH II's proposed trial design and that they will make an announcement when more information becomes available. Specifics in terms of the proposed trial design have not been made public, although Dr. Chan did provide some insight including that;

- they plan to pursue a primary endpoint that would drive adoption of CytoSorb (for use during cardiac surgery) and one that insurers would reimburse for. Clearly the implication is that they want to be able to show a clinical benefit (as opposed to, for example, a sole focus on reduction in free hemoglobin)
- study is expected to focus on valve replacement surgeries (i.e. longer duration, higher risk)

Management still hopes to have IDE approval from FDA in relatively short-order and have the study started before current year-end. But, given that there is only ~six weeks left in the year and holidays are usually not the most productive time for government agencies, we think that it is not unlikely commencement of REFRESH II will not happen until sometime next year.

As a refresher, we have included results of REFRESH I (along with our related commentary) below.

CAR-T Cell Cancer Therapy Opportunity: the feasibility of CytoSorb as a treatment for cytokine release syndrome (CRS) could soon become more clear given the recent FDA 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.[1] 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

[1] 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.

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. Another factor that could play in CTSO's favor is the fact that Dr. June Carter, who recently joined CytoSorbents' scientific advisory board, also led the CTL019 (i.e. Kymriah) program at the University of Pennsylvania.

Novartis and Gilead are also seeking approval in Europe, which could come in short-order. At that point, CytoSorb could be employed to treat CRS. CTSO would likely pursue investigator-initiated studies overseas, as they have done with other indications, in order to build the experience database – which, assuming positive results, could drive adoption of CytoSorb for CRS. Given the extraordinary efficacy already seen with these two initial therapies and the recent and growing massive inflow of investment dollars targeting immunotherapy development, this is an application that we think, if validated, could hold enormous growth potential for CTSO.

Add'l Clinical Evidence Indicates CytoSorb Associated w/ Improved Outcomes in Sepsis, Cardiac Surgery

CytoSorbents recently announced the publication of two unrelated studies (one in sepsis, the other in cardiac surgery), data from both of which provided additional evidence of CytoSorb's utility in, and relationship with, removing cytokines and other inflammatory mediators from circulation and improved patient outcomes.

CytoSorb Used in Refractory Septic Shock Patients: *Indicates Improved Survival vs. Standard of Care…*

Published in September in the Journal of Artificial Organs, *Extracorporeal cytokine elimination as rescue therapy in refractory septic shock: a prospective single-center study*[2] (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[3] 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.

[2] 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
[3] 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.

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)
    - 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

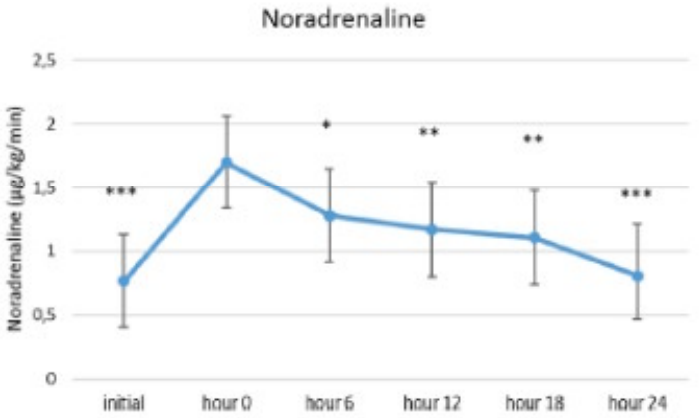

Fig. 1 Noradrenaline dose before and during treatment with CytoSorb®. Values are shown as means with 95% CIs. Difference vs. "hour 0" (CytoSorb® start): $*p < 0.05$, $**p < 0.01$, $***p < 0.001$. Initial and start $n = 20$, hour 6, 12 and 18 $n = 19$, hour 24 $n = 18$

SOURCE: Frisecke S., et al

Secondary Endpt: Significant Increase in Lactate Clearance

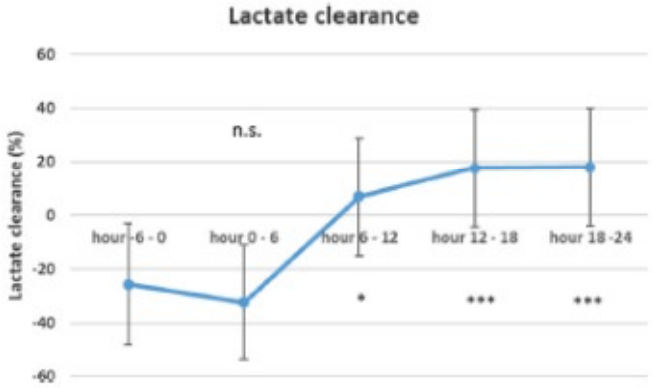

Fig. 2 Lactate clearance before and during treatment with CytoSorb®. Values are shown as means with 95% CIs. Difference vs. "hour -6 - 0" (6 h before CytoSorb® start): $*p < 0.05$, $***p < 0.001$, *n.s.* not significant

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.

Add'l Support for CytoSorb During Valve Replacement Cardiac Surgery: ***Infective Endocarditis Rates Rising…***
A manuscript of a retrospective case series involving 39 patients with infective endocarditis undergoing valve replacement surgery using CytoSorb was published in May 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.[4]

As a reminder, in addition to plasma free hemoglobin, results from REFRESH I showed CytoSorb use was also associated with significant reductions in the activated complements C3a and C5a, high levels of which are also associated with poor outcomes. CytoSorbents has yet to finalize design of REFRESH II but has indicated that they will look to enrich for procedures for which CytoSorb may provide the greatest incremental benefit. Valve replacement surgery is clearly a front-runner in that regard – results of this infective endocarditis (procedural growth of which is growing as a result of the opioid epidemic) seem to further support that consideration.

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

REFRESH Refresher…

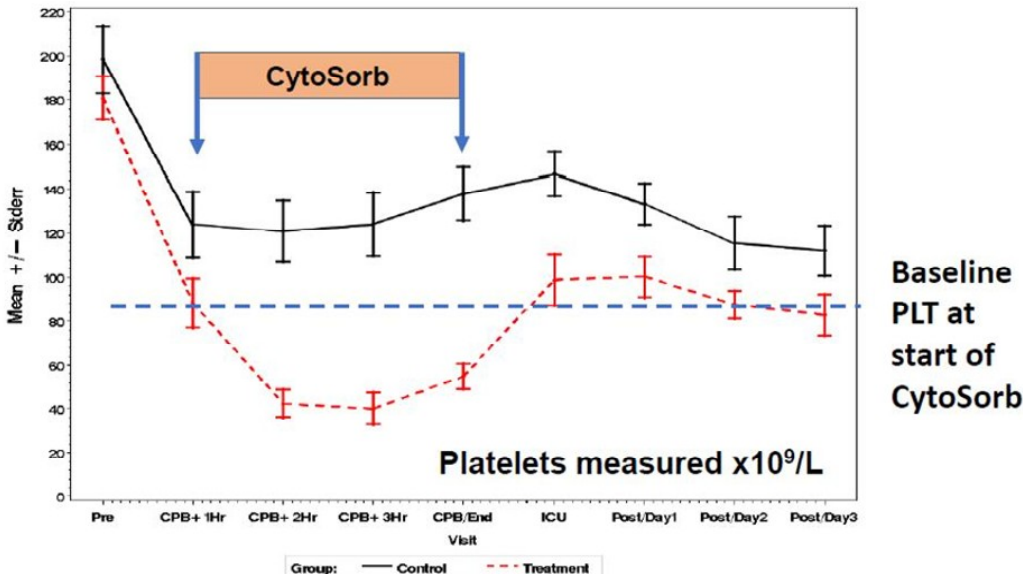
As a reminder, REFRESH I was a multi-site 40+-patient randomized study comparing CytoSorb plus standard-of-care (SOC) to SOC alone (1:1) in the reduction of free hemoglobin in patients undergoing elective complex cardiac surgery requiring cardiopulmonary bypass with anticipated duration of more than 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….
A clinical study by Windsant, et al. indicated that hemolysis (including plasma free hemoglobin) during cardiac surgery is a contributor to postoperative kidney injury.[5] 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

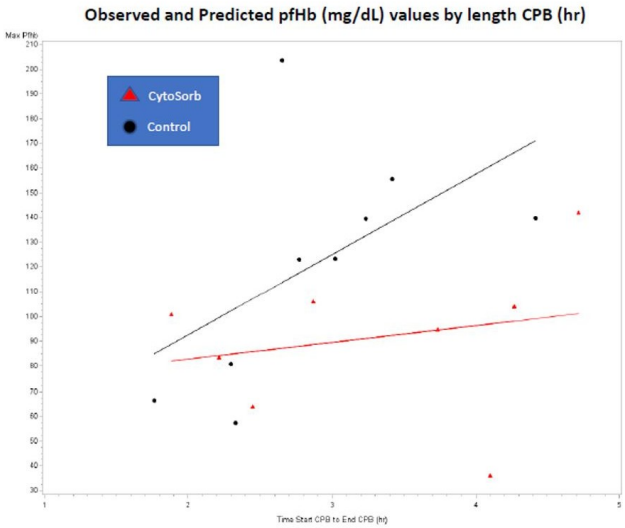
Valve replacement patients in the CytoSorb group fared better as it relates to PfHb levels. Among those patients in REFRESH I that underwent valve replacement surgery that lasted between 3 and 4.5 hours, CytoSorb demonstrated a statistically significant reduction in plasma free hemoglobin as compared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

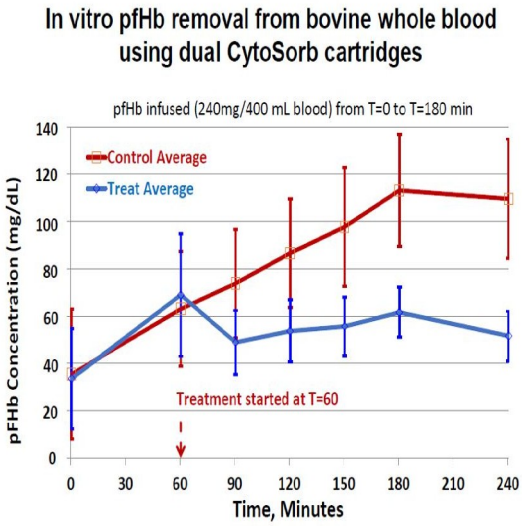
CPB Length	Mean Reduction of pfHb (mg/dL)	P-value
3.0	35 mg/dL	0.09
3.5	48 mg/dL	0.05
4.0	61 mg/dL	0.05
4.5	74 mg/dL	0.07

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.

[5] 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





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.

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 is expected to build on those findings. While the REFRESH II study design has yet to be finalized and could change based on findings from REFRESH I and interaction with FDA, management provided their current thoughts related to that topic on recent earnings calls. Included is;

- N = 300-500
- enriching for procedures associated with high PfHb – such as valve replacement surgery
- primary endpoint: outcomes-related endpoint such as acute kidney injury, organ function or possibly a composite endpoint

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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 Q1 sales growth given that some hospitals in Germany may have delayed purchasing as they still awaited reimbursement amounts, that headwind appears to have begun to reverse with both Q2 and Q3 showing strong sequential product sales growth. If reimbursement expands to other parts of Europe, that would likely provide additional upside

- **accelerating adoption in Germany**, the largest (yet still barely tapped) medical device market in Europe. 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 (in 1st 5 countries) is expected to grow to additional territories throughout 2018. This will greatly expand FMS's footprint

- **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

- **distribution/geographic expansion**: we expect additional territories and distribution agreements will continue to come online on a regular basis. Agreement with Aferetica for distribution in Italy was just extended through 2021 - CTSO believes this could generate $10M or more in sales through that time

- **clinical data / validation**: has been and continues to be the driving force behind adoption. In addition to REFRESH I, a fairly regular flow of clinical data from case studies and investigator-initiated trials should be forthcoming. CytoSorb has now been used in more than 30k human treatments – up from 17k one-year ago

- **increasing use in a number of critical care applications** where CytoSorb has been associated with positive patient outcomes including sepsis

- **ECMO kit launch**: provides seamless and rapid connection of CytoSorb to extracorporeal membrane oxygenation. CTSO noted on the Q2 2017 call (August) that CytoSorb had been used more than 1k times with ECMO

- **increased capacity**: a new manufacturing facility, which is expected to increase capacity to support up to $80M in sales, is expected to come online in Q1 2018

Valuation

We expect to see continued strength in product sales growth through 2018, as well as more strides on the operational front. We see several catalysts that begin to make either an initial or a greater impact including 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 have made only minor adjustments to our model following Q3 results. We now look for 2017 and 2018 revenue of $14.4M and $21.3M (revised from $14.2M and $21.1M).

We show CTSO nearly reaching GAAP full-year operating profitability in our out-year (2020) in our model and also believe management's guidance of reaching a level of break-even operating profitability (excluding clinical trial-related and non-cash expenses) in 2018 is also achievable. We note that we do not currently model any contribution from potential cancer-related applications - as such, eventual validation for such an indication would likely provide upside to our estimates (and possibly our price target as well).

Based on our 10-year DCF model, which uses a 13% discount rate to account for certain risks and uncertainties that CytoSorbents faces, and a 2% terminal growth rate, the shares are valued at approximately $12.

FINANCIAL MODEL

CytoSorbents Inc.

	2016 A	Q1A	Q2A	Q3A	Q4E	2017 E	2018 E	2019 E	2020 E
CytoSorb Sales	$8,206.1	$2,596.1	$3,041.0	$3,448.7	$3,366.5	$12,452.3	$19,690.0	$29,516.0	$41,700.0
y-o-y growth	102.9%	62.5%	64.1%	60.9%	28.8%	51.7%	58.1%	49.9%	41.3%
Total Royalties/Grants/Other	$1,321.8	$517.4	$525.2	$375.6	$483.0	$1,902.0	$1,563.0	$1,160.0	$1,005.0
y-o-y growth	76.8%	143.2%	42.1%	39.9%	2.6%	43.9%	-17.8%	-	-
Revenue	$9,527.9	$3,113.5	$3,566.2	$3,824.3	$3,849.5	$14,353.5	$21,253.0	$30,676.0	$42,705.0
YOY Growth	98.8%	72.0%	60.5%	58.6%	24.8%	50.6%	48.1%	44.3%	39.2%
Cost of Goods Sold	$3,953.8	$1,254.5	$1,482.0	$1,516.9	$1,574.9	$5,828.3	$7,038.7	$9,102.9	$11,904.8
Gross Income	$5,574.1	$1,859.0	$2,084.2	$2,307.4	$2,274.6	$8,525.3	$14,214.4	$21,573.1	$30,800.3
Gross Margin	58.5%	59.7%	58.4%	60.3%	59.1%	59.4%	66.9%	70.3%	72.1%
SG&A	$12,282.7	$2,947.0	$3,927.5	$3,918.5	$3,961.0	$14,754.0	$17,445.3	$20,690.7	$24,728.1
SG&A % of Prod Sales	149.7%	113.5%	129.2%	113.6%	117.7%	118.5%	88.6%	70.1%	59.3%
R&D	$4,783.5	$469.5	$487.6	$537.9	$622.4	$2,117.5	$7,287.0	$6,956.0	$7,295.0
R&D % Tot Sales	50.2%	15.1%	13.7%	14.1%	16.2%	14.8%	34.3%	22.7%	17.1%
Operating Income	($11,492.1)	($1,557.5)	($2,330.9)	($2,149.0)	($2,308.8)	($8,346.2)	($10,518.0)	($6,073.6)	($1,222.9)
Operating Margin	-	-	-	-	-	-	-	-	-
Total Other Expense	$765.3	($179.5)	($1,214.5)	($94.8)	$249.6	($1,239.2)	$772.8	$361.1	$44.1
Pre-Tax Income	($12,257.3)	($1,378.0)	($1,116.4)	($2,054.3)	($2,558.4)	($7,107.1)	($11,290.8)	($6,434.7)	($1,267.0)
Taxes (benefit)	($318.6)	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0
Tax Rate	2.6%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
Preferred Dividend	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0
Net Income	($11,938.8)	($1,378.0)	($1,116.4)	($2,054.3)	($2,558.4)	($7,107.1)	($11,290.8)	($6,434.7)	($1,267.0)
Net Margin	-125.3%	-44.3%	-31.3%	-53.7%	-66.5%	-49.5%	-53.1%	-21.0%	-3.0%
EPS	($0.47)	($0.05)	($0.04)	($0.07)	($0.09)	($0.26)	($0.36)	($0.19)	($0.04)
YOY Growth		-	-	-	-				
Diluted Shares O/S	25,433	25,504	27,954	28,206	28,600	27,566	31,500	33,500	34,500

Brian Marckx, CFA

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