Zacks Small-Cap Research

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CytoSorbents Corporation (CTSO-NASDAQ)

CTSO: Additional Evidence Supporting CytoSorb in Sepsis and Cardiac Surgery

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 (10/26/17)	$6.05
Valuation	**$12.00**

OUTLOOK

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

Published in September in the Journal of Artificial Organs, *Extracorporeal cytokine elimination as rescue therapy in refractory septic shock: a prospective single-center study* (Germany) evaluated the use of CytoSorb treatment in 20 patients with refractory septic shock.

Meanwhile, 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.

Results from these types of studies have been instrumental in helping guide the company in making informed decisions relative to how best to proceed relative to sepsis and cardiac surgery clinical programs.

SUMMARY DATA

52-Week High	**$6.70**
52-Week Low	**$3.30**
One-Year Return (%)	**2.54**
Beta	**-0.52**
Average Daily Volume (sh)	**146,815**
Shares Outstanding (mil)	**28**
Market Capitalization ($mil)	**$170**
Short Interest Ratio (days)	**N/A**
Institutional Ownership (%)	**7**
Insider Ownership (%)	**6**
Annual Cash Dividend	**$0.00**
Dividend Yield (%)	**0.00**
5-Yr. Historical Growth Rates	
Sales (%)	**59.7**
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	3664 E	3877 E	14221 E
2018					21078 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 E	-0.09 E	-0.26 E
2018					-0.34 E
2019					-0.20 E

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

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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*[1] (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 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[2] 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)
    - 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

[1] 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
[2] 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.

Primary Endpoint: Significant Reduction in Vasopressors

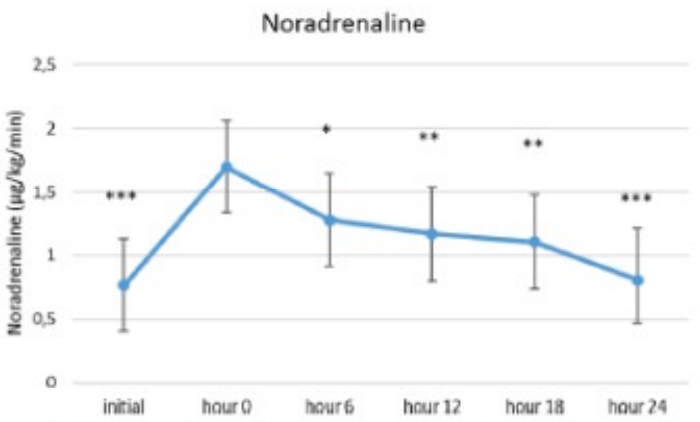


Fig. 1 Noradrenaline dose before and during treatment with CytoSorb®. Values are shown as means with 95% CIs. Difference vs. "hour 0" (CytoSorb® start): $*p < 0.05$, $**p < 0.01$, $***p < 0.001$. Initial and start $n = 20$, hour 6, 12 and 18 $n = 19$, hour 24 $n = 18$

SOURCE: Frisecke S., et al

Secondary Endpt: Significant Increase in Lactate Clearance

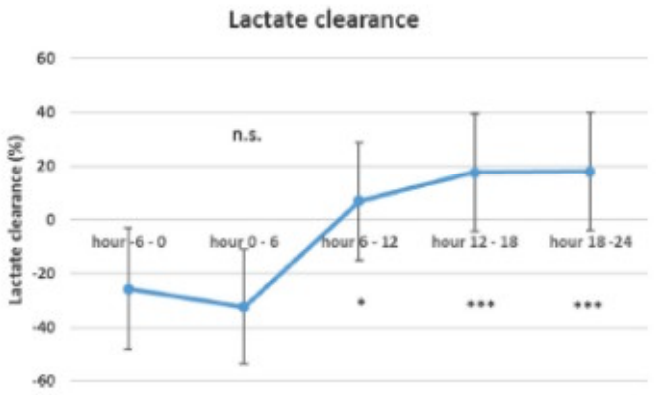


Fig. 2 Lactate clearance before and during treatment with CytoSorb®. Values are shown as means with 95% CIs. Difference vs. "hour -6 - 0" (6 h before CytoSorb® start): $*p < 0.05$, $***p < 0.001$, *n.s.* not significant

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.[3]

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.

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

FINANCIAL MODEL

CytoSorbents Inc.

	2016 A	Q1A	Q2A	Q3E	Q4E	2017 E	2018 E	2019 E	2020 E
CytoSorb Sales	$8,206.1	$2,596.1	$3,041.0	$3,136.4	$3,366.5	$12,140.0	$19,690.0	$29,516.0	$41,700.0
y-o-y growth	*102.9%*	*62.5%*	*64.1%*	*46.3%*	*28.8%*	*47.9%*	*62.2%*	*49.9%*	*41.3%*
Total Royalties/Grants/Other	$1,321.8	$517.4	$525.2	$528.0	$510.0	$2,080.0	$1,388.0	$1,160.0	$1,005.0
y-o-y growth	*76.8%*	*143.2%*	*42.1%*	*96.6%*	*8.3%*	*57.4%*	*-33.3%*	-	-
Revenue	$9,527.9	$3,113.5	$3,566.2	$3,664.4	$3,876.5	$14,220.6	$21,078.0	$30,676.0	$42,705.0
YOY Growth	*98.8%*	*72.0%*	*60.5%*	*51.9%*	*25.7%*	*49.3%*	*48.2%*	*45.5%*	*39.2%*
Cost of Goods Sold	$3,953.8	$1,254.5	$1,482.0	$1,499.3	$1,536.3	$5,772.1	$7,086.8	$9,398.1	$12,321.8
Gross Income	$5,574.1	$1,859.0	$2,084.2	$2,165.1	$2,340.2	$8,448.5	$13,991.2	$21,277.9	$30,383.3
Gross Margin	*58.5%*	*59.7%*	*58.4%*	*59.1%*	*60.4%*	*59.4%*	*66.4%*	*69.4%*	*71.1%*
SG&A	$12,282.7	$2,947.0	$3,927.5	$3,427.0	$3,884.0	$14,185.5	$16,579.0	$20,690.7	$24,728.1
SG&A % of Prod Sales	*149.7%*	*113.5%*	*129.2%*	*109.3%*	*115.4%*	*116.8%*	*84.2%*	*70.1%*	*59.3%*
R&D	$4,783.5	$469.5	$487.6	$584.0	$748.0	$2,289.2	$7,287.0	$6,956.0	$7,295.0
R&D % Tot Sales	*50.2%*	*15.1%*	*13.7%*	*15.9%*	*19.3%*	*16.1%*	*34.6%*	*22.7%*	*17.1%*
Operating Income	($11,492.1)	($1,557.5)	($2,330.9)	($1,845.9)	($2,291.8)	($8,026.1)	($9,874.8)	($6,368.8)	($1,639.9)
Operating Margin	-	-	-	-	-	-	-	-	-
Total Other Expense	$765.3	($179.5)	($1,214.5)	$249.6	$249.6	($894.8)	$772.8	$361.1	$44.1
Pre-Tax Income	($12,257.3)	($1,378.0)	($1,116.4)	($2,095.5)	($2,541.4)	($7,131.3)	($10,647.6)	($6,729.9)	($1,684.0)
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)	($2,095.5)	($2,541.4)	($7,131.3)	($10,647.6)	($6,729.9)	($1,684.0)
Net Margin	*-125.3%*	*-44.3%*	*-31.3%*	*-57.2%*	*-65.6%*	*-50.1%*	*-50.5%*	*-21.9%*	*-3.9%*
EPS	($0.47)	($0.05)	($0.04)	($0.07)	($0.09)	($0.26)	($0.34)	($0.20)	($0.05)
YOY Growth		-	-	-	-				
Diluted Shares O/S	25,433	25,504	27,954	28,200	28,600	27,564	31,500	33,500	34,500

Brian Marckx, CFA

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