Zacks Small-Cap Research

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Medgenics Inc (MDGN-AMEX)

MDGN: Highly Promising Prelim MDGN-201 Data

Current Recommendation	**Outperform**
Prior Recommendation	N/A
Date of Last Change	06/08/2014
Current Price (10/16/14)	$5.09
Target Price	**$15.00**

OUTLOOK

New management team brought on in late 2013 with goal of accelerating development of flagship Biopump technology for orphan and rare diseases. Biopump, a novel ex-vivo gene therapy which uses the patient's own skin to produce and deliver proteins/peptides, has significant advantages over traditional gene therapies. Initial clinical studies demonstrated efficacy and excellent safety. With proof-of-concept accomplished, Biopump is being further validated in a recently initiated phase I/II study - preliminary data from which was very promising. Rare/orphan disease markets are particularly attractive due to certain incentives and inherent economics. Clinical development may also be accomplished faster, cheaper and with lower risk.

SUMMARY DATA

52-Week High	**$9.00**
52-Week Low	**$4.71**
One-Year Return (%)	**-17.87**
Beta	**0.94**
Average Daily Volume (sh)	**78,022**
Shares Outstanding (mil)	**19**
Market Capitalization ($mil)	**$94**
Short Interest Ratio (days)	**12.20**
Institutional Ownership (%)	**12**
Insider Ownership (%)	**26**
Annual Cash Dividend	**$0.00**
Dividend Yield (%)	**0.00**
5-Yr. Historical Growth Rates	
Sales (%)	**N/A**
Earnings Per Share (%)	**N/A**
Dividend (%)	**N/A**
P/E using TTM EPS	**N/A**
P/E using 2014 Estimate	**N/A**
P/E using 2015 Estimate	**N/A**
Zacks Rank	**N/A**

Risk Level	**Above Avg.,**
Type of Stock	**Small-Growth**
Industry	**Med-Biomed/Gene**

ZACKS ESTIMATES

Revenue
(in '000s of $)

	Q1 (Mar)	Q2 (Jun)	Q3 (Sep)	Q4 (Dec)	Year (Dec)
2013	0 A	0 A	0 A	0 A	0 A
2014	0 A	0 A	0 E	0 E	0 E
2015					0 E
2016					0 E

Earnings per Share

	Q1 (Mar)	Q2 (Jun)	Q3 (Sep)	Q4 (Dec)	Year (Dec)
2013	-$0.24 A	-$0.11 A	-$0.33 A	-$0.29 A	-$0.97 A
2014	-$0.28 A	-$0.21 A	-$0.16 A	-$0.27 E	-$0.92 E
2015					-$0.92 E
2016					-$0.87 E

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

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WHAT's NEW…

Highly Promising Trial Data with Next-Gen Vector, Orphan Indications Revealed. Q3 Results

On Tuesday Medgenics released financial results for Q3 and also presented the initial clinical data from the EPODURE phase I/II study using its second-generation vector. In addition, the company revealed three orphan targets that they expect to pursue - two of which are EPO-related and dovetail off of the proof-of-concept already achieved from the EPODURE preclinical and clinical studies. Human trials related to these two orphan targets are expected to commence in early-to-mid 2015.

Q3 Results, meaningfully better than our estimates…
MDGN continues to do a nice job with conserving resources as the company makes significant headway with furthering their product development programs. Q3 operating expenses were just $3.9M and, net of R&D expense offsets from grants, came down by about $200k (~4%) from Q2. Operating loss of $3.9M was much better than our $4.8M (loss) estimate. Excluding ~$800k in (non-cash) income related to revaluation of warrants, net income and EPS were approximately ($3.8)M and ($0.16), compared to our ($4.8)M and ($0.25) estimates.

Cash used in operating activities was $1.9M and $8.6M in the three and six months ending 9/30/2014. MDGN exited the quarter with $14.7M in cash and equivalents. Management expects cash burn to average roughly $1M/month which implies the current cash balance should be sufficient to fund operations until at least this time next year.

Initial 2nd-Gen Trial Data Looks Highly Promising…
On the conference call management walked through the initial results of the EPODURE phase I/II study which is using the 2nd generation viral vector.

As a reminder, a Biopump (which the company is now calling a Transduced Micro-Organ) converts a small slice of a patient's own skin (roughly the size of a toothpick) into protein-producing "micro-organ", following excision, ex-vivo processing and re-implantation into the patient. Once re-implanted, the micro-organ has shown to effectively produce and secrete targeted proteins in clinically relevant amounts and durations of time. One or more Transduced Micro-Organs can be implanted - the number of which is patient-dependent. EPODURE (which the company is now calling $TARGT_{EPO}$) is the company's proprietary erythropoietin-producing Biopump. TARGT stands for "transduced autologous restorative gene therapy".

$TARGT_{EPO}$ produces natural erythropoietin and is being evaluated in clinical studies in patients with chronic kidney disease (CKD) and end-stage renal disease (ESRD). If effective $TARGT_{EPO}$ could potentially replace erythropoietin stimulating agents (ESAs), which are injected into CKD/ESRD patients to maintain hemoglobin levels. ESAs have serious drawbacks, however, including that they are expensive, cause spikes in serum EPO levels and have been associated with cardiac risks

Initial clinical studies of $TARGT_{EPO}$, results of which were presented in 2012, used a first generation viral vector - the viral vector is a key component in processing of the Transduced Micro-Organ. While the study (n=19) showed $TARGT_{EPO}$ effectively increased EPO levels in these CKD/ESRD patients, the duration of effect was short lived and EPO levels declined below the therapeutic level within 30 days. Despite this, hemoglobin levels were maintained in the key range of 9g/dl - 11g/dl for most of the patients through three months and in almost one-half of the patients for six months. These results were considered very positive in the sense that they demonstrated proof-of-concept.

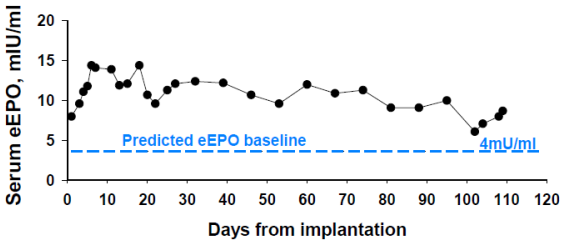
In June 2014 the company initiated a new phase 1/2 study titled: *Safety and Efficacy of Sustained Erythropoietin Therapy of Anemia in chronic Kidney Disease Patients and End-Stage Renal Disease Dialysis Patients Using EPODURE Biopump.* This study, coined MDGN-201, uses a new generation viral vector with the goal of maintaining hemoglobin in a pre-defined range (9g/dl - 12g/dl) for more than six months. It has been designed as a dose-escalating study with up to 18 patients (three cohorts of up to six patients each). Patients are removed from ESAs after a run-in period.

Initial results of this MDGN-201 study were announced yesterday (10/15/2014). And while these initial results are from just three patients (all given the lowest dose) with follow-up no longer than four months, we characterize the data as highly promising. In all three patients results showed hemoglobin levels were

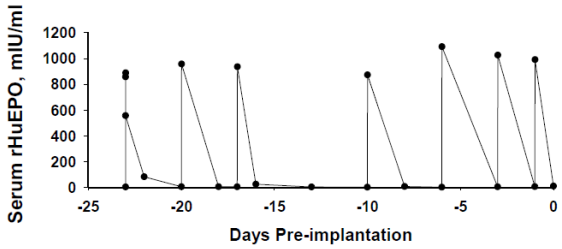
maintained in the 9g/dl - 12g/dl range and that serum EPO levels were much more well-controlled during the $TARGT_{EPO}$ therapy as compared to the run-in period when the patients were given ESA's (again, ESAs are associated with spikes and troughs of serum EPO which has been associated with potentially compromised therapeutic effect and health risks).

Serum EPO Levels Much More Constant With $TARGT_{EPO}$ Than During ESA Run-In Period

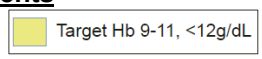
Patient #1 4-Months of $TARGT_{EPO}$ Therapy



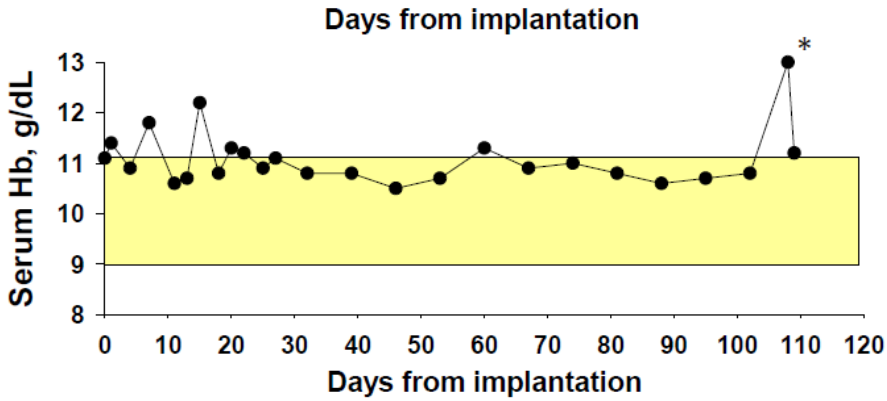
Patient #1 Run-In Period With ESA Injections



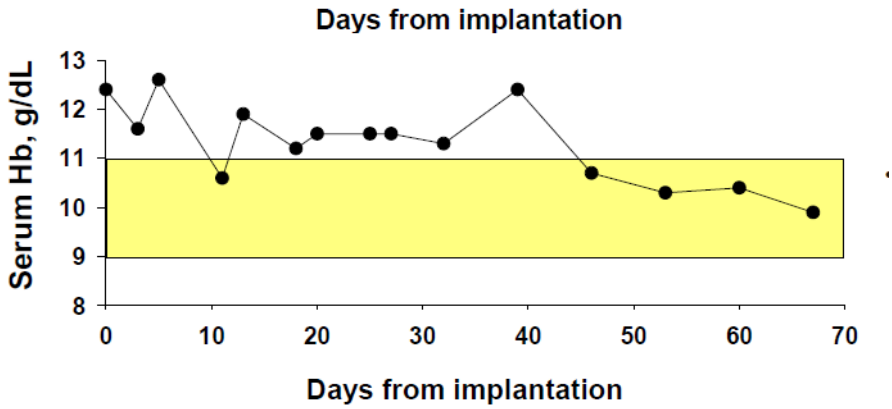
Hemoglobin Largely Maintained at 9g/dl - 12g/dl Range In All Three Patients



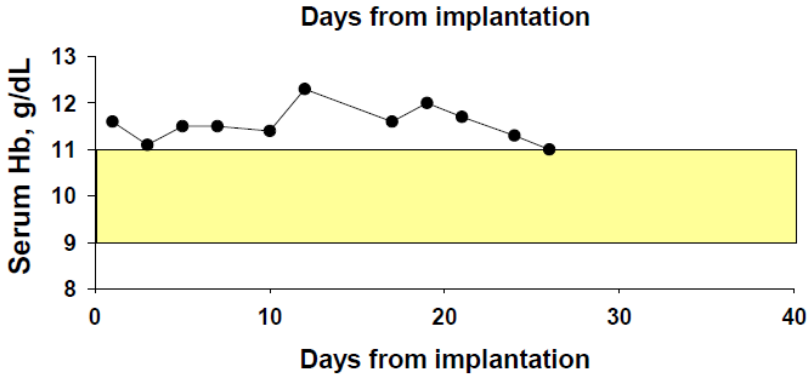
Patient #1 Four Months of $TARGT_{EPO}$ Therapy



Patient #2 Two Months of $TARGT_{EPO}$ Therapy



Patient #3 One Month of TARGT$_{EPO}$ Therapy



And while potentially still early to determine, investigators are seeing a trend of increasing reticulocytosis in patient #1 (i.e. - the one in treatment the longest, four months). Reticulocytosis is where the body starts producing more immature red blood cells and evidence of such would be a significant development as it may indicate that TARGT$_{EPO}$ therapy may help induce the body's natural function in producing red blood cells.

Additional Data Should Provide Even More Insight…
Medgenics will present this data at the European Society for Gene and Cell Therapy (ESGCT) meeting, being held in The Hague, Netherlands later this month. The trial will shortly begin enrolling another three patients - all in the lowest-dose cohort which are expected to complete enrollment by year-end. And while management noted they do not expect to hold additional investor calls when new data comes out, they do expect to present follow-on data at industry events.

As noted, we view this initial trial data with the 2nd-gen vector as highly encouraging and in fact, interpret these results as about as good as could have hoped. Along with consistent delivery of EPO and maintenance of hemoglobin in the target range, there were no adverse treatment-related safety issues. Additional positive follow-on data from both the to-be enrolled patients as well as longer-term results from these patients should provide even greater insight into the efficacy and utility of TARGT$_{EPO}$ and the Transduced Micro-Organ technology.

Orphan Targets Identified, Two of Which Are EPO Related
MDGN remains committed to their prior plan of not going after the overall EPO/ESA market targeting ESRD/CKD, which is dominated by a few well-entrenched and large pharmas including J&J, Amgen and Roche. Aside from the competition, this market has become even less attractive with changes to Medicare reimbursement which bundles the dialysis procedure with related supplies and drugs - cutting the profitability of ESA's.

Instead, and also in-line with the company's previous strategy, MDGN will look to leverage their technology in rare diseases. As we have noted in our ongoing coverage of MDGN, the worldwide orphan disease market, estimated at $50B+, looks to be particularly attractive given certain incentives that are in place that allow for shorter development, smaller clinical trials and regulatory timelines, a guaranteed term of market exclusivity and financial assistance through fee waivers, tax credits and grants. These incentives, along with the attractive commercial economics (i.e. - high selling prices and small sales force) of the rare disease market, affords the potential for high margins and profitability in just a single indication.

Exactly what that (or those) rare disease(s) were that MDGN would pursue were unknown until yesterday. The company announced that they expect to pursue two indications related to EPO, those being 1) ESRD patients that are hypo-responsive to ESAs - a U.S. population that the company estimates at approximately 40k - 70k and 2) Beta Thalassemia, a rare blood disorder associated with anemia (i.e. - low hemoglobin) and low levels of EPO. The company estimates that there are ~16k people in the U.S. and Europe combined that suffer from Beta Thalassemia.

We view the pursuit of both of these indications as making good strategic sense. Most obviously, the EPO-producing Transduced Micro-Organ, $TARGT_{EPO}$, is well on its way to being validated as safe and effective. MDGN would potentially have to make no significant changes to the technology in order to adapt it to both ESA hypo-responders as well as beta thalassemia patients. This keeps costs and risks as low while still targeting attractive markets with potential for orphan designation. For each indication the company believes they can run a 10 - 15 patient initial validation study, results of each of the studies which could be available in the first half of 2015. If results are positive, pivotal (although still small) studies would then be pursued.

ESA Hypo-Responsive…

This is a relatively small sub-group of the ~400k Americans that have ESRD and are being treated with ESAs. Hypo-responsive ESRD patients require large doses of ESAs to maintain hemoglobin levels. Hypo-responsive ESRD patients can be defined as those that need a monthly dose of ESA that is in the 90th percentile. These patients may be more susceptible to ESA-associated risks (such as cardiac risks) due to the higher dosing and the variability in serum EPO levels inherent with recombinant EPO injections. A more consistent delivery of EPO via $TARGT_{EPO}$ would reduce the serum spikes and troughs of EPO injections and potentially induce more effective hemoglobin production and maintenance.

And of course, since these patients require more ESA than a non hypo-responsive ESRD patient, cost to treat these patients is greater. MDGN estimates that it costs approximately $30k+/year to treat a hypo-responsive ESRD patient with ESAs and dialysis. We think this actually may be on the conservative side as have found estimates from different sources indicating the cost to treat an "average" ESRD patient can be $40k or more. With ~50k hypo-responsive ESRD patients in the U.S. receiving ESAs, this would equate to a market size of ~$1.5B or more. While this is just a rough estimate, it may provide a general guide for potential pricing of an eventual $TARGT_{EPO}$ product targeting the hypo-responsive ESRD market.

Beta Thalassemia…

Beta Thalassemia is a rare blood disease which reduces the body's ability to produce hemoglobin. This can have serious consequences. The disorder usually appears very early in life and often stunts weight gain and overall growth in children. Organs, including the heart and liver, and bones can also be negatively effected. People with beta thalassemia often need frequent blood transfusions to increase hemoglobin levels. Blood transfusions have certain disadvantages including the potential for; iron overload (and thus requires iron chelation therapy), antigenic differences of red blood cells between donor and patient, and infection. Blood transfusions are also costly - cost estimates for blood transfusions vary widely from $2k to $8k per procedure.

There are two types of beta thalassemia, thalassemia major and thalassemia intermedia. MDGN expects to target the thalassemia intermedia market, a population which they estimate is approximately 16k people in the U.S. and Europe combined. The company further estimates that it costs ~ $100k/year to treat a thalassemia intermedia patient (including transfusion and iron chelation costs) which calculates to a total potential market of almost $1.6B.

MDGN's $TARGT_{EPO}$ could be a viable substitute for or complement to blood transfusions that beta thalassemia patients undergo. If a complement, it could at least potentially reduce the number of transfusions.

Other Potential Applications for $TARGT_{EPO}$ …

So while hypo-responsive ESRD patients and beta thalassemia are clearly the front-runners in terms of the company's focus on rare diseases, management also talked about other potential applications for $TARGT_{EPO}$. These are 1) anemic CKD patients which are candidates for transplant 2) peritoneal dialysis patients and 3) myelodysplastic syndrome. As these are back-burner potential indications that may be pursued in the future, we will limit our discussion about these until and if there is a significant likelihood of pursuit of one or more of these potential targets.

TARGT Peptide Program…

MDGN's major focus to-date has been with protein therapy, most notably EPO. The company announced that they are now pursuing, in parallel with the EPO targets, endogenous peptides. The short half lives of small endogenous peptides provides therapeutic challenges when administered externally - including the need to use high doses and short effect. Since TARGT would produce the peptide naturally and provide a continuous flow (at the "correct" concentration), these challenges could potentially be overcome.

The company's initial focus will be on glucagon-like peptide-2 (GLP-2), which is produced naturally by the intestinal endocrine L cell and certain neurons. It promotes intestinal growth and enhances intestinal function. It's half life is approximately only 5 - 7 minutes.

MDGN expects to target short bowel syndrome, an orphan indication with $TARGT_{GLP-2}$. Short bowel syndrome (SBS) is typically the result of surgical removal of part of the small intestine as a result of a variety of disorders. SBS patients often suffer from malabsorption and may require intravenous nutrition. It is estimated that there are approximately 3k - 5k SBS patients in the U.S.

Gattex (teduglutide), marketed by NPS Pharma, is a GLP-2 analog that has orphan designation for SBS and was approved by FDA in late 2012. Gattex promotes intestinal absorption and is dosed once per day via subcutaneous injection. NPS has priced the therapy at approximately $295k per person per year. It is estimated that there are approximately 3k - 5k SBS patients in the U.S. As such the calculated potential market for Gattex is $1B+.

$TARGT_{GLP-2}$ could potentially eliminate or reduce peaks and troughs and potential related health risks associated with bolus injections. Development of $TARGT_{GLP-2}$ is in preclinical stage and has been used in mice which showed secretion of GLP-2 for a term of 60 days. MDGN will provide further development updates in the future.

BACKGROUND

TARGT Platform Technology

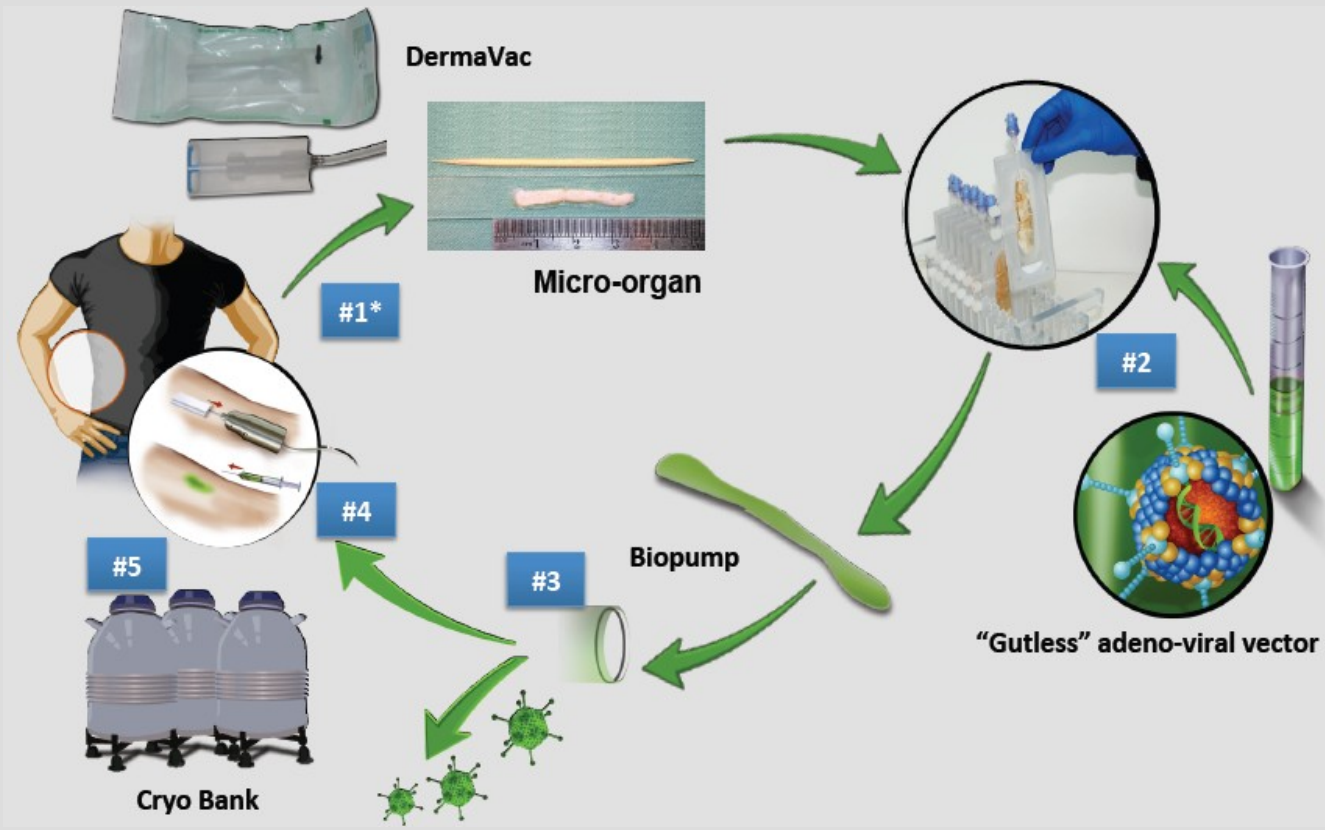
Transduced Autologous Restorative Gene Therapy (TARGT), which the company had previously called "Biopump", is a novel alternative to the frequent protein injections required to treat certain acute and chronic diseases such as anemia, HCV and others, including rare diseases. The technology is protected with 49 issued (and another 58 filed) patents.

TARGT works by converting a small slice of a patient's own skin (roughly the size of a toothpick) into protein/peptide-producing "micro-organ", following excision, ex-vivo processing and re-implantation into the patient. Once re-implanted, the micro-organ has shown to effectively produce and secrete targeted proteins in clinically relevant amounts and durations of time.

TARGT "Micro-Organ"



Treatment via TARGT is a several-step process. The following graphic and related description of each step is taken directly from Medgenics' public filings and investor presentations;



(1) **Harvesting Patient's Micro-organs (MOs)** – our proprietary device, the DermaVac, is used to extract a small piece of tissue via a form of needle biopsy from the skin's lower level – the dermis – of the patient under local anesthesia. The DermaVac positions the skin and guides a high-speed rotating hollow core needle, providing a precise and straightforward removal of the tissue. It is minimally-invasive, enabling rapid healing. After harvesting, the MOs are transferred to a Biopump processing center.

(2a) **Viral vector fluid** – the MO is placed into nutritional media containing the appropriate concentration of viral vector, which is engineered to contain the gene necessary for production of a selected protein and to effectively transfer the gene to the nuclei of the cells in the MO without integrating into the chromosomes.

(2b) **Processing each MO into a TARGT (Biopump)** – the MO is processed using the viral vector fluid, whereby the vector particles transfer the genes into the cells of the MO (transduction), thereby converting the intact tissue MO into a

Biopump protein/peptide production unit. The MOs are transferred at the harvest site in a sealed cassette and transported to a local or regional Biopump processing center..

(3a) **Measure daily protein production per Biopump for dosing** – protein production levels of each Biopump is measured to determine the correct number of Biopumps to implant into the patient in order to deliver the intended aggregate dose.

(3b) **Washing and release testing** – prior to being released for use, the Biopumps undergo a washing protocol to remove all of the residual unabsorbed vector and undergo testing to verify they meet release criteria for use.

(4) **Implantation** the Biopumps are transported to the treatment center for implantation in the patient. The calculated number of Biopumps are implanted back into the patient, whereby they produce and deliver the required protein to the subject patient's body.

(5) **Additional MOs or Biopumps not implanted in the patient can be cryostored for future use**

The DermaVac harvesting device allows for efficient removal of micro-organs. To-date MDGN has produced more than 20k Biopumps from in-vitro "tummy tuck" tissue and in clinical trials has demonstrated that the Biopumps produced from the MO's can safely deliver predetermined proteins over a sustained period of time. The Biopump technology under development includes refinements to the product inputs (most notably a new viral vector to enhance efficacy duration) as well as optimizing the process that provides optimum durability of protein/peptide secretion.

Relative to the viral vector - viruses are unique in their efficiency in transporting genes into cells. Viral vectors are laboratory modified viruses which are used to deliver genetic material into the cells (a process called transduction). MDGN's first-generation viral vector was used in initial pre-clinical and early stage clinical studies to demonstrate proof-of-concept, where it has shown excellent safety and clinically meaningful protein expression. A second generation viral vector has demonstrated longer duration of efficacy in preclinical studies. It is now being used in a clinical trial (MDGN-201), positive preliminary data from which was announced in mid October. This preliminary data appears to show a better therapeutic profile (i.e. - more uniform delivery and longer duration) than the first generation viral vector.

Advantageous Alternative To Current Methods…

Biopump is a novel ex-vivo gene therapy platform allowing continuous and autologous protein and peptide production that is significantly differentiated from other protein replacement therapies. Protein replacement therapy is used to treat a number of common chronic conditions including anemia caused by kidney disease, and rare and orphan diseases such as hemophilia and Gaucher's disease.

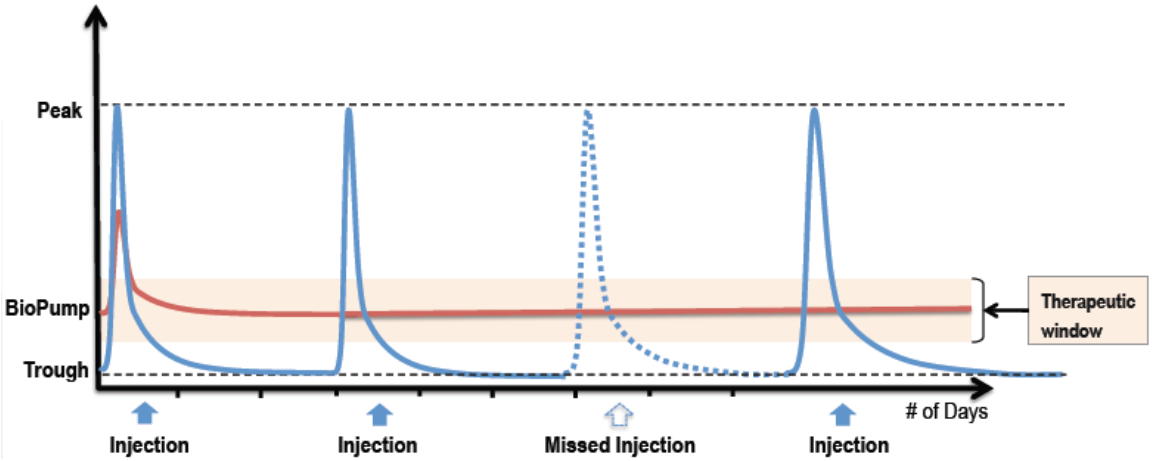
Biopump protein production creates an autologous protein from the patient himself, as opposed to recombinant proteins, which are produced in cell culture (human or animal). Autologous protein production enables the patient's own "fingerprint" or glycosylation, which is considered to have several potential advantages over non-autologous proteins. These advantages include extended duration, improved cell uptake, and lower immunogenicity/toxicity over traditional protein replacement. By contrast, non-autologous proteins have the potential to be recognized as foreign, and thereby elicit an immune response in some individuals, which may result in lower efficacy or reactions requiring discontinuation of therapy.

Finally, Biopump protein production is continuous, which allows the potential for a patient to be treated for six months following the procedure. Continuous and autologous protein production more closely mimics the patient's physiological production of protein, versus the typical bolus injections of current protein therapies. Most recombinant protein therapy involves frequent dosing, via injection, of large amounts (bolus) of protein. A typical regimen can be 2 - 3 (or more, depending on the protein and condition being treated) injections per week. Frequent bolus injections are required given the inherent short half-lives in the circulatory system and rapid clearance of recombinant proteins (examples in table).

Protein	Half life (hours)	Weekly dosing
interferon-alpha	5	3
pegylated interferon alpha	40	1
erythropoietin (ESA's)	8 - 25	1 - 3

Bolus injections, usually infusions of protein, result in relatively high initial concentrations in the blood immediately following administration. The protein level during the initial spike typically greatly exceeds that of the desired therapeutic level. Trough levels below the therapeutic range may also result. Levels outside the therapeutic range may be associated with less effective treatment or higher risk of adverse events.

BLUE: **Peaks and troughs outside of therapeutic range associated with typical protein therapy**
ORANGE: Biopump therapy much more consistent and sustained within therapeutic range



SOURCE: Medgenics

Trial Data Is Promising

Biopump has demonstrated clinically meaningful protein production and excellent safety in early-stage clinical studies. Proof-of-concept was accomplished with $TARGT_{EPO}$ (formerly known as EPODURE), MDGN's erythropoietin-producing Biopump, with a first-generation viral vector in patients with anemia from CKD. In early June the company announced the enrollment of their new phase 1/2 $TARGT_{EPO}$ trial (MDGN-201) in patients with CKD and ESRD, designed to test its second generation viral vector and implantation protocol. In pre-clinical models, which have been highly predictive of clinical results, Biopumps with the second generation viral vector showed significantly greater protein production and longer duration in comparison to the first generation product. Preliminary data from MDGN-201 was announced in mid-October and looks to be highly encouraging - we discuss the data later.

Phase I/II Dose-Escalation Study

Proof-of-concept was demonstrated in the initial phase I/II study using EPODURE for the treatment of anemia in pre-dialysis patients with chronic kidney disease (CKD). The study, which began in 2008, was conducted at two sites in Israel, Hadassah Medical Center and Tel Aviv Sourasky Medical Center. The open label, dose escalation study contained three $TARGT_{EPO}$ dosage groups; EPO of 20, 40 and 60 IU/kg/day - these dosage were chosen to closely correspond to FDA's recommend dosing range of EPO from 50 to 150 IU/kg three times per week (~ 20 - 65 IU/kg/day). This was primarily a safety study although key efficacy endpoints were also of interest, namely hemoglobin response to $TARGT_{EPO}$ and duration of effect.

EPO injections were discontinued at least four weeks prior to the study for any patients that had been receiving EPO injections. Ten micro-organs were harvested from abdomen tissue of each patient via DermaVac and using local anesthesia. The samples were processed over two weeks in a GMP laboratory to convert them into

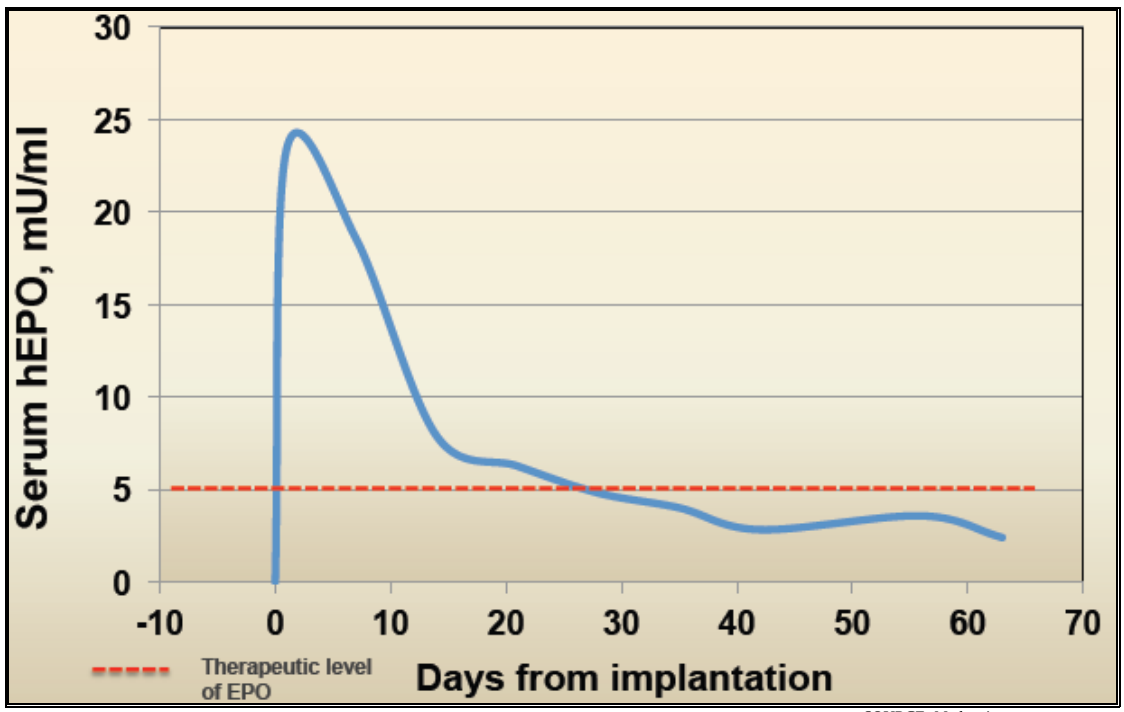
EPODURE Biopumps using the first-generation vector. Each Biopump was calibrated to produce the predetermined (20,,40, 60 IU/kg/day) EPO based on the patient's weight. The determined number of $TARGT_{EPO}$ Biopumps were then implanted in the patient under local anesthesia.

Summary results were presented in November 2012 at the American Society of Nephrology meeting. Safety was considered excellent with no serious adverse events.

Serum EPO became rapidly elevated within the first day after implantation, although declined below the therapeutic level within 30 days. Despite this short durability of EPO production, many of the patients did not require the use of supplemental EPO injections in order to maintain hemoglobin (hgb) levels. Five of the seven patients in the low dose level (20 IU/kg/day), seven of seven patients in the mid dose level (40 IU/kg/day) and two of five patients in the high dose level (60 IU/kg/day) did not require the use of supplemental EPO for three months or longer. In addition three of the seven patients in the low dose level, five of seven patients in the mid dose level and one of five patients in the high dose level did not require the use of supplemental EPO for six months or longer.

Fourteen of the 19 patients' hemoglobin levels were maintained above 9g/dl for at least three months and in nine patients for at least six months without the need for supplemental EPO injections. For reference, FDA's current guidelines are for hemoglobin to be maintained at a level high enough to avoid the need for increased transfusions and below 11g/dl. Key for MDGN in terms of demonstrating safety was the ability to deliver EPO at levels in a safe range (i.e. - below 11g/dl). MDGN hopes to show maintenance of hgb in the 9g/dl - 11g/dl for more than six months in their phase I/II ESRD study (MDGN-201), which uses the second generation vector.

1st Generation Viral Vector Rapidly Increased Serum EPO in Initial Phase I/II Study



SOURCE: Medgenics

Viral vectors for transduction used have included Helper dependent AdenoVirus (serotype 5) (HDAD) and Adeno associated virus (AAV LK19). Good results have been obtained with both, however the secretion profiles vary with HDAD showing higher levels of secretion but a more pronounced reduction in transgene production over time and AAV having a lower but flatter secretion profile. The company believes that the two vector systems are complimentary, with preference the disease target and transgene.

The company has continued to improve the platform. Recently presented data showed the “second generation” HDAD vector system, together with modifications to culture conditions and insertion technique, resulted in a

substantially higher level of production and slower “decay” curve, in-vitro and in-vivo. This new vector system, expressing erythropoiten, is now being used in the second clinical trial (MDGN-201) in CKD and ESRD patients.

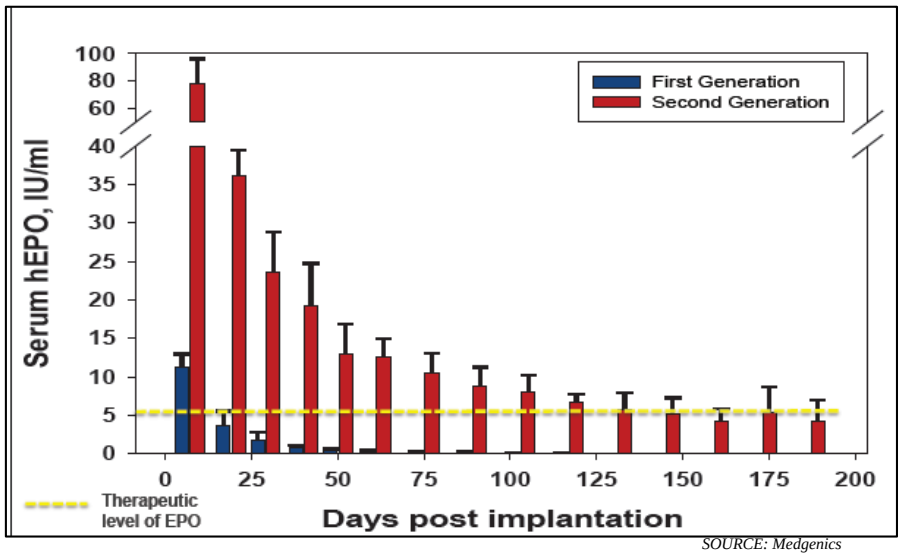
MDGN-201, Phase I/II Study With Next-Gen Vector…

In June 2014 the company, initiated a new phase 1/2 study titled: *Safety and Efficacy of Sustained Erythropoietin Therapy of Anemia in chronic Kidney Disease Patients and End-Stage Renal Disease Dialysis Patients Using EPODURE Biopump*[1]. The study's moniker is MDGN-201. Per clinicaltrials.gov, the estimated final data collection date for primary outcome measures is December 2015 and should allow for a one-year follow-up of most patients.

Aside from the use of the new generation viral vector and new implantation techniques, the ESRD/CKD study is similar in design to that of the initial study. Primary outcome will be maintenance of hemoglobin in the range of 9g/dl - 11g/dl for more than six months. Duration of $TARGT_{EPO}$ secretion will be measured by serum levels above baseline. Patients will receive their own individually targeted dose of EPO delivered via $TARGT_{EPO}$ which will be determined by body weight, the average EPO previously administered, and historical hgb levels.

This phase I/II open label study, which is being conducted in Israel, is also designed to be dose ascending with three cohorts; lowest dose of 18-25 IU/kg/day, middle dose of 35-45 IU/kg/day and highest of 55-65 IU/kg/day. Initial patients will receive the lowest of the three doses. Total enrollment could include as many as 18 patients across three dosage cohorts but this will also be dependent on interim data. If the lowest dose provides sufficient efficacy, the higher dose cohorts may not be enrolled.

Data From 2 Separate SCID Mouse Models Highlighting Superior Performance of 2nd-Gen "Gutless" Vector Which Is Being Used in Phase II ESRD Study



SOURCE: Medgenics

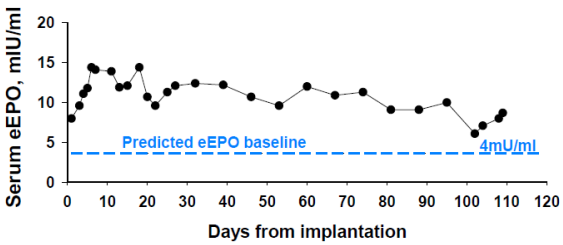
Preliminary Clinical Data Looks Highly Promising…

Initial clinical data of this MDGN-201 study were announced this in mid-October. And while these initial results are from just three patients (all given the lowest dose) with follow-up no longer than four months, we characterize the data as highly promising. In all three patients results showed hemoglobin levels were maintained in the 9g/dl - 12g/dl range and that serum EPO levels were much more well-controlled during the $TARGT_{EPO}$ therapy as compared to the run-in period when the patients were given ESA's (again, ESAs are associated with spikes and troughs of serum EPO which has been associated with potentially compromised therapeutic effect and health risks).

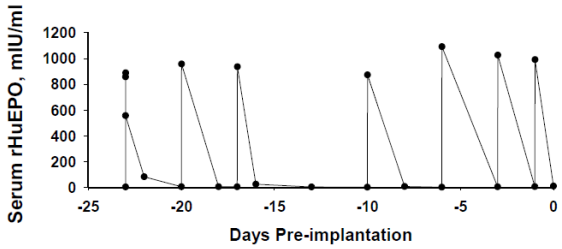
[1] clinicaltrials.gov. Identifier NCT02117427

Serum EPO Levels Much More Constant With TARGT$_{EPO}$ Than During ESA Run-In Period

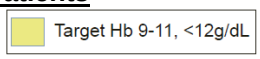
Patient #1 4-Months of TARGT$_{EPO}$ Therapy



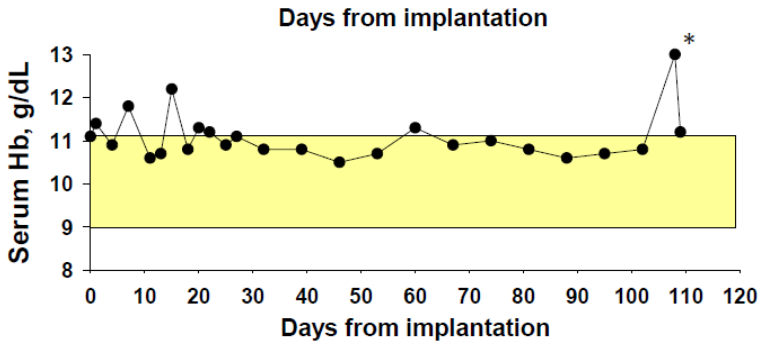
Patient #1 Run-In Period With ESA Injections



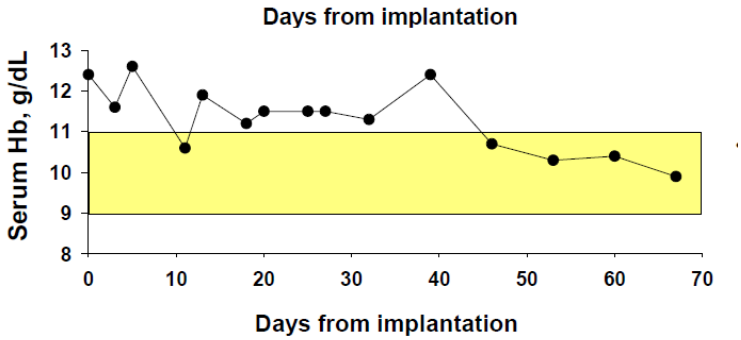
Hemoglobin Largely Maintained at 9g/dl - 12g/dl Range In All Three Patients



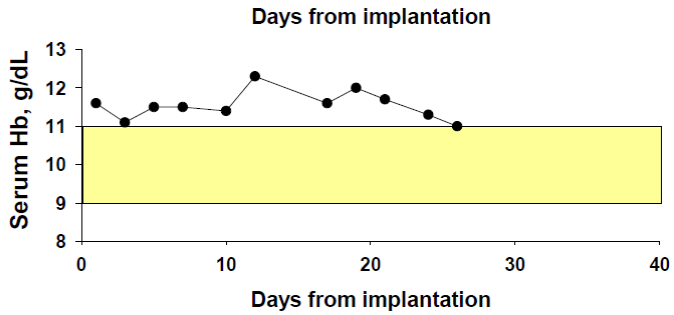
Patient #1 Four Months of TARGT$_{EPO}$ Therapy



Patient #2 Two Months of TARGT$_{EPO}$ Therapy



Patient #3 One Month of TARGT$_{EPO}$ Therapy



And while potentially still early to determine, investigators are seeing a trend of increasing reticulocytosis in patient #1 (i.e. - the one in treatment the longest, four months). Reticulocytosis is where the body starts producing more immature red blood cells and evidence of such would be a significant development as it may indicate that $TARGT_{EPO}$ therapy may help induce the body's natural function in producing red blood cells.

Additional Data Should Provide Even More Insight…

Medgenics will present this data at the European Society for Gene and Cell Therapy (ESGCT) meeting, being held in The Hague, Netherlands later in October. The trial will shortly begin enrolling another three patients - all in the lowest-dose cohort which are expected to complete enrollment by year-end. And while management noted they do not expect to hold additional investor calls when new data comes out, they do expect to present follow-on data at industry events.

As noted, we view this initial trial data with the 2nd-gen vector as highly encouraging and in fact, interpret these results as about as good as could have hoped. Along with consistent delivery of EPO and maintenance of hemoglobin in the target range, there were no adverse treatment-related safety issues. Additional positive follow-on data from both the to-be enrolled patients as well as longer-term results from these patients should provide even greater insight into the efficacy and utility of $TARGT_{EPO}$ and the Transduced Micro-Organ technology.

STRATEGY: Commercialize $TARGT_{EPO}$ For Orphan Diseases

Orphan Targets Identified, Two of Which Are EPO Related

MDGN remains committed to their prior plan of not going after the overall EPO/ESA market targeting ESRD/CKD, which is dominated by a few well-entrenched and large pharmas including J&J, Amgen and Roche. Aside from the competition, this market has become even less attractive with changes to Medicare reimbursement which bundles the dialysis procedure with related supplies and drugs - cutting the profitability of ESA's. It is possible, however that MDGN could license or partner their technology for the overall ESRD/CKD market.

Instead targeting the overall CKD/ESRD market, and also in-line with the company's previous strategy, MDGN will look to leverage their technology in rare diseases. As we have noted in our ongoing coverage of MDGN, the worldwide orphan disease market, estimated at $50B+, looks to be particularly attractive given certain incentives that are in place that allow for shorter development, smaller clinical trials and regulatory timelines, a guaranteed term of market exclusivity and financial assistance through fee waivers, tax credits and grants. These incentives, along with the attractive commercial economics (i.e. - high selling prices and small sales force) of the rare disease market, affords the potential for high margins and profitability in just a single indication.

Exactly what that (or those) rare disease(s) were that MDGN would pursue were unknown until mid-October. The company announced that they expect to pursue two indications related to EPO, those being 1) ESRD patients that are hypo-responsive to ESAs - a U.S. population that the company estimates at approximately 40k - 70k and 2) Beta Thalassemia, a rare blood disorder associated with anemia (i.e. - low hemoglobin) and low levels of EPO. The company estimates that there are ~16k people in the U.S. and Europe combined that suffer from Beta Thalassemia.

We view the pursuit of both of these indications as making good strategic sense. Most obviously, the EPO-producing Transduced Micro-Organ, $TARGT_{EPO}$, is well on its way of being validated as safe and effective.

MDGN would potentially have to make no significant changes to the technology in order to adapt it to both hypo-responders as well as Beta Thalassemia patients. This keeps costs and risks as low as possible while still targeting attractive markets with potential for orphan designation. For each indication the company believes they can run a 10 - 15 patient initial validation study, results of each of the studies which could be available in the first half of 2015. If results are positive, pivotal (although still small) studies would then be pursued.

ESA Hypo-Responsive…

This is a relatively small sub-group of the ~400k Americans that have ESRD and are being treated with ESAs. Hypo-responsive ESRD patients require large doses of ESAs to maintain hemoglobin levels. Hypo-responsive ESRD patients can be defined as those that need a monthly dose of ESA that is in the 90th percentile. These patients may be more susceptible to ESA-associated risks (such as cardiac risks) due to the higher dosing and the variability in serum EPO levels inherent with recombinant EPO injections. A more consistent delivery of EPO via $TARGT_{EPO}$ would reduce the serum spikes and troughs of EPO injections and potentially induce more effective hemoglobin production and maintenance.

And of course, since these patients require more ESA than a non hypo-responsive ESRD patient, cost to treat these patients is greater. MDGN estimates that it costs approximately $30k+/year to treat a hypo-responsive ESRD patientwith ESAs and dialysis. We think this actually may be on the conservative side as have found estimates from different sources indicating the cost to treat an "average" ESRD patient can be $40k or more. With ~50k hypo-responsive ESRD patients in the U.S. receiving ESAs, this would equate to a market size of ~$1.5B or more. While this is just a rough estimate, it may provide a general guide for potential pricing of an eventual $TARGT_{EPO}$ product targeting the hypo-responsive ESRD market.

Beta Thalassemia…

Beta Thalassemia is a rare blood disease which reduces the body's ability to produce hemoglobin. This can have serious consequences. The disorder usually appears very early in life and often stunts weight gain and overall growth in children. Organs, including the heart and liver, and bones can also be negatively effected. People with beta thalassemia often need frequent blood transfusions to increase hemoglobin levels. Blood transfusions have certain disadvantages including the potential for; iron overload (and thus requires iron chelation therapy), antigenic differences of red blood cells between donor and patient, and infection. Blood transfusions are also costly - cost estimates for blood transfusions vary widely from $2k to $8k per procedure.

There are two types of beta thalassemia, thalassemia major and thalassemia intermedia. MDGN expects to target the thalassemia intermedia market, a population which they estimate is approximately 16k people in the U.S. and Europe combined. The company further estimates that it costs ~ $100k/year to treat a thalassemia intermedia patient (including transfusion and iron chelation costs) which calculates to a total potential market of almost $1.6B.

MDGN's $TARGT_{EPO}$ could be a viable substitute for or complement to blood transfusions that beta thalassemia patients undergo. If a complement, it could at least potentially reduce the number of transfusions.

Other Potential Applications for $TARGT_{EPO}$ …

So while hypo-responsive ESRD patients and beta thalassemia are clearly the front-runners in terms of the company's focus on rare diseases, management also talked about other potential applications for $TARGT_{EPO}$. These are 1) anemic CKD patients which are candidates for transplant 2) peritoneal dialysis patients and 3) myelodysplastic syndrome. As these are back-burner potential indications that may be pursued in the future, we will limit our discussion about these until and if there is a significant likelihood of pursuit of one or more of these potential targets.

TARGT Peptide Program…

MDGN's major focus to-date has been with protein therapy, most notably EPO. The company announced that they are now pursuing, in parallel with the EPO targets, endogenous peptides. The short half lives of small endogenous peptides provides therapeutic challenges when administered externally - including the need to use high doses and short effect. Since TARGT would produce the peptide naturally and provide a continuous flow (at the "correct" concentration), these challenges could potentially be overcome.

The company's initial focus will be on glucagon-like peptide-2 (GLP-2), which is produced naturally by the intestinal endocrine L cell and certain neurons. It promotes intestinal growth and enhances intestinal function. It's half life is approximately only 5 - 7 minutes.

MDGN expects to target short bowel syndrome, an orphan indication with $TARGT_{GLP-2}$. Short bowel syndrome (SBS) is typically the result of surgical removal of part of the small intestine as a result of a variety of disorders. SBS patients often suffer from malabsorption and may require intravenous nutrition. It is estimated that there are approximately 3k - 5k SBS patients in the U.S.

Gattex (teduglutide), marketed by NPS Pharma, is a GLP-2 analog that has orphan designation for SBS and was approved by FDA in late 2012. Gattex promotes intestinal absorption and is dosed once per day via subcutaneous injection. NPS has priced the therapy at approximately $295k per person per year. It is estimated that there are approximately 3k - 5k SBS patients in the U.S. As such the calculated potential market for Gattex is $1B+.

$TARGT_{GLP-2}$ could potentially eliminate or reduce peaks and troughs and potential related health risks associated with bolus injections. Development of $TARGT_{GLP-2}$ is in preclinical stage and has been used in mice which showed secretion of GLP-2 for a term of 60 days. MDGN will provide further development updates in the future.

Attractiveness of Orphan Disease Market

The Orphan Drug Act of 1983 (ODA) was signed into law to encourage and facilitate the development of drugs that treat rare diseases. The act defines rare diseases as those affecting less than 200k people (~1 in 1,500) in the U.S. The ODA includes several incentives to promote the development of drugs for rare diseases, something that might otherwise be an unprofitable endeavor for life sciences companies. Incentives include seven-year marketing exclusivity from the date of FDA approval (or until patent expiration, whichever is longer), tax credits equal to 50% of related development costs (with a 15-year carry-forward provision), grant funding, waiver of PDUFA (Prescription Drug User Fee Act) application fees, FDA fast-track approval and research design support.

A similar act was passed in Europe where "rare" is defined as diseases affecting less than 300k people (1 in 2,000). Other countries also have some form of an orphan disease law including Japan, Australia and most countries in South and Latin America.

These incentives have resulted in significant interest from drug manufacturers in developing orphan drugs. Since the law was passed over 400 orphan drugs have been developed in the U.S. to treat over 2,700 diseases with many of these drugs reaching blockbuster status. In fact in 2012, approximately one-third of drug approvals in the U.S. were for orphan designations.[2] There are currently approximately 7,000 diseases categorized as rare and this is increasing at a rate of approximately 250 per year.

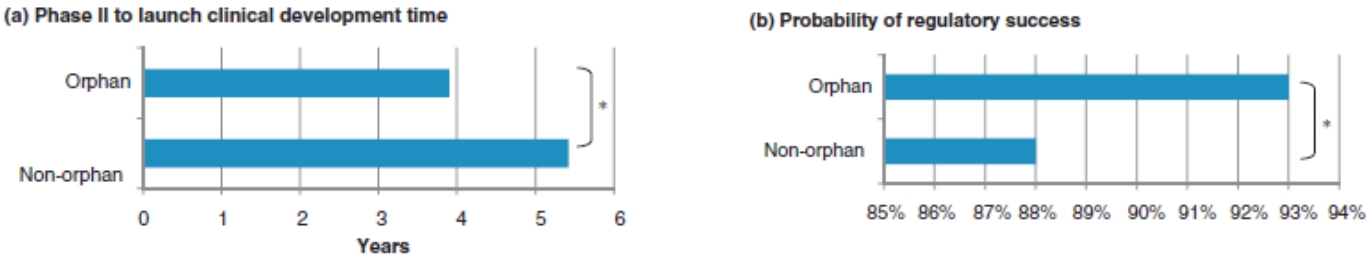
Other advantages include that development can be done quicker and clinical trials accomplished with much smaller patient enrollment as compared to development of drugs targeting non-orphan diseases. Shorter development times and fast-track approval means orphan drugs may reach commercialization faster than traditional drugs. Orphan drugs also appear to have a better track record in terms of chances of approval with one study (which included only those candidates that were eventually filed for approval) showing the success rate of orphan drugs from phase I to approval to be approximately 22%, compared to ~11% for non-orphan candidates.[3]

Orphan drugs can also command significantly higher prices than their non-orphan counterparts as a result of the relatively tiny patient populations, high unmet need and lack of competing products (which is further facilitated by the seven-year exclusivity). The combination of quicker time-to-market, higher prices, rapid market penetration and typically lower commercialization and marketing costs (i.e. - smaller sales force and more direct targeting as a result of the smaller patient population) offers high revenue potential, very attractive margins and beefy return on investment with orphan drugs - this is despite the fact that these drugs target only a relatively small patient pool.

A study done by Thomson Reuters Life Sciences Professional Services and Pfizer titled, *Orphan Drug Development: an economically viable strategy for biopharma R&D*[4], published in the July 2012 issue of Drug Discovery Today found that the economics and payback from development of orphan drugs is more favorable that that of non-orphan drugs. With key drivers that included the ODA incentives, shorter development

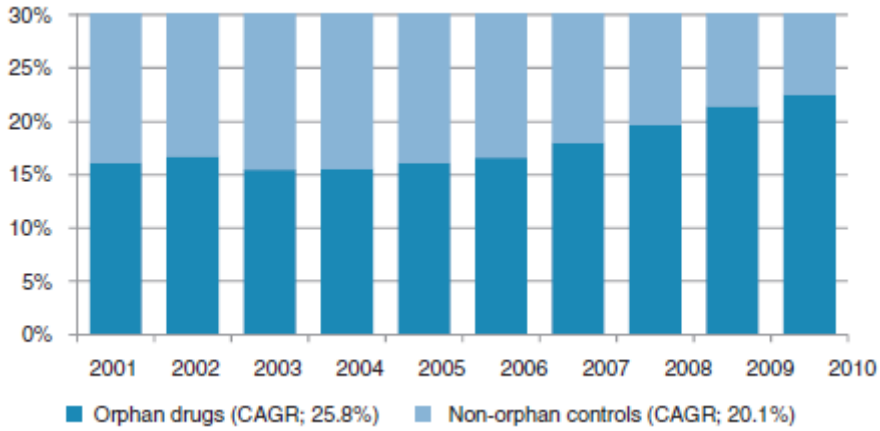
[2] Clark Herman, *The Orphan Drug Act at 30 Years: What's Next?*. PharmaExec.com. Jan 8, 2013. Jim Ajer, BioMarin Pharmaceutical Inc.
[3] D.E. Fagnan, et al., Financing drug discovery for orphan diseases, Drug Discovery Today (2013)
[4] Meekings K, Williams C, Arrowsmith J. *Orpah drug development: an economically viable strategy for biopharma R&D.* Drug Discovery Today Jul 2012, V 17, 13/14. 660-664

timelines (~30% shorter for orphan vs. non-orphan), higher probability of regulatory approval following submittal (~93% for orphan vs. 88% for non-orphan), premium pricing and lower marketing costs, among others.



SOURCE: Drug Discovery Today[4]

The study also found that the value of drugs which were indicated for more than one orphan disease were about four times as great as those indicated for only one orphan disease. The compilation of benefits are likely behind the significantly faster recent growth (~26% vs. 20% CAGR from 2001 - 2010) of the orphan drug market as compared to their non-orphan counterparts (see chart). These are clearly also the reasons why Medgenics sees the orphan market as particularly attractive.



SOURCE: Drug Discovery Today[4]

In terms of overall value of orphan versus non-orphan drugs, the Thomson Reuters study found that despite a the much smaller patient pool, the present value of revenues of orphan drugs is similar to that of non-orphan drugs. Using a sample set of 86 orphan drugs and 291 non-orphan drugs, the study found that the average present value of orphan drugs was $12.1B versus $11.5B for non-orphan drugs and an average per-year value of $406M for orphan and $399M for non-orphan drugs.

According to Brian Lester, senior analyst and managing director at Manning & Napier, life sciences companies with an orphan disease focus command a higher value than traditional non-orphan drug companies as a result of the competitive benefits and continued optimism for the profitability of these companies. He also notes that he expects this competitive edge over the primary care business model to be maintained in the future.

This, combined with pharmaceutical companies increasingly looking to diversify into new drug areas to increase profitability which includes the orphan drug space, potentially puts a premium value on companies such as Medgenics in an acquisition scenario. And as drugs and technologies that can address more than one orphan indication are worth significantly more than single-indication orphan drugs, Medgenics' platform technology could eventually command substantial value.

FINANCIAL CONDITION

As of the most recent reporting period (ending 9/30/2014) the company had approximately $14.7M in cash and equivalents. The balance sheet is debt and preferred stock-free. Cash burn has averaged approximately $9.8M annually over the last three fiscal years and was $12.7M in 2013. The company believes the current cash balance will be sufficient to maintain operations through Q3 2015.

A significant portion of cash usage to-date has been related to R&D activities, specifically for earlier development of INFRADURE, HEMODURE and initial preclinical and clinical trials of EPODURE. We think R&D expense may stay relatively flat over the course of 2014 and first half of 2015 as INFRADURE and HEMODURE have recently been shelved and development will instead focus on the Israeli-based MDGN-201 and small clinical studies for the two near-term orphan candidates.

We do not expect MDGN to generate any meaningful revenue for at least the next several years during which time the focus will be on further development of the $TARGT_{EPO}$ as well as potentially the $TARGT_{GLP-2}$ platform. The near-term includes completing the MDGN-201 phase I/II study in Israel, commencing initial clinical validation studies in the two near-term orphan targets and additional preclinical work on $TARGT_{GLP-2.}$
MDGN has generated a total net loss of over $86M since its inception in early 2000. The company has been, and will need to continue to be, successful in raising capital to maintain operations. MDGN raised almost $82M since inception, mostly via the issuance of common stock. This includes $28.9M raised in 2013. The company has also been the recipient of several grants from Israel's Office of the Chief Scientist (OCS) which has helped to fund their development efforts - this includes a ~$2.2M grant awarded in April 2014.

Given the relatively early nature of product development and commercialization strategies that are still very much in the feasibility/proposal stages, it is difficult to gauge how much additional capital the company may need to raise to get to the point of commercialization of their first product or to cash flow positive (if either of those ever do happen). Factors that could have a significant bearing on capital needs include cost and success in development and implementation of the new vectors, initial success of the MDGN-201 phase I/II trials, potential partnering for the overall CKD/ESRD market, timing and success of development for an orphan designation, receiving additional grants from Israel's Office of the Chief Scientist, and outlicensing versus direct sales commercialization strategies, among many others.

INVESTMENT CONSIDERATIONS

Near-Term Trial Data Will Steer Development Strategies
Expect flow of preclinical and human trial data which will provide more insight into the safety, performance and overall utility of the Biopump technology. This includes additional near-term clinical data from MDGN-201 and preclinical data from the $TARGT_{GLP-2}$ program. Clinical studies could commence and have initial data by mid-2015 on the EPO orphan targets, ESA hypo-responders and beta thalassemia.

As noted, we view this initial trial data with the 2nd-gen vector as highly encouraging and in fact, interpret these results as about as good as could have hoped. Along with consistent delivery of EPO and maintenance of hemoglobin in the target range, there were no adverse treatment-related safety issues. Additional positive follow-on data from both the to-be enrolled patients as well as longer-term results from these patients should provide even greater insight into the efficacy and utility of $TARGT_{EPO}$ and the Transduced Micro-Organ technology.

Development and Commercialization Runway
Pursuit of orphan targets has the potential to reduce the risk of clinical trials as a result of the ODA incentives, relatively fast pace (relative to non-orphan drugs) and small size (typically less than 100 patients) of clinical trials, and the inherently higher regulatory approval rate of such drugs - although this will still be a costly and likely multi-year process. Presumed higher probability of success with an orphan indication is particularly beneficial in terms of de-risking development.

As such, if one or more of MDGN's product candidates does eventually reach commercialization, it is unlikely to happen or generate any significant revenue for at least the next few years, if ever. The aforementioned Thomson Reuters study found the average time from phase II to launch for orphan drugs is approximately 3.9 years. Another study (Kaitin and DeMasi[5]) found orphan drug trials from phase I to NDA take approximately 5.9 years and the approval process adds about another year (~7 yrs from phase I to approval).

[5] Kaitin, K, DiMasi J. *Pharmaceutical Innovation in the 21st Century: New Drug Approvals in the First Decade*. Clinical Pharmacology Therapy. 89, 183-188

An example of timeframe for orphan indication trials is Synageva BioPharma which is developing sebelipase alfa (SBC-102), an orphan designated compound for lysosomal acid lipase deficiency. In May 2011 Synageva presented preclinical mouse data on the compound, in December 2011 phase I/II had completed enrollment and in February 2013 their phase III study had commenced with data expected later this year. So over the course of approximately only four years, development progressed from preclinical mouse studies to (expected) announcement of phase III data.

If MDGN can follow a similar timeline, we would expect phase III data could be available sometime in 2018. Assuming Fast-Track Approval and Priority Review, it is conceivable MDGN could have an orphan designated Biopump on the market by late 2018 or 2019.

Competitiveness
So while no Biopump candidate is likely to launch in the near-term, we think certain significant competitive advantages provide it with the potential to be successful if and when the technology does reach the commercial market. Biopump may also be more "competitive" to other products, namely injected therapies, in terms of development cost and timelines, speed to market and derivative indications.

Biopump, which essentially uses the patient's own skin as a "protein factory", does not require an expensive GMP (Good Manufacturing Practices) protein production plant like recombinant proteins do. Recombinant protein plants can cost several hundred million dollars and take years to build. Manufacture of proteins for clinical trials can also be a time consuming and a relatively expensive process - particularly as protein manufacturing is scaled up for larger studies. As such, cost and time of development can be much less with Biopump compared to injectable proteins. Biopump may also be more easily developed for a variety of indications than recombinant proteins given that Biopump is being developed as a platform technology and much of the indication-dependent modifications may be able to be validated in preclinical studies - meaning that the Biopump technology may not require significant time or investment to "retool" from indication to indication (although each indication will require separate regulatory approval).

There are several clinical benefits of Biopump versus injected proteins. The use of native tissue means there is less risk of immunogenicity or other adverse treatment-related side effects and potential for much longer duration of therapeutic effects. In the event that treatment needs to be discontinued, Biopump can be ablated to immediately stop protein delivery - that is not possible with injected proteins. Biopump delivers protein in a fashion that much more closely resembles that of the human body compared to recombinant proteins which are delivered in frequent bolus injections and have peaks which massively overshoot the optimal therapeutic range which are then followed by troughs which fall below the therapeutic range. Biopump also offers a much lower treatment burden and advantageous patient convenience compared to protein injections which may be required several times per week for months or even years. Superior patient comfort can also result in greater compliance.

Commercialization
As an approved commercial product is still years away, MDGN has yet to outline a definitive commercialization strategy for Biopump. The current general plan includes to market a orphan-designated product with an in-house sales force. In terms of the overall CKD/ESRD market, the company may look to license rights or partner.

As the CKD/ESRD market is highly concentrated among only a few companies on both the drug (J&J, Amgen, Roche) and clinic side (DaVita, Fresenius) the potential list of interested partners may be short. But these also may be highly interested in the $TARGT_{EPO}$ technology given the huge market for EPO (~$3B U.S., ~$9B global), the aggressiveness of EPO manufacturers in defending their market share, and significantly reduced sales of EPO products as a result of FDA actions including black box warnings as well as recent cuts by Medicare in reimbursement for the drugs.

Timing and the strategy for commercialization for any orphan indication is also highly uncertain. However, MGDN has indicated that they would likely consider selling $TARGT_{EPO}$ direct with their own sales force for an orphan indication. Given that rare diseases are defined as only affecting 200k or fewer Americans and orphan drugs have no competition, MDGN would conceivably only need a skeleton-crew sales force and fairly modest marketing budget. The inherent economics of orphan designation, including high selling prices and guaranteed seven years of marketing exclusivity, also play into MDGN's favor if they chose to "go it alone" for an orphan indication.

The respective U.S. patient populations and market opportunities for ESA hypo-responders and beta thalassemia is ~70k / $1.5B and ~16k / $1.6B, respectively.

Feasibility of Commercial Production
Until recently all processing of harvested Biopumps was done manually by highly trained personnel in GMP clean rooms in Israel. This "open system" is relatively costly and inefficient and while potentially viable to support small clinical trials, it is not intended for or necessarily economically feasible for commercial-scale Biopump processing.

The company is working on a more commercially-viable system for Biopump processing. This includes development of closed chambers for Biopump processing instead of the open system and establishment of a contract manufacturing center in California. In the closed chamber system, MO's can be harvested at one location, placed in the closed chamber and sent to the contract manufacturing center where the MO's are processed into functioning Biopumps inside the chamber. MDGN has demonstrated that the closed chamber system can produce Biopumps that are comparable to those processed in the open, clean room system.

As the Biopump system is very different than conventional protein therapies in terms of production and distribution, the economics of Biopump may also be very different. Given the early stage there are a plethora of unknowns related to the economics of Biopump commercialization including the size of respective target markets, selling prices and infrastructure costs, among many others. The cost and efficiency of Biopump processing is likely to be a major determinant of the potential profitability of the technology. So while the viability of economical commercial scale production is currently unclear, the company has made significant headway in streamlining the processing function via the closed chamber processing system. Additional refinements in order further automate the system will presumably lower the cost of production and improve the chances of feasible and economical commercial production.

Experienced Management / Board
An investment in MDGN is very much an investment in the new management of the company as well, which we view as top-notch, which has significant and relevant experience in large molecule drug development and commercialization, and which has already implemented significant changes - the totality of which we think offers greater chance of ultimate success of the TARGT platform. Management has already made substantive strategic changes including de-prioritizing INFRADURE and HEMODURE in order to conserve resources, reduce risk and focus on the highest potential markets - those being orphan diseases. The new strategy also includes licensing commercial rights of $TARGT_{EPO}$ for any non-orphan designations - a decision that makes sense given the incestuous nature of the EPO industry and vast distribution and sales infrastructure that would be required to service the relatively large ESRD/CKD market.

Confidence in leadership and strategic direction of the company is further bolstered by the resumes of the Board of Directors. This includes in Sol Barer, the founder and former Chairman of Celgene.

VALUATION

Given the early stage of the company along with various uncertainties that are inherent of most development stage companies, valuation is less than straightforward. We think the most reasonable methodologies are to use a pure-play development stage orphan drug company as a comparable and DCF valuation based on annual revenue of an "average" orphan drug.

Comparable Methodology ~ $300M Market Value
Synageva BioPharma (GEVA) is developing sebelipase alfa (SBC-102), an orphan-designated compound for lysosomal acid lipase deficiency. The market for SBC-102 has been estimated at approximately $600M per year. The company went public in 2011 with the stock commencing trading in July 2011. In December 2011 GEVA completed enrollment of their phase I/II study for SBC-102 - at that time the company had an approximate $310M market value. GEVA's current market cap is $2.4B.

We think it is reasonable to equate MDGN's current product development status with that of GEVA's when enrollment had completed for SBC-102 and when the company traded at a market value of ~$300M. While

MDGN has yet to commence enrollment for an orphan designated clinical trial, we think their development status is comparable for several reasons. $TARGT_{EPO}$ had demonstrated efficacy (with no safety concerns) in phase I/II trials and was slated to enter phase II studies in the U.S. until MDGN decided to amend the IND with the next-gen vectors. Preliminary clinical data from MDGN-201, announced in mid-October was highly encouraging. And while $TARGT_{EPO}$ is not yet orphan-designated, the TARGT technology had already received orphan designation for INFRADURE - as such, it is conceivable it could receive orphan designation for other targets.

"Average" Orphan Company Value ~$250M

We also use an "average" orphan company valuation methodology based on statistics from the study which we cited in the body of this report done by Thomson Reuters Life Sciences Professional Services and Pfizer. According to that study, the average per-year revenue of orphan drugs is approximately $600M. We have built a DCF model that more conservatively assumes $450M of revenue is generated over the remaining patent life of one orphan designated Biopump product. Other assumptions are that this product launches in 2020 (we think 2018 or 2019 launch is also reasonable), has 14 - 15 years of patent life remaining, revenue falls 50% per year each year after patent expiration and, given the high selling prices of orphan drugs, commands gross margins of 80% - 85%. We estimate operating expenses at just 20% of revenue given that orphan drugs can typically be detailed with a small sales force and relatively little overall marketing support. Using a 10% discount rate values the company at approximately $1.1B. Discounting this by the ~22% probability (per Thomson study) that an orphan drug in phase I eventually is approved, values the company at approximately $250M.

Value MDGN at $275M

Average of these two methodologies puts the value of MDGN at approximately $275M. We also think that there is potential additional value from the possibility of licensing $TARGT_{EPO}$ for the broader CKD/ESRD population which is not considered in this figure. We also note that this $275M valuation only assumes eventual approval for one orphan indication. As explained in the Thomson study, the value of drugs which were indicated for more than one orphan disease were about four times as great as those indicated for only one orphan disease.

We value the company at $275M or approximately $15/share. Further successful progression through the development pathway should provide for additional de-risking and potential upside to our current $15/share target price.

FINANCIAL MODEL

Medgenics, Inc.

	2013	Q1A	Q2A	Q3A	Q4E	2014 E	2015 E	2016 E	2017 E
Total Revenues	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0
YOY Growth	-	-	-	-	-	-	-	-	-
Cost of Goods Sold	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0
Gross Income	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0
Gross Margin	-	-	-	-	-	-	-	-	-
SG&A	$10,521.0	$3,093.0	$2,864.0	$2,305.0	$2,748.0	$11,010.0	$12,385.0	$12,858.0	$12,998.0
% SG&A	-	-	-	-	-	-	-	-	-
R&D, net of grants	$7,297.0	$2,142.0	$773.0	$1,565.0	$2,178.0	$6,658.0	$7,876.0	$8,864.0	$9,991.0
% R&D	-	-	-	-	-	-	-	-	-
Operating Income	($17,818.0)	($5,235.0)	($3,637.0)	($3,870.0)	($4,926.0)	($17,668.0)	($20,261.0)	($21,722.0)	($22,989.0)
Operating Margin	-	-	-	-	-	-	-	-	-
Financial expense, net	$706.0	($117.0)	($202.0)	$832.0	($124.0)	$389.0	$0.0	$0.0	$0.0
Total Other Income (Expense)	$706.0	($117.0)	($202.0)	$832.0	($124.0)	$389.0	$0.0	$0.0	$0.0
Pre-Tax Income	($17,112.0)	($5,352.0)	($3,839.0)	($3,038.0)	($5,050.0)	($17,279.0)	($20,261.0)	($21,722.0)	($22,989.0)
Tax expense (benefit)	$17.0	$0.0	$1.0	$0.0	$0.0	$1.0	$0.0	$0.0	$0.0
Tax Rate	*-0.1%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*
Net Income	($17,129.0)	($5,352.0)	($3,840.0)	($3,038.0)	($5,050.0)	($17,280.0)	($20,261.0)	($21,722.0)	($22,989.0)
YOY Growth	*13.7%*	*-64.5%*	*4.5%*	*44.7%*	*-17.8%*	*2.8%*	*17.3%*	*7.2%*	*5.8%*
Net Margin	-	-	-	-	-	-	-	-	-
EPS	($0.97)	($0.28)	($0.21)	($0.16)	($0.27)	($0.92)	($0.92)	($0.87)	($0.82)
YOY Growth	*-28.9%*	*42.5%*	*27.3%*	*-59.7%*	*-2.3%*	*-19.2%*	*0.4%*	*-5.7%*	*-5.5%*
Diluted Shares O/S	17,629	18,872	18,716	18,818	18,951	18,839	22,000	25,000	28,000

Brian Marckx, CFA

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LEADERSHIP

Management

Michael F. Cola
President and Chief Executive Officer
Mr. Cola served as President of Specialty Pharmaceuticals at Shire plc, a global specialty pharmaceutical company, from 2007 until April 2012. He joined Shire in 2005 as EVP of Global Therapeutic Business Units and Portfolio Management. Prior to joining Shire, he was with Safeguard Scientifics, Inc., a growth capital provider to life sciences and technology companies, where he served as President of the Life Sciences Group.
While at Safeguard, Mr. Cola served as Chairman and CEO of Clarient, Inc., a cancer diagnostics company subsequently acquired by GE Healthcare, and as Chairman of Laureate Pharma, Inc., a full-service contract manufacturing organization serving research-based biologics companies. Prior to Safeguard Scientifics, Mr. Cola held senior positions in product development and commercialization at AstraMerck, a top 20 U.S. pharmaceutical company, and at AstraZeneca, a global biopharmaceutical company.
Mr. Cola received a B.A. in biology and physics from Ursinus College and an M.S. in biomedical science from Drexel University. He serves on the Board of Directors of Vanda Pharmaceuticals Inc., NuPathe Inc. and Pennsylvania BIO, the statewide association representing the bioscience community. He also currently serves as Chairman of the Board of Governors of the Boys & Girls Clubs of Philadelphia.

John H. Leaman, M.D.
Chief Financial Officer
Dr. Leaman served as VP of Commercial Assessment at Shire plc, a global specialty pharmaceutical company, with responsibility for the strategic assessment of licensing and M&A opportunities, including Shire′s acquisition of SARcode Bioscience Inc. Prior to joining Shire in 2011, from 2007 to 2011, Dr. Leaman was a Principal at Devon Park Bioventures, a venture capital fund targeting investments in therapeutics companies, where he oversaw the fund′s investment and corporate board duties in life science investments including Proteon Therapeutics, Inc., Inotek Pharmaceuticals Corp., ZS Pharma, Inc. and MicuRx Pharmaceuticals, Inc.
Prior to that, he was an Associate Principal at McKinsey & Company, where he provided consulting services to senior management of several top 20 pharmaceutical companies including M&A and corporate finance, payer/reimbursement strategies and strategic product development.
He received an M.D. and an M.B.A. from the University of Pennsylvania′s School of Medicine and Wharton School, respectively. He received a degree in Psychology, Philosophy and Physiology at Oriel College, University of Oxford, while completing a Rhodes scholarship. Dr. Leaman received a B.S. in biology from Elizabethtown College.

Garry A. Neil, M.D.
Global Head Research and Development
Dr. Neil was a Partner at Apple Tree Partners, a life sciences private equity fund. Prior to joining Apple Tree Partners in 2012, he was Corporate VP of Science & Technology at Johnson & Johnson, and Group President at Johnson & Johnson Pharmaceutical Research and Development. Prior to joining Johnson & Johnson in 2002, he held senior positions at AstraZeneca, EMD Pharmaceuticals and Merck KGaA. Under his leadership a number of important new medicines for the treatment of cancer, anemia, infections, central nervous system and psychiatric disorders, pain, and genitourinary and gastrointestinal diseases gained initial or expanded approvals.
Dr. Neil holds a B.S. from the University of Saskatchewan and an M.D. from the University of Saskatchewan College of Medicine. He completed postdoctoral clinical training in internal medicine and gastroenterology at the University of Toronto. Dr. Neil also completed a postdoctoral research fellowship at the Research Institute of Scripps Clinic. He serves on the Boards of Reagan Udall Foundation and the Foundation for the U.S. National Institutes of Health (NIH), and is a member of the Science Management Review Board of the NIH. He is past Chairman of the Pharmaceutical Research and Manufacturers Association (PhRMA) Science and Regulatory Executive Committee and the PhRMA Foundation Board.

Nir Shapir, Ph.D.
Vice President of Reseach and Development
Dr. Shapir joined Medgenics in August 2010. From 2006-2010 he held various professional positions in the R&D Chemistry Assay Development Division of Beckman Coulter, Inc., Chaska, Minnesota, including Group Manager of Technology Development; Manager of Discovery and Technology; and Staff Development Scientist Team Leader.
Dr. Shapir received his Ph.D. from the Hebrew University of Jerusalem Faculty of Agriculture, Food and Environmental Quality Sciences. He was a Postdoctoral Associate in the Biochemistry, Molecular Biology & Biophysics Department and BioTechnology Institute of the University of Minnesota.

Phyllis K. Bellin MBA
Director of Finance & Administration
Ms. Bellin received an MBA from Columbia University, New York and worked at Citibank (member of Citigroup Inc.) before coming to Israel in 1980. Since then, Ms. Bellin has managed finance and administration for several early

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stage, high-tech ventures in Israel. Most recently, she was a founder and vice president, finance and administration for Gintec Active Safety Ltd. and RoadEye Ltd.

Board of Directors

Sol J.Barer, Ph.D.
Chairman of the Board of Directors
Dr. Barer spent most of his professional career with the Celgene Corporation, one of the fastest growing and most profitable global biopharmaceutical companies with a market capitalization of $25 Billion, products in over 70 countries with revenues of $4.7 Billion in 2011. He was Chairman of Celgene from January 2011 until June 2011, Executive Chairman from June 2010 until Jan 2011 and Chairman and Chief Executive Officer from May 2006 until June 2010. Previously he was appointed President in 1993 and Chief Operating Officer in 1994 before assuming the CEO position. He also served as Senior Vice President, Science and Technology, and Vice President/General Manager, Chiral Products, from October 1990 to October 1993, and Vice President, Technology, from September 1987 to October 1990.Dr. Barer is presently a consultant to the corporation on strategic matters and R&D.
Dr Barer joined the Celanese Research Company in 1974 and formed the biotechnology group that was subsequently spun out to form Celgene.
Dr. Barer serves as Chairman of the Board of ContraFect, Chairman of the Board of Cerecor and Chairman of the Board of InspireMD and is on the Board of Directors of Aegerion Pharmaceuticals, Amicus Therapeutics and Edge Therapeutics. He also serves as Chair of the Board of Trustees of BioNJ the New Jersey biotechnology organization, is on the Board of Trustees of Rutgers - The State University of New Jersey, the Board of Trustees of the Liberty Science Center and the Board of Trustees of the Tourette Syndrome Association. He also serves as an advisor to a number of biotechnology/medical companies. In 2011 he was Chairman of the University of Medicine and Dentistry of New Jersey Governor's Advisory Committeewhich recommended sweeping changes in the structure of New Jersey's medical schools and public research universities. He previously served as a Commissioner of the NJ Commission on Science and Technology.
Dr. Barer was named one of "The 50 Most Powerful People in N.J. Health Care," in 2012, inducted into the NJBiz Hall of Fame in 2011 and was named as one of NJ's top 10 scientists by New Jersey Business in 2008.
Dr. Barer holds numerous professional awards including the"Lifetime Achievement Award" (International Myeloma Foundation), "Outstanding Individual Award"(The Biotech Meeting 2010), "Dream & Promise Award" (Children's Brain Tumor Foundation) "Odyssey Award" (Center for Medicine in the Public Interest), the "Corporate Vision Award" (Gilda's Club), the "Sparkle of Hope Award" (Community Hope), "Master Entrepreneur Award" (Ernst & Young), "The Hall of Distinguished Alumni Award" (Rutgers University Alumni Federation), "Dr. Sol J. Barer Award for Vision, Innovation and Leadership" (BioNJ), "Science and Technology Industry Medal" (R&D Council of NJ), "Rutgers University Graduate School Annual Distinguished Alumnus Award", "Winthrop-Sears Medal" (The Chemists Club and the Chemical Heritage Foundation), and "Albert Einstein Award in Life Sciences" (Global Capital Associates and Jerusalem Fund, Israel), "DART/NYU Biotechnology Achievement Award in Applied Biotechnology" (Biotechnology Study Center of the New York University School of Medicine).
Dr. Barer and his wife have been honored for community service including the "Overlook Lifetime Achievement Award for Community Service" (Overlook Hospital), the "Community Service Award" (Contact We Care), "Outstanding Philanthropists" (American Foundation for Philanthropy-NJ) and the "Community Service Award" (Union County Torah Center).
Dr. Barer received a Ph.D. in Organic Chemistry from Rutgers University and B.S. from Brooklyn College. Dr. Barer has been married to his wife Meri for 42 years. They have four children and twelve grandchildren.

Eugene Andrew Bauer, M.D.
Executive Member of the Board of Directors
Dr. Bauer has been a member of Medgenics' Board since March 2001. He has been Chairman of the Board since July 2005, assuming the role of Executive Chairman of the Board in October 2010. He is a Lucy Becker Emeritus Professor in the School of Medicine at Stanford University, having served as Dean of the Stanford University School of Medicine from 1995-2001 and as Chair of the Department of Dermatology at the Stanford University School of Medicine from 1988-1995.
Dr. Bauer is currently Chairman of the Board of Directors of Vyteris, Inc., a public company and the maker of the first FDA-approved ready-to-use drug delivery patch. He also serves as a director of a number of other life science and development stage biopharmaceutical companies and medical services companies, including privately held MediSync Bioservices and Dr. Tattoff, Inc. He was a co-founder and emeritus member of the board of directors of Connetics Corporation, a publicly traded, dermatology-focused therapeutics company which was acquired by Steifel Laboratories and sold to GlaxoSmithKline, Inc. He also served as a director of Protalex, Inc., Peplin Biotech, Ltd., PetDRx, Inc. and Modigene Inc., a life sciences company that is developing technology to lengthen the life of various proteins, including EPO and IFN-α.
For 25 years Dr. Bauer was an NIH-funded investigator and has served on review groups for the NIH. He has been elected to several societies including the Institute of Medicine of the National Academy of Sciences. Dr. Bauer received an M.D. from Northwestern University.

Isaac Blech
Director
Mr. Blech is a renowned biotechnology industry investor, who, over the past three decades, has founded and

served on the board of several companies which have produced major advances in a broad array of diseases, including the diagnosis of Chlamydia, herpes, syphilis and HIV, and the treatment of cystic fibrosis, sexual dysfunction, multiple myeloma and brain cancer. The companies he established include Celgene Corporation, ICOS Corporation, Nova Pharmaceutical Corporation, Pathogenesis Corporation and Genetics Systems Corporation.
Mr. Blech is a major shareholder and a Director of BillMyParents, Inc. (formerly Socialwise, Inc.), an innovator in e-commerce for the youth market; ContraFect Corporation, a company developing therapies for infectious diseases; and Premier Alliance Group, Inc., a public financial consulting company. Mr. Blech is also a major shareholder of Stratus Media Group, Inc., a public company that owns, promotes and operates live entertainment events, and a founder, Director and major shareholder of Cerecor Inc., a private company developing new treatments for central nervous system disorders.
From February 2011 until his election as a director in June 2011, Mr. Blech served as a member of the Medgenics Strategic Advisory Board.

Alastair Clemow, Ph.D.
Director
Dr. Clemow was appointed to the Medgenics' Board in August 2010. He serves as President and Chief Executive Officer of Regentis Biomaterials, a private company developing an innovative material for cartilage repair. Previously, he held positions of president and chief executive officer in a number of companies that he helped found, including Nexgen Spine, Inc., which developed an artificial spinal disc; Gelifex, Inc., which developed an innovative spinal nucleus replacement implant and which was acquired in 2004 by Synthes Spine, Inc.; and Minimally Invasive Surgical Technologies, Inc., which developed a novel series of implants for minimally invasive total knee replacement and which was acquired in 2005 by MAKO Surgical Corp.
From 2000 to 2004, Dr. Clemow served as Principal of Tanton Technologies, Inc., an organization that provided strategic and technical assessment of new medical device opportunities for large, mid-cap and early stage development companies. From 1981 to 2000, Dr. Clemow held numerous positions with Johnson & Johnson, including Vice President of Worldwide Business Development for Ethicon Endo-Surgery, Inc.; Vice President of New Business Development for Johnson & Johnson Professional, Inc.; and Director of Research and Development of Johnson & Johnson Orthopedics. In those capacities, Dr. Clemow was responsible for acquiring or developing what today represents billions of dollars of Johnson & Johnson revenue.
Dr. Clemow serves or has served on the boards of numerous private and public companies including Encore Medical; Echo Healthcare Acquisition Corp.; BioMedical Enterprises, Inc.; and Kinetic Muscles, Inc.
Dr. Clemow holds an M.B.A. in Finance from Columbia University and a Ph.D. in Metallurgy from University of Surrey, Guildford, U.K.

Michael F. Cola
(bio above)

Wilbur H. (Bill) Gantz
Director
Mr. Gantz is President of PathoCapital, an investor in healthcare companies. He previously served as Executive Chairman and Chief Executive Officer of Ovation Pharmaceuticals, Inc., which was sold to Lundbeck, AG in 2009, and as Chairman, Chief Executive Officer and President of PathoGenesis Corporation, a biopharmaceutical company that was sold to Chiron, Inc. in 2000. Prior to founding PathoGenesis, from 1987 to 1992 he served as President of Baxter International, Inc., a manufacturer and marketer of healthcare products. He joined Baxter in 1966 and held various management positions, including Vice President, Europe and President, International Division, prior to being named Executive Vice President and Chief Operating Officer in 1980.
Mr. Gantz holds a BA degree from Princeton University, where he graduated cum laude, and an MBA from Harvard Business School

Joseph J. Grano, Jr.
Director
Mr. Grano is Chairman and CEO of Centurion Holdings LLC, a provider of advisory services to public and private clients on all facets of business strategy and capital markets access. Previously he was Chairman and CEO of UBS Financial Services Inc. UBS/PaineWebber, subsequent to the merger between UBS and PaineWebber in 2000. Prior to joining PaineWebber he held various senior management positions at Merrill Lynch including Director of National Sales.
Mr. Grano is the former Chairman of the Board of Governors of NASD and was a member of the NASD′s Executive Committee. He was appointed by President George W. Bush in 2002 to serve as the Chairman of the Homeland Security Advisory Council, a position he held until August 2005.
Mr. Grano was a captain in the U.S. Special Forces (Green Berets), and is a member of the City University of New York's Business Leadership Council and a former member of the National Board of D.A.R.E. He holds honorary Doctor of Law degrees from Pepperdine University and Babson College, as well as an honorary Doctor of Human Letters degree from Queens College. He serves on the Board of Directors of the YMCA of Greater New York and of Lenox Hill Hospital in New York City.

Joel Stephen Kanter
Director

Mr. Kanter has been a member of our Board since August 2000. Since 1986 he has served as President of Windy City, Inc., a privately held investment company specializing in early stage venture capital. Mr. Kanter serves on the board of directors of several public companies, including Magna-Lab, Inc., formerly involved in the development of a cardiac MRI device; Vyteris, Inc., a drug delivery company that manufactures the first FDA approved ready-to-use drug delivery patch; and WaferGen, Inc., which develops, manufactures and sells systems for gene expression and genotyping.
Mr. Kanter is also on the board of a number of private concerns including DTS America, Inc., a medical imaging company; First Wave Technologies, providing business expertise to seed stage companies and projects; MediSync Bioservices, an owner and operator of clinical research organizations; Pacific Biosciences, Inc., the manufacturer of the Clarisonic dermatological product; and Prescient Medical, Inc., a cardiology products company that has developed a methodology for identifying and treating vulnerable plaque. He is a trustee and past president of the board of trustees of The Langley School in McLean, Virginia, and a trustee of Union Institute & University.
Mr. Kanter is also the current board chair of the Black Student Fund and a vice-chair of the Kennedy Center's National Committee on the Performing Arts.

Stephen D. McMurray, M.D.
Director
Dr. McMurray was appointed to the Medgenics' Board in December 2005. He is Vice President, Clinical Integrated Care Management Services for Village Health, a subsidiary of Davita Inc. Dr. McMurray was one of the founders of Renal Care Group, Inc., a company that provided chronic dialysis services. He served on the Board of Renal Care Group until its US $3.5 billion acquisition by Fresenius in March 2006. He is a past member of the Renal Physicians Association Board and has authored a myriad of articles on renal-related topics published in professional medical journals.
Dr. McMurray is active in developing processes to improve patient care and outcomes. He served as the Medical Director of the Fresenius Medical Care Health Plan from May 2006 to July 2010 and as Medical Director of Integrated Care for Fresenius Medical Care – North America from March 2006 to July 2010. Dr. McMurray received an M.D. from Indiana University Medical School in 1972, followed by medicine residency and nephrology fellowship at Indiana University Medical Center.

Andrew L. Pearlman, Ph.D.
Director and Senior Advisor
Dr. Pearlman founded and served as CEO and President of Medgenics. He has over 25 years′ experience founding and managing biotechnology and medical device companies, as well as inventing and developing biomedical technology.
Prior to founding Medgenics, Dr. Pearlman founded and served as CEO and chief scientist for TransScan Research & Development Co., Limited, under whose leadership the company's product, the T-scan 2000 breast impedance scanner, was the first new medical imaging method for cancer detection to receive FDA pre-market approval in over 20 years. He has also founded or co-founded several other companies in the fields of diagnosis and patient monitoring.
Dr. Pearlman holds a Ph.D. in biophysics from the University of California, Berkeley, where he completed his doctoral thesis under Nobel Laureates Professors Melvin Calvin and Donald Glaser.

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Hold/Neutral: The analyst expects that the company will perform in line with the broader U.S. equity market over the next one to two quarters.
Sell/Underperform: The analyst expects the company will underperform the broader U.S. Equity market over the next one to two quarters.

The current distribution is as follows: Buy/Outperform- 15.9%, Hold/Neutral- 78.3%, Sell/Underperform – 5.5%. Data is as of midnight on the business day immediately prior to this publication.