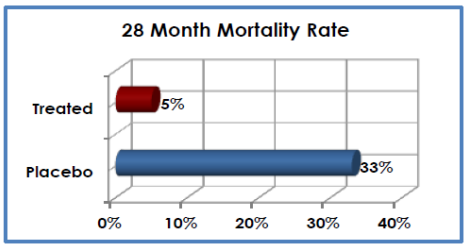
January 28, 2013

Regenerative Cell Therapy: A Year of Inflection:Part II

An Update from our Cardiologist Dinner and Post San Francisco Thoughts

Companies mentioned include:
Aastrom (ASTM) – Buy – $1.28
Abbott (ABT) – NR – $32.79
Athersys, Inc. (ATHX) – Buy – $1.25
Baxter (BAX) – NR – $68.00
Cytori Therapeutics, Inc. (CYTX) – Buy – $2.79
CytoMedix (CMXI) – NR – $0.68
Dendreon (DNDN) – Buy – $6.25
Immunocellular (IMUC) – Buy – $1.98
Mesoblast Limited (MSB AUX) – Buy – $29.35
NeoStem, Inc. (NBS) – NR – $0.61
Osiris Therapeutics, Inc. (OSIR) – NR – $8.45
Pfizer (PFE) – NR - $27.00
Neuralstem (CUR) – Sell – $1.26
Pluristem (PSTI) – Buy – $3.05
ReNeuron (RENE.L – £$2.72 – NR)
Teva Pharmaceuticals (TEVA) – NR – $37.73

Cytori's cell therapy could be the first to the marketplace. Our channel checks suggest Baxter's autologous trial and Amorcytes are having trouble enrolling patients, while Cytori's is ahead of schedule.



Source: Cytori

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- We held a Cardiology Dinner with three world-class key opinion leaders, Emerson Perin, MD, Kenneth M. Borow, MD, and Warren Sherman, MD. Representatives from Mesoblast and Cytori were present, and, as such, a lot of the discussion was focused on how these therapies may develop and how cell therapy may impact the current standard of care in CV medicine.

- A few take-away messages: The Cytori U.S. CMI trial is enrolling rapidly. Our experts tells us the liposuction is "no big deal;" however, our experts were negative on Baxter's GcSF-based cell therapy.

- We reviewed the Mesoblast data, and our experts found the high-dose data absolutely compelling when considering all the parameters of cardiac health and cardiac MACE. Dr. Borrow reviewed the design and assumptions on Mesoblast pivotal trial.

- We also discussed the implications of cell therapy for the device companies. How will a successful cell therapy change the use of defibrillators? Our experts were very positive about bio-absorbable stents, and Abbott was mentioned favorably.

- In this update, we review the several key issues in cell therapy cardiology—from trial design to manufacturing. We conclude that cell therapy is coming, and Cytori and Mesoblast are both ideally positioned. We are also watching the enrollments on the Aastrom PIII trial.

SEE PAGE 26 FOR IMPORTANT DISCLOSURES AND DISCLAIMERS

A REVIEW OF OUR CARDIOLOGISTS DINNER

We held a dinner with three of the most prominent cardiologists in the cell therapy space last week—Emerson Perin, MD, Kenneth M. Borow, MD, and Warren Sherman, MD, FACC, Director, Stem Cell Research and Regenerative Medicine, Center for Interventional Vascular Therapy, Columbia University Medical Center. Last week, Dr. Sherman held a conference (*http://celltherapy.crf.org/)* in which thought leaders from all over the world met at NYPH/Columbia University Medical Center to review the latest developments in the cell therapy- cardiology space.

A few thoughts about the dinner:

1. **Ejection fraction is not a good, and definitely not an approvable endpoint** in a cardiac trial. Rather, the FDA and EU will focus on measures that assess total cardiac health. This means composite endpoints, which will likely include cardiac MACE. MVO_2 was also discussed as a valid endpoint for certain ischemic disease states such as is present in CMI (Chronic Myocardial Ischemia).

2. **Our expects found the high-dose arm of the Mesoblast P2 data to be profound** in that:
    a. All cardiac measures pointed to real improvements in cardiac health and function.
    b. Cardiac MACE was striking between the high-dose and control arms, with zero cardiac MACE rates in the high-dose group.
    c. MVO_2 is a valid measure when done properly, as it has been used in the Cytori CMI trial.
    d. There exists a critical mass, a critical-dose threshold that must be achieved, above which additional cells don't matter (and in fact, additional cells may result in crowding and a loss of effect, so finding the right dose is critical).
    e. The Mesoblast P3 at n=1700 is powered for a "cardiac" meaningful QOL difference, and the assumptions are conservative.

3. **One doctor discussed Baxter and NeoStem, saying that the trials are very difficult in terms of enrolling patients**. His hospital has not yet been able to enroll a single patient in the NeoStem STEMI trial, (We did check with NeoStem management who implied that the trial is close to reaching its half way mark), and he has had patients fall out of the Baxter CMI trial. Our physician said administering GcSF to patients (Baxter trial) creates a host of unwanted adverse events. As such, he does not believe if a Mesoblast or Cytori trial shows equivalent data that the Baxter cell therapy will be viable. This may explain our other channel checks that have shown that Baxter has been shopping its cell therapy division to buyers, looking for a strategic exit.

4. **Our cardiologists were positive on Cytori**. They all agreed that liposuction is no big deal and that patients are actually excited to have it done. Get a love handle busted in the process of having your heart fixed. Liposuction was viewed as "patient friendly" versus an extensive bone marrow harvest (NeoStem) or GcSF apheresis cell collection (Baxter).

5. **One doctor stated that the key difference (in his opinion) between Mesoblast's approach and Cytori's is the homogeneous cell population associated with Revascor versus Cytori's heterogeneous population.** He remarked that the difference in results will need to be shown clinically. Cytori argued that retreatment (should it be needed) is safer with autologous therapy.

6. **Cell aging—synesis.** We enjoyed a discussion on autologous versus allogeneic therapies and the impacts of synesis. One of our experts remarked that adipose tissue may be somewhat insulated from the effects of synesis versus marrow-derived sources. This would clearly be positive for Cytori and negative for autologous-marrow-derived companies (Baxter, NeoStem, and Aastrom). With that said, the discussion turned to passage-induced cell aging and a discussion on how old, even healthy donor-sourced cells truly are, given the number of cycles the cells have seen as a result of their expansion.

7. **All doctors agreed that therapies that are off-the-shelf ready** (or virtually so, like Cytori), have a significant advantage if they are equivalent to processed therapies in terms of efficacy. So highly processed cell therapies that takes days to make likely won't be successful in the future, unless they have a real definable efficacy advantage (which our panelists seemed to believe is unlikely). In addition, cost of good will be relevant. If an autologous therapy and an allogeneic therapy are equivalent, COGS become a critical factor. We know that in the case of Cytori, COGS may actually be lower than allogeneic. In the case of Aastrom, we believe COGS may be in line to slightly higher. Other highly processed autologous therapies are suggested to have very high COGS (much lower margins). The extreme example of this is Dendreon's Provenge.

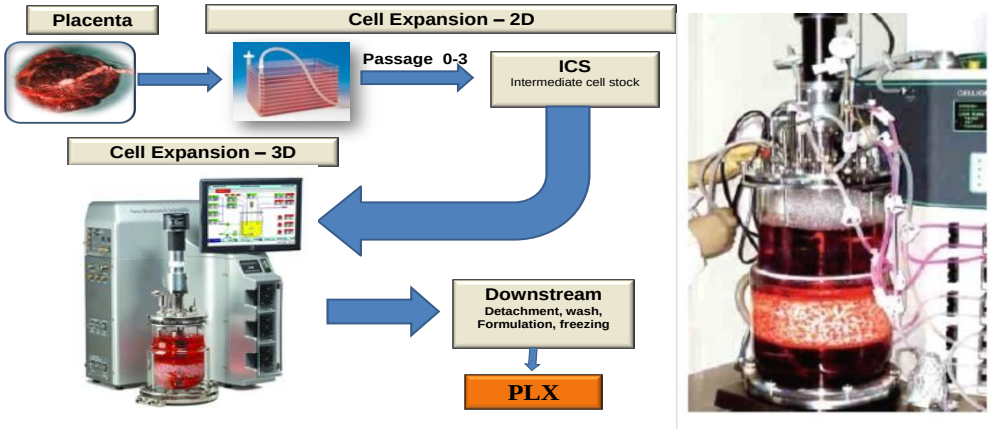
8. **Dose is key.** We had some discussion on dosing and manufacturing. The ability to treat local disease (heart disease) allows relatively low doses (20-200 million cells). These yields are feasible with the majority of manufacturing processes in place today. However, as our discussion migrated towards treating more systemic disease, our panelists agree that higher doses will be needed. This means manufacturing will be a critical success factor for our companies.

Manufacturing is Critical, and Not All Approaches are Robust

a. Mesoblast was emphatic that its manufacturing operation through Lonza is now ready to go, to supply the clinical needs of a 1,700-person global CHF trial. We know that the Mesoblast cell line is a precursor MSC, is very potent, and is expanded, with tight controls in place. We also know that with Lonza (Singapore) Mesoblast has developed certain strategic tax advantages that complement its manufacturing process.

b. We recently reviewed Pluristem's manufacturing progress. The new facility is coming on-line each day, and the company has invested significant resources into process controls around their 3D-BioReactor expansion process. Pluristem intends to manufacture several variations of its PLX cells, optimized for the disease – therapeutic target it is pursuing. For example, as the company pursues critical limb ischemia (CLI), the plan is to produce a cell product optimized to treat ischemic conditions. By controlling the bioreactor parameters, Pluristem believes it can in fact develop a tailored product for ischemia and a different variation for treating fibrotic disease (for IPF as an example).

Exhibit 1. Pluristem has a 3D BioReactor with detailed process controls, which are used to control the product for both consistency and quality. The 3D process is said to be 70x more efficient than traditional 2D methods.

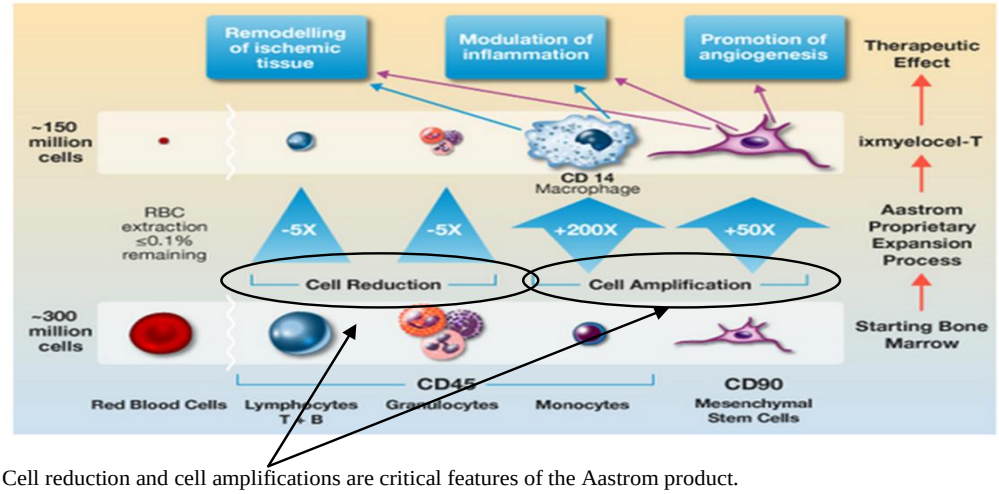


Source: Pluristem

c. We also spent time with Athersys. Athersys (also working with Lonza) has a robust process in place. Athersys is prepared to develop systemic high-dose therapy (cell doses > 1 billion). In this regard, Athersys believes it is in a strong position to treat certain conditions (GvHD and stroke), where high-dose systemic therapy is needed to develop a consistent effect. We include a discussion of the Athersys stroke trial in the last pages of this report as we find the trial, the dose, and the mechanism of action to be exciting and well thought out. **As such, the PII data set expected this year may be among the most important events in the cell therapy space in 2013, in our opinion.**

d. Aastrom: We have spent considerable time discussing COGS with the Aastrom management team and new CEO, Dan Orlando. We believe Aastrom—now in a pivotal PIII trial in CLI—has its core technology based on its cassette "pod" based manufacturing systems. Aastrom has spent the past decade perfecting this system. The company sees COGS at 10% of the target commercial price, ensuring biotech like margins. We note that in CLI unlike heart disease, we might expect multiple treatments required. As such, if a benefit does exist for autologous versus allogeneic therapy, it may show up in retreatment scenario. Aastrom is unique among the cell therapy companies as it does manipulate (expands/shrinks) its "selected" cells within the normal populations mix to create the right heterogeneous "optimized" mix of cells. If in fact, a heterogeneous population is better than a homogeneous one, Aastrom would benefit with the potential to optimize its heterogeneous mix. **This debate (heterogeneous or homogeneous) represents a critical "wild card" that will only be resolved with clinical data.**

Exhibit 2. Aastrom's ixmyelocel-T has now been fully characterized. We view this as a very important advance the company has made over the past year – and one that will be critical for meeting regulatory "potency" and manufacturing QC requirements**.** Aastrom believes that the uniqueness of its product revolves around the amplifications of certain specific cell types such as CD90+ (MSCs) and CD14+auto+ (M2 Macs), as well as the cell reduction of other cell types.



Cell reduction and cell amplifications are critical features of the Aastrom product.
Source: Aastrom

Other comments from our dinner:

1. Our cardiologists expressed great excitement about bio-absorbable stents, particularly the Abbott stent. They seem to all agree that a bio-absorbable stent would make a metal stent obsolete in the future.

2. Doctors also said in the future, defibrillator use is likely to go down as cell therapy rises. One doctor said: "Would you want a metal can with wires in your chest"?

3. Cell therapy is real. The next forefront will be our ability to move beyond trophic effects of cells and to our ability to rebuild tissue. We are not there yet, but that is clearly where the research is heading.

4. Cell therapy works. We have no doubt. We have seen some patients rebound in astonishing ways. However, it's been hard to predict who will benefit maximally versus minimally. More consistent manufactured therapies in larger, better controlled studies should yield the answers. We are excited by the work that Baxter, Cytori, NeoStem, and others are doing.

5. Regulators understand what we are doing more and more. Ejection fraction is not the endpoint; it's cardiac health. Fears over allogeneic (immune rejection) are becoming less, as regulators see data that's shows that cells trigger changes, in other resident cells, that drive the long term benefits.

Conclusion: Our doctors were very positive for Cytori and Mesoblast trials in CMI and CHF, respectively. They were not positive for the Baxter (CMI) trial based on the use of GcSF and the cumbersome collection process. All of our experts agreed and were very excited for Abbott's bio-absorbable stent, and believe we will see a rapid conversion once it's introduced, making the use of metals stents obsolete.

Our fundamental question around cell therapy is: Is it real? Is there a product that can be successfully commercialized? Can cell therapy really go beyond what's possible with traditional medicine? Can disease that is untreatable today be treated, and can unmet medical needs be met? **We believe the answer is yes. Our doctor panelists agreed.** The uniformly positive answer is based on our and their review of mountains of human trial data, and these clinicians' independent, individualized case experiences, where patients who were expected to die resumed normal active lives.

In fact, we believe the question "is cell therapy real?" is the wrong one to ask. Smart investors can review the data from hundreds of trials, most of which have been ad-hoc investigator-led studies that have all suggested positive trends. However, what the industry had previously lacked was well designed, controlled studies. That has now changed. Studies like Aastrom's Phase III trial in CLI, Baxter's Phase III trial in CMI, Cytori's Phase III trial in STEMI (and Phase II Pilot study in CMI), Pluristem's Phase II/III CLI study, Athersys' Phase II ulcerative colitis study (and now a Phase II stroke study), and, of course, Mesoblast's 1,700-patient Phase III study in CHF (sponsored by Teva) are just a few of the current, well designed trials that are likely to lead to new breakthrough treatments for large medically untreated conditions today. Just imagine if Athersys is successful is bringing to life the first treatment for stroke victims that minimizes the secondary damage and aids in the recovery. What is the value creation to society?

It's not just on the regenerative medicine side. We must also include oncology and immunology. In fact, we would argue that Athersys' MultiStem in the settings of stroke, ulcerative colitis, and GvHD is acting on the immunological side of the body. We are admittedly fascinated with Immunocellular's third-generation cell therapy for the treatment of glioblastoma (fatal brain cancer). The Phase II trial is fully enrolled and data is expected by year end. The treatment has few (if any) side effects, and we believe it has the potential to dramatically alter treatment outcomes (survival). While Dendreon's Provenge represents a milestone in the industry, it is a first-generation therapy—that is, in our opinion, not ideal. Its efficacy is not dramatic versus the standard of care, it is expensive, and the treatment is cumbersome. By comparison, Immunocellular's third-generation dendritic vaccine has several critical advances that include targeting multiple antigens (six in total), the ability to manufacture multiple doses in one setting and cryopreserve them (which cuts the cost per dose to a fraction of Provenge's), and the product ICT-107 using "Super DCs," which secrete IL12; IL12 is critical for T cell killing. Thinking beyond Immunocellular and ICT-107 is the plasmid-based technology behind companies like Inovio. Inovio is developing synthetic vaccines focused on cancers and infectious diseases based on the company's SynCon technology. The technology enables the design of an ex-vivo plasmid like (engineered) construct that can produce T-cell responses once introduced into the body (no harvesting of immune system cells needed).

So what is it going to take for valuations to reflect our enthusiasm? First, **clinical data**. As we mentioned previously, we believe investors will take notice of clinical data, and we are on the precipice of a lot of data: Data from Immunocellular's phase II trial in glioblastoma, data from Cytori's Phase II pilot study in CMI, Phase II data from Athersys' (and its partner Pfizer) global ulcerative colitis study and stroke trial, progress in Aastrom's pivotal CLI trial, progress in NeoStem's Phase II STEMI trial, progress in Baxter's phase III CMI trial, the start of Mesoblast's (and Teva's) Phase III CHF trial, and many, many others. But just as it has taken time and capital for these companies to advance their clinical programs (clinical trials to mature and the data to emerge; while not every trial will produce stunning results, for those that do, it should represent significant advances and will have been worth the wait, in our opinion), it is also taking time for our second point: **stakeholder awareness**. While smart institutions follow the data, companies have yet to engage stakeholders. What we mean by stakeholders comes down to a combination of not just those in the medical community (doctors and key opinion leaders, or KOLs), but also patients themselves. The media has been so focused over the controversies involved in embryonic research that it has been slow to understand the impact that cell therapy can have on chronic disease.

We believe cell therapy represents a pathway towards easing the burdens of chronic diseases like heart failure, creating sharp pharmaco-economic value and improved quality-of-life outcomes.

Companies themselves have not directly targeted stakeholders, who tend to be savvy and research the latest trials and treatments. We believe the combination of clinical data and stakeholder awareness sets the stage for a rebound in valuation in the sector.

On the regenerative side, there is a focus in cardiology. As discussed, we see 2013 as a year where we will begin to see results from multiple late-stage trials underway. These trials are evaluating the use of stem cells as a therapeutic to either arrest the progression of heart disease or to even reverse the disease state itself. The largest heart cell therapy trial ever undertaken is the endeavor of an EU consortium funded public trial, known as BAMI, a 3,000 person trial that will use bone marrow cells (autologous) injected into the heart five days post infarct. While BAMI is exciting, it is doubtful that this trial will be completed in a timely manner, in our opinion, and it's not clear how a therapy will be developed from the trial. The trial, however, is intended to prove that stem cells can repair and arrest the progression that typically follows severe heart attacks. The more interesting commercial trial we would focus upon is the Mesoblast (partnered with Teva) 1,700-patient global trial in CHF. Teva's new CEO Dr. Jeremy Levin has now openly stated Teva's support and intention to move forward with this trial. Some of the other advanced trials include Baxter's phase III trial evaluating the use of GcSF-derived stem cells that are harvested from the patient via apheresis. Other trials use a bone marrow harvest; for one company, this is small at 50cc (Aastrom), while another company's is large (NeoStem) at > 300 cc of tissue. More recently, the use of adipose tissue (fat) has come into focus as a rich source of cells that can be harvested via liposuction (Cytori). These methods are all autologous—your own cells. Generally speaking, autologous methods are expensive as they involve offsite processing of the cells—in some cases, in cultures (expanded), and in other cases, enriched for a specific cell type. In the case of adipose stem cells, they are processed "while you wait" (on site in an hour or less), and at a very low cost of goods (Cytori). All of these methods have pros and cons and will also have to compete against the cells in a bottle, or allogeneic sources. In this case, the cells are initially developed from a donor source, processed at a cGMP factor, fully tested for potency and safety, and cryopreserved so that they can be administered to the patient when needed, especially true in an acute setting. The product is controlled for quality and may be homogeneous (all one cell type) or heterogeneous (many cells types), but within a set of release criteria. These cells are in effect an active biological therapeutic—an off-the-shelf-ready product. The cost of goods of a mass-produced, allogeneic product is likely to be the lowest in the industry versus a custom-produced, offsite-manufactured product, which will likely have the highest cost of goods.

This thinking points us to a series of questions:

1. Should cell therapy be used in the acute setting—and if so, does it have to be off-the-shelf-ready (allogeneic) or adipose-derived (virtually off the shelf) ready?
2. The Battle between autologous versus allogeneic. Can patients be retreated with an allogeneic therapy? Do allogeneic therapies (expanded) induce artificial cell synesis (aging). Are aging and co-morbidities the Achilles heel of autologous therapy? Is adipose-derived cell therapy advantageous over bone marrow as a source ?
3. As cell therapy is shown to "work," will it work for some indications and not others?
4. Will one cell therapy product work better than another?
5. Will COGS matter and, if so, when?
6. How important is patient convenience and fitting into the existing treatment paradigm?
7. Will cell therapy raise the costs of treating disease or lower it?
8. When will cell therapy be available?

So what's new since our last update? Cardiology is coming into focus; manufacturing is critical as is dose; and the arguments between autologous and allogeneic continue to advance. As clinical trials advance, so does the need for cash. Athersys, Cytori, Pluristem (and on the oncology side, Immunocellular) have all raised capital and head into 2013 with strong balance sheets.

Balance sheet strength may become a powerful differentiating factor for companies in the period ahead. We say this because those companies that are on the verge of completing Phase II proof-of-concept studies that lack balance sheet strength will need to raise capital for larger Phase III pivotal studies. These companies will either need to find a partner or raise capital themselves. In these instances, we believe the challenge they face will be the SWOT analysis that investors will perform. When will the company be able to bring the product to the marketplace? At what cost of goods? At what patient convenience? Is the therapy readily available (good for acute setting) or does it require processing? Is the therapy invasive and, if so, how invasive? Is there risk associated with the harvest? How do these factors competitively compare?

Clinically, we have seen movement.

- Teva has firmly decided to move forward with Mesoblast on its 1,700 person trial. The company confirmed this at its analyst day and at JP Morgan conference in SFO.

- Cytori's U.S. phase II (pilot-PMA) CMI trial is now rapidly enrolling (our experts confirm that channel checks are positive). We may see data by year end. Progress in Japan and unit placement of systems is now driving revenues, and we may see Cytori move to a self-sustaining revenue model, while trials in the United States and Europe progress.

- Pluristem has a new manufacturing facility advancing through review with a high capacity (150,000 patient doses). This sets the stage for the start of the phase II/III CLI study. Pluristem has provided a detailed update on its new control systems that, coupled with its bioreactors (3D), allow it to control the product for quality, consistency, and product attributes.

- Aastrom and Immunocellular have new CEOs at the helm (at Aastrom, the new CEO has commercial experience). Baxter is in fact shopping its cell therapy division. We await updates on Aastrom's progress in enrolling patients in CLI.

- NeoStem has divested its interest in China, and the company is now focused on two parts—as a clinical manufacturing company and the ownership of the Amorcyte trial. PCT continues to win clinical contracts (positive), but we see at best only an incremental ability to produce free cash flow versus its value as a strategic asset. PCT represents a manufacturing solution for Amorcyte's cell therapy. We are also concerned that trial enrollment maybe falling behind schedule (our channel checks have been negative), causing a depletion of capital resources. Good results at NeoStem could lead to two PIII STEMI trials that are even larger and longer and may cost > $100 million. A strategic partner seems like the only way forward for the company. On that front, we wonder if a Baxter cell therapy-NeoStem combination could happen in 2013. The product fit and IP overlap is excellent, and PCT solves Baxter's manufacturing problems with a consolidated IP estate.

Some of the key issues both companies face are the time to the marketplace, the funding to complete pivotal trials, competition against less expensive therapies that are off-the-shelf ready with equivalent efficacy and less risk, and being patient friendly (no bone marrow harvest; no GcSF). If Cytori, Athersys, Mesoblast, and Pluristem (for example) are successful, they could make these highly processed, more expensive, and less patient-friendly therapies obsolete.

We also know that Baxter has been looking to divest its current CD34+ autologous cell therapy business. Why? Unofficially, Baxter seems to be implying that the current pipeline of opportunities is running into P&L pressures. However, we believe this is not really the underlying problem. According to Baxter's most recent filing, the company has $3.1 billion in cash (September 30, 2012), but it does have substantial debt, too. In the quarter, the company reported $3.4 billion in revenues and $583 million in net income. Baxter is a profitable, cash-generating company.

We believe that Baxter has concerns regarding the treatment paradigm (autologous) and the cost of goods sold. Dendreon's problems have been keenly watched by major pharma and biotech companies that shun the concept of personalized autologous therapy.

Once identified as candidates for therapy, CMI patients need to have their cells extracted and processed. This process requires apheresis (single site), manufacturing at a central location (which is labor- and process-intensive), and subsequently returning to the clinical site for patient injection. We estimate this process at commercial scale to be (best case) $10,000 per unit or higher.

Baxter's intense process and high COGS compare to:

1. **Local autologous processing**—that is, patient samples processed on site at the hospital and then immediately delivered back to the patient. This is the Cytori process, in which patients undergo a modest liposuction and then cells are processed and returned. We estimate the COGS of this process to be a minimal $250-$500 per unit. We estimate the process time to be approximately one hour. We also note (as do the authors in the cited article; front page: "Buying New Soul") that adipose tissue appears to represent a more robust source of cells that are protected from the age factors (cell senescence)

2. **Standardized autologous process.** This is the Aastrom model, in which a small patient sample (50 cc) of bone marrow is harvested. Over a period of days, the cell population is expanded (the good cells) and minimized (the bad cells), and then a finalized, optimized product is returned to the clinical site. Aastrom's origins are in manufacturing, and we believe COGS will be optimized around 10%.

3. **Allogeneic: "pills in a bottle."** Of course, the ultimate competition for an autologous product is an allogeneic one, in which cell aging and a loss of therapeutic potency is removed from the equation. Here too we believe COGS are likely in the sub $1,000 per unit range. We also like the treatment paradigm, as this is a product that is truly "off-the-shelf" ready and can be delivered to the patient with no prior intervention.

4. **What about cell aging (cell senescence)?** The authors of the article "Buying New Soul," (Emerson C. Perin, MD, PhD; James T. Willerson, MD) have shown that dysfunction of stem cells harvested from the bone marrow of aged patients has been clearly demonstrated and verified in cell therapy trials of autologous bone marrow cells in patients with heart failure. The authors site the FOCUS-HF (First Bone Marrow Mononuclear Cell United States Study in Heart Failure) trial, **which showed that the regenerative capacity of the mesenchymal compartment of bone**

marrow cells was greater in younger patients than in older patients, **and this improved proliferative ability translated into better clinical outcomes**. In the largest study of cell therapy with autologous bone marrow cells in patients with chronic heart failure, better functional outcomes also were identified in younger patients and were associated with the presence of specific cell phenotypes.

5. **Using stem cells from other tissue sources may circumvent the problem.** The authors of "Buying New Soul" discuss the impact of age on the decline in potency seen in bone marrow cells. The authors go on to discuss animal results that have shown that adipose tissue seems to be a promising source of stem cells. "In a preliminary study in patients with ischemic cardiomyopathy, we have shown that the transendocardial injection of adipose-derived regenerative cells was safe and feasible, with encouraging efficacy data. **The resiliency of adipose tissue is evidenced by patients' ability to gain weight easily, even in the presence of multiple comorbidities known to inhibit stem cell function**. **It may be that certain tissues are less exposed to the detrimental effects of disease and aging".**

6. **However, our expert cardiologists suggest that allogeneic cells may also have age problems as a result of expansion (passages).** Our experts agree that, right now, it's not a question of which therapy or which approach works better than another. Instead our experts tells us, it's the ability to treat patients with a therapy that "works," is easy to use (for patients and doctors), is cost effective, and fits well within the existing treatment paradigm.

Generally speaking, our experts agreed that it is no longer a question of if—but when? They cited "mountains of pre-clinical" and now clinical evidence that cell therapy is effective in treating everything from the primary damage associated with heart attacks to the chronic damage associated with myocardial ischemia and congestive heart failure. Our experts also discussed the enormous potential for cell therapy to not only be used as an effective treatment for arrhythmias, but also a substantially cheaper treatment compared to some of the pacemaker and defibrillator options that are in use today. As such, our experts suggest that the future of cell therapy may make many of the standard-of-care treatments in use today obsolete. Clinically, our experts cited several trials that they believe have shown great promise, such as:

- Baxter's CMI trial (now in Phase III); however, our experts tell us enrollment is slow and keeping patients in the trial has been a problem.
- Amorcyte: PII STEMI trial (Amorcyte is a subsidiary of NeoStem) of bone-marrow enriched CD 34+ cells, similar to the Baxter product. Again, our experts have said patient consent and subsequent enrollment has been a problem.
- Cytori's (APOLLO PII Trial) and now the ADVANCE (PIII European) trial, both in STEMI (heart attacks).
- Cytori's PRECISE trial (PI/II) and now the ATHENA trial (PII-Pilot) in CMI patients. Our experts tell us that the CMI trial is enrolling ahead of plan.
- Aastrom's PII trial in DCM (dilated cardio myopathy patients) and the PIII CLI trial.
- BAMI: (public consortium): EU-sponsored, 3,000-person study using bone marrow for MI.
- Mesoblast: 1,700-patient, Phase III CHF trial sponsored by Teva expected to begin in early 2013.
- Athersys: PI/II proof-of-concept study in MI using off-the-shelf ready MultiStem.
- Osiris: completed PII proof-of-concept study in MI, using off-the-shelf ready Prochymal.

Exhibit 3. Some of the approaches of public companies in the cardiology space

Company	Cell Type	Source	Type and COGS	Manufacturing	Development Status
Athersys	MAPC (Multipotent adult progenitor cells), expanded ex-vivo and highly enriched.	Single Donor, Expanded in Culture	Allogeneic - universal compatibility, LOW COGS	cGMP Manufacturing able to produce millions of doses from a single batch of cells processed.	Phase II Trial for ulcerative colitis, Phase II trial for Stroke, Phase I proof of concept in MI completed
Aastrom	Bone Marrow derived population of cells which is expanded over a period of days. Good cells are expanded, "bad" cells are reduced.	Adult bone marrow harvest (50 cc)	Autologous adult cells, Low to Medium COGS	Expanded and Population optimized with good cells expanded and bad cells shrunk.	Phase 3 trial in CLI, Phase II trial in DCM
Baxter	CD 34+ GcSF derrived MSC's	Adult peripheral blood	Autologous adult cells, High COGS	Validated industrial scale production, millions of doses of cells from a single donor	Phase III trial in CMI
Cytori	Adherent stromal cells (ASC) derived from adipose tissue, on site	Adipose Tissue	Autologous adult cells - LOW COGS	On-site in 60 minutes or less, minimal manipulation. Stem cells extracted from adipose tissue.	Phase III trial in STEMI, Phase II trial in CMI
Mesoblast	Highly selected precursor MSC cells that are immune-privledged and believed to be up to 10,000 > potency than MSC's	Single Donor	Allogeneic - universal compatibility - LOW COGS	Large production facility in Singapore where cells are expanded and tightly monitored for passages. Cell type selected with MaB technology.	Large Phase III (N=1700) in CHF
NeoStem	Bone Marrow derived >300 cc (invasive procedure) and processed with 72 hour life from harvest to return. Process enriches the sample for CD 34+ cell type	Adult bone marrow harvest > 300cc	Autologous adult cells - HIGH COGS	Cells are harvested from Bone Marrow for up > 300 cc. Cells are processed over 24-72 hours and returned to patient. Cells are enriched for CD 34 content.	Phase II trial is now enrolling.
Osiris	Mixed population of stem cells expanded ex-vivo	Single Donor	Allogeneic - universal compatibility LOW COGS	Cells from a single donation can be expanded to >10,000 doses, cGMP manufacturing	Phase 3 complete, Prochymal (Intravenous MSC infusion) in steroid refractory GvHD

Source: Maxim

Heart disease. The American Heart Association (AHA) estimates that 80 million American adults (approximately one in three) have one or more forms of cardiovascular disease. These diseases cost the United States alone approximately $500 billion a year, with the burden growing as the population ages.

The principal aim of cardiovascular therapies is to reduce morbidity and mortality from congestive heart failure, heart attacks, strokes, and other blood-vessel-related diseases. The consequences of heart attacks and the progression of congestive heart failure are currently poorly serviced. The delivery of stem cells to a patient for therapeutic purposes is a new approach to therapeutic intervention, and, to date, there are no products approved; however, multiple trials are underway. These include an academic trial in Europe, known as "BAMI," to evaluate the use of autologous MSC (bone marrow derived mesenchymal cells) for myocardial infarction (MI).

Baxter is pursuing its first Phase III trial (n=464) in angina (heart pain), and it our understanding that a second EU trial is being planned; however, we are also aware that Baxter has hired investment bankers to pursue strategic alternatives (sale) of the cell therapy division. What this may portend for the cell therapy program remains a key question. By comparison to our expectation for Mesoblast, the Baxter trial is small. We expect Mesoblast's Phase III trial to enroll 1,700 patients over a two-year period. Should the Mesoblast product work, based on a COGS argument alone, we believe Baxter's product would be obsolete as autologous COGS cannot likely compete with the cost-effective allogeneic counterpart. The differences in COGS may be north of $10,000. In addition, we believe that the apheresis process that Baxter uses will likely never be permitted in congestive heart failure patient versus more stable CMI patients, as the apheresis process may not be safe for severely ill CHF patients. We have similar concerns for bone marrow harvests that end up much north of 50cc. Dr. Andreas Zeiher, a world renowned opinion leader and lead investigator in the BAMI trial, supports this view. These differences may explain Baxter's decision to seek strategic alternatives (a sale).

However, the argument of "allo" versus "auto" is much more complex. In the case of cardiac disease, the autologous bulls argue that the regenerative properties of the therapy must persist. We know that allogeneic cells do not. As such, if autologous shows a long-term mortality benefit (versus allogeneic, because your own cells integrate back into the damaged tissue and continue to promote the process of blood vessel formation) versus a short-term paracrine effect of allogeneic, an autologous product might have an efficacy advantage in those indications.

In the publication cited below, the experiment attempts to show that the persistence of autologous cells creates a long-term sustainable benefit. We call this the "The Suicide Gene Experiment."

Mechanism of Improved Cardiac Function After Bone Marrow Mononuclear Cell Therapy: Role of Cardiovascular Lineage Commitment.

Our allogeneic thought leaders respond with the following: 1. Allogeneic cells are off the shelf, ready to go. 2. In the case of an acute heart attack, right at the time of stent placement, the cells can be delivered via intra coronary artery and begin to work immediately. 3. The cells can both down regulate the inflammatory cascade, mitigating the immediate secondary damage to muscle and then 4. go to work responding to the hypoxic environment that has developed, creating neo arterial flow, secondary branches, and micro-vasculature, allowing the muscle to stabilize and heal.

The key question then is: clinically, will it matter? If Mesoblast's Revascor shows a benefit (all signs point to yes), given its COGS and an ideal easy fit into the treatment paradigm, it becomes the "category killer," in our opinion.

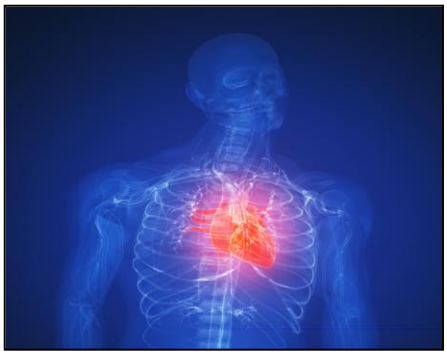
We believe Revascor has the potential to make the autologous approaches to heart failure and cardiac related conditions obsolete—*with a few exceptions (one of which may be Aastrom's expanded and optimized marrow derived product, now in a Phase III trial for CLI).*

Mesoblast's cardiovascular product development programs are aimed at several conditions, including congestive heart failure (CHF), acute myocardial infarct (AMI-stabilizing hearts post heart attack), and chronic myocardial ischemia (CMI, also known as or angina or heart pain), with potential applications in critical limb ischemia (CLI), pulmonary arterial disease (PAD), and a host of related indications. Unlike small or even large molecule therapies, cells may be able to address a wide range of conditions, restoring balance to our body in a way that a small molecule that is isolated to a single target can never achieve.

Congestive heart failure. The most recent statistics from AHA suggest that up to 6.6 million people in the United States suffer from heart failure, with an additional 670,000 new cases diagnosed each year. This is the No. 1 cause of mortality and hospitalization in the Western world.

Exhibit 4. An Enlarged Heart

CHF is a chronic condition characterized by an enlarged heart and insufficient blood flow to the extremities of the body. The condition develops over time and can be caused by many factors that put an excess demand on the heart muscle, including high blood pressure, incompetent valves, infections of the heart muscle or valves, or congenital heart problems. The heart itself becomes enlarged and the muscle walls thin.



Although patients are initially treated with drug therapy, the only current method of treating end-stage disease is a heart transplant or mechanical assist device. Only around 3,000 heart transplants are performed annually in the United States, leaving a large unmet medical need.

Mesoblast's target market is CHF patients in NYHA class II to IV with an ejection fraction of less than 35%. According to the company, the estimated market size in the United States alone is currently 2.5 million patients (41% of 6.2 million pre-existing sufferers), with 201,000 newly diagnosed (30% of 670,000) each year. Our estimates are slightly more conservative.

Source: http://www.cochrane.org/features/stem-cell-treatment-acute-myocardial-infarction

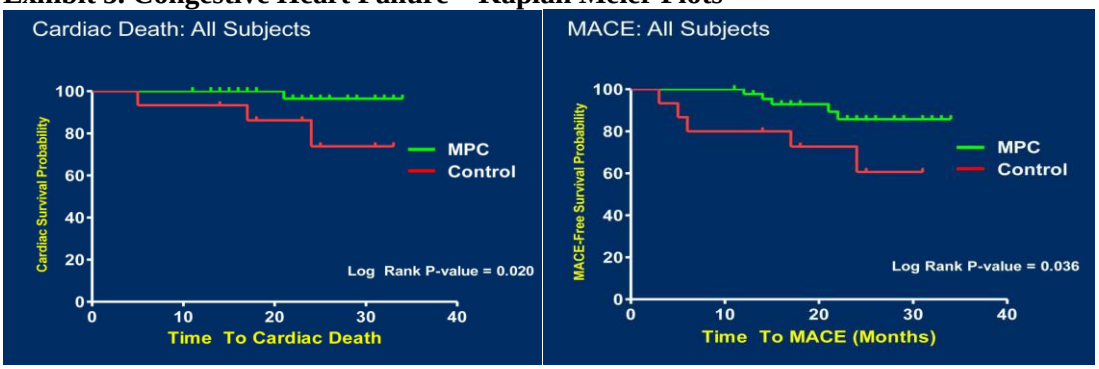
Mesoblast's therapy Revascor will be evaluated in a Phase III trial to treat moderate to severe congestive heart failure patients. We anticipate the trial to be highly powered (N=1,700) and to take up to two years to enroll. Our assumption is 90% for a 10% difference in all-cause mortality. We believe the trial strategy here is twofold: 1. Run one global trial that is well designed and well powered, with accepted endpoints (mortality); and 2. leverage the data base from that trial to leap-frog the product to other indications with smaller, faster follow-on trials. It is our understanding that Teva has asked for the larger trial, and that the FDA is likely to say yes.

How was the Phase II data? The data was very strong for a small study, with significant p-values (which it was not powered to show) and, more importantly, with "no deaths" in the treated group out to two years versus the control group (at 20%, in line with historical expectations for these patients).

The Phase II trial (n=60) was randomized, multi-centered, and placebo-controlled. The goal was to compare the safety and efficacy of three doses of Revascor on top of maximal approved therapies versus maximal therapies alone. Patients had to be classified as "moderate-to-severe" according to the New York Heart Association (NYHA) class II or III status, with ejection fractions below 40%. The trial enrolled both ischemic and non-ischemic heart failure patients.

All patients were randomized 3:1; controls to MPCs at 25M, 75M, or 150M cell doses. Cells were locally injected using the NOGA Myostar catheter system in a single injection. The primary stated endpoint of the trial was safety and feasibility, which was met (meaning that there were no adverse events associated with MPCs at any dose and no clinically relevant immune responses to donor cells as reported by the company).

Exhibit 5. Congestive Heart Failure – Kaplan Meier Plots



Source: Mesoblast

The Data:

- MACE was significantly reduced in MPC-treated patients over a mean 22-month follow-up (p=0.036).
- MACE risk over time was reduced by 78% in MPC-treated patients vs. controls (p=0.011), with a 60-90% risk reduction at every MPC dose.
- Cardiac mortality was significantly reduced in MPC-treated patients compared with controls over a mean 22-month follow-up (2% vs. 20%, p=0.02).
- The company reports that the highest dose of Revascor completely prevented any deaths or episodes of heart failure hospitalization over 18 months of follow-up.
- Highest dose showed evidence of remodeling (reduction in heart volumes: End systolic volume, ESV) and improvement in functional capacity (increased walking distance), which are key parameters in congestive heart failure.

In Mesoblast's completed Phase II trial, the composite endpoints of cardiac mortality and heart failure hospitalization were reduced from 20% in controls to 0% over 18 months of follow-up by a single intracardiac injection of the highest 150-million-cell dose of Revascor.

Patients who received this dose also showed concordant improvement in end-systolic volumes and total distance walked over six minutes – key parameters reflecting reversal of adverse left ventricular remodeling and increased functional capacity.

The company also reports that over a mean follow-up period of 18 months, 0/15 patients who received the highest dose of MPC (150M) had been hospitalized for heart failure or had died. It is our informal understanding that this is still true at two years. In contrast, 3/15 (20%) of the controls and 6/30 (20%) patients who received low (25M) or mid-range (75M) doses of MPC had either been hospitalized with heart failure or had died. This clinical improvement associated with the 150M dose was accompanied by evidence of cardiac remodeling (reduction in left ventricular end systolic volumes compared with controls at 6 months, p=0.015) and improved functional capacity (gain of 52.6 meters over a six-minute walk compared with controls at 12 months, p=0.06).

Next steps. The company expects Revascor to progress to a Phase III trial in early 2013We assume an enrollment of 1,700, 90% powered for a 10% difference.

As others have noted, it is our expectation that the FDA may request the pivotal study to contain an interim safety assessment point, where a small number of patients (n=100) will be initially assessed for safety and tolerability of the procedure itself (sham and treatment arms) after a lead-in period (30 days).

Heart attacks – AMI. At the other end of the disease spectrum, Mesoblast is evaluating the MPC technology for the treatment of acute coronary artery disease and heart attacks.

An allogeneic product means that every emergency room in the country can have ready access to Revascor and that it can be used in conjunction with all the standard life-saving procedures, such as clot-busting and stent technologies, at the earliest and most effective time. As such, the treatment paradigm allows the interventional cardiologist to inject a small volume of liquid cells (a few ccs) that contains the active dose right at the time of stent placement.

The key question is: Does that make sense? As previously discussed, the autologous companies will argue that one should wait some period of time for the hypoxic signals to peak so that cells can appropriately home. Delivering cells too early minimizes their effect as they become destroyed in the ensuing cytokine – inflammatory chaos of the initial ischemic event. Where we find this argument flawed is how it relates to the secondary damage that occurs post the initial ischemic event.

The allogeneic companies make two claims: 1. The inflammatory cascade creates secondary damage that, if turned off, effectively limits consequential damage. That's exactly what these cells do but that's only their first mission. 2. These cells persist for weeks. They do home along the same SDF-1 (stromal derived factor) gradient and will follow as the hypoxic signal (hypoxic induced factor or HIF) builds. The cells are in effect "on board" and ready to respond as needed.

It is unknown whether most of the damage occurs initially or over time, and the reality is probably that it is a deadly combination of both—the immediate inflammatory cascade and the secondary ischemic stress. If an allogeneic cell can remediate the initial damage and revascularize the heart in response to HIF, it represents a more economically viable approach that in effect makes the autologous approach obsolete.

Cytori is currently working with EU regulators to develop a label indication for Celution for the treatment of acute heart attack patients. Cytori is working in Europe (like in the United States) along a device pathway with a "notified body." Recall that in Europe, Celution is already approved for the reinfusion of cells treating tissue ischemia. As such, we believe that Cytori has a unique opportunity to win European approval based on one pivotal study (ADVANCE trial, N=216 patients) with preparations now underway and the first enrolled patient by Thanksgiving, according to our estimate.

Does the Cytori model make sense in the acute MI setting? We believe so. The initial ischemic event, a blockage in a blood vessel to a coronary heart artery, creates the ischemic crisis. The trauma-ER team knows that "the clock is ticking," and the goal is to unblock the artery and restore blood flow as soon as possible. Restoring blood flow, however, has its own sets of complications, such as reperfusion injury. Administering cells at the time the artery is unblocked may not be ideal. It may in fact be better to wait 24-72 hours. This allows patients to be evaluated at the 72-hour mark to see if they are recovering on their own, or if the heart is beginning to scar (become fibrotic) and lose tissue. Cytori's autologous cells and process fits this paradigm neatly. The cells can be administered at the 48-72 hour mark. The cells are safely harvested using liposuction, processed in under an hour, and returned via infarct related artery – all of this at a cost of goods that is similar to allogeneic products (sub $1,000). The cells (your own, or autologous cells) can then work to ameliorate the deleterious localized inflammation and, more importantly, fibrosis, as well as promote neo-angiogenesis in a longer-term integrated fashion.

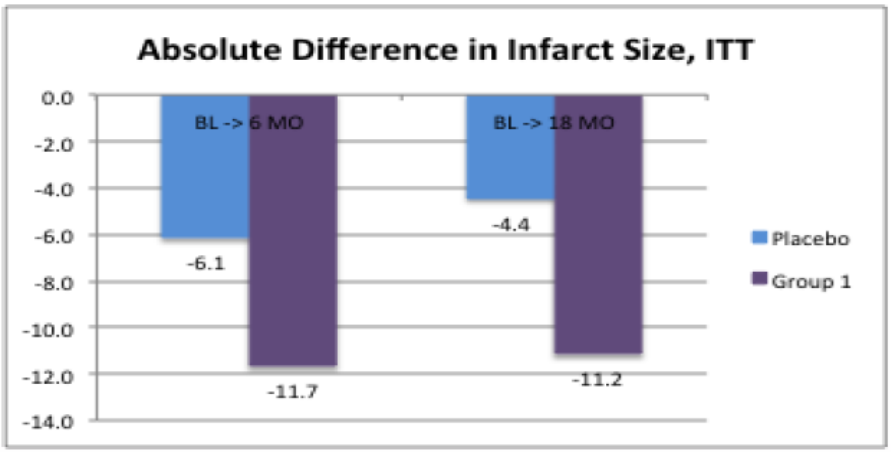
APOLLO. Cytori's European clinical trial evaluated adipose-derived stem and regenerative cells (ADRCs) in patients with acute myocardial infarction (heart attack or AMI). APOLLO was a small trial (N=14-patient) that was a prospective, randomized, double-blind, placebo-controlled, feasibility trial. In the trial, all patients were treated with the standard of care and subsequently underwent an abdominal liposuction. Each patient's adipose tissue was processed by the Celution System. ADRCs were extracted, washed, and concentrated into a syringe of clinical grade cells. Within 36 hours of the myocardial infarction and no longer than 24 hours after undergoing percutaneous coronary intervention, patients received an injection of either 20 million ADRCs (n=10) or a placebo (n=4).

We note a paper published in the *International Journal of Cardiology*, ICJA 11698, "*The effect of freshly isolated autologous tissue resident stromal cells on cardiac function and perfusion following acute myocardial infarction."* This article reviews a porcine model, in which immediately following the induced infarct cells were introduced via IRA. The study concluded that the introduction of adipose derived cells at the time of vessel reperfusion is feasible and improves ventricular function.

We believe that, mechanistically, the introduction of cells following the initial acute ischemic insult allows the cells to ameliorate the inflammatory response and subsequent fibrotic scarring, as well as promote the process of neo-angiogenesis through the SFDF1 gradient where an ischemic condition exists or is developing.

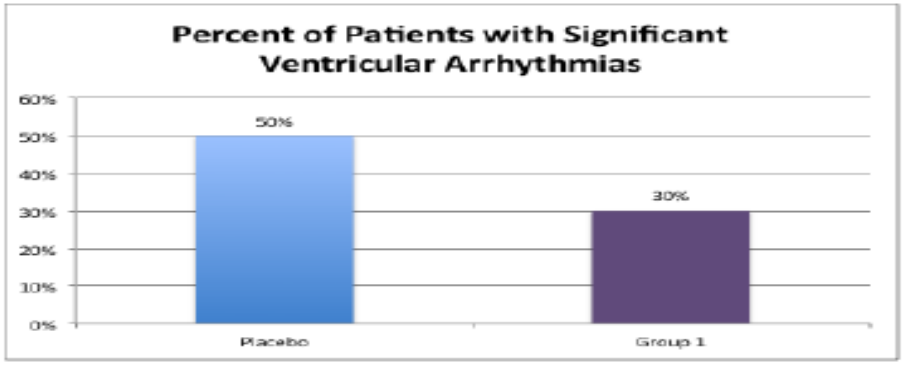
Exhibit 6. Differences in Infarct Size in the APOLLO Trial

At both 6 months and 18 months in the APOLLO trial, treated patients showed a significant difference in infarct size. Infarct size correlates well with survival and adverse events. The results also showed through in ventricular arrhythmias.



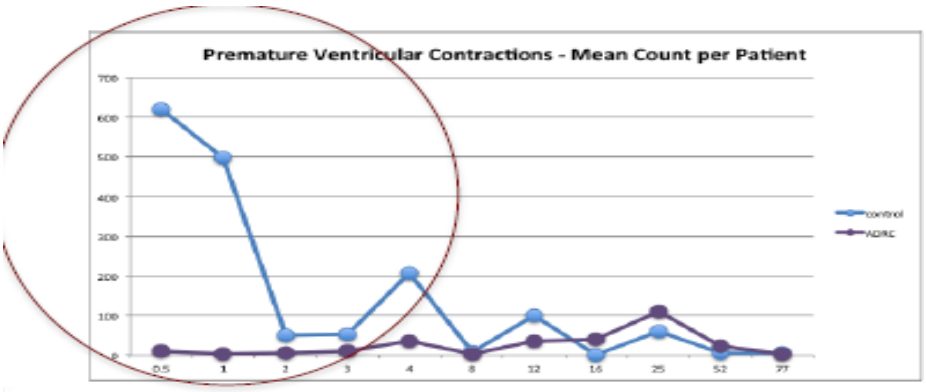
Source: Cytori

Exhibit 7. The results also showed through in ventricular arrhythmias, with the untreated group showing greater numbers of arrhythmias.



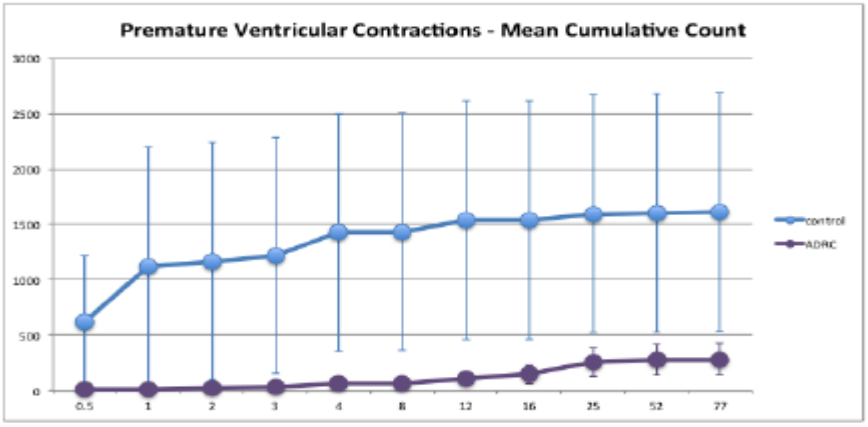
Source: Cytori

Exhibit 8. A Higher Frequency of Recordings with Ventricular Premature Beats (VPBs) in the Control Group



Source: Cytori

Exhibit 9. A Higher Number of Ventricular Contractions in the Control Group



Source: Cytori

The results:

1. The percentage of left ventricle (LV) infarcted was reduced by 52% (31.6 ± 5.3% to 15.3 ± 2.6% at six-month follow-up, p=0.002) in the ADRC-treated patients, as opposed to no change in the placebo-treated AMI patients (24.7 ± 9.2 % vs. 24.7 ± 4.1%). The difference between the groups was not statistically significant.

2. There was a significant improvement of the perfusion defect in ADRC-treated patients from 16.9 ± 2.1% to 10.9 ± 2.4% at six-month follow-up (change of 6.0%, p=0.004) as compared to a deterioration in the placebo group by 1.8% (15.0 ± 4.9% to 16.8 ± 4.3%).

3. Left ventricular ejection fraction (LVEF), measured by SPECT, improved with an absolute difference of +5.7% (p=0.114). In ADR-treated patients, LVEF improved by 4% (52.1% to 56.1%), as compared to a deterioration of 1.7% in the placebo group (52.0% to 50.3%).

In addition, the trial also showed an improvement as measured by SPECT, an improvement in blood flow into the heart muscle (perfusion defect), and a reduction in scar formation (infarct size).

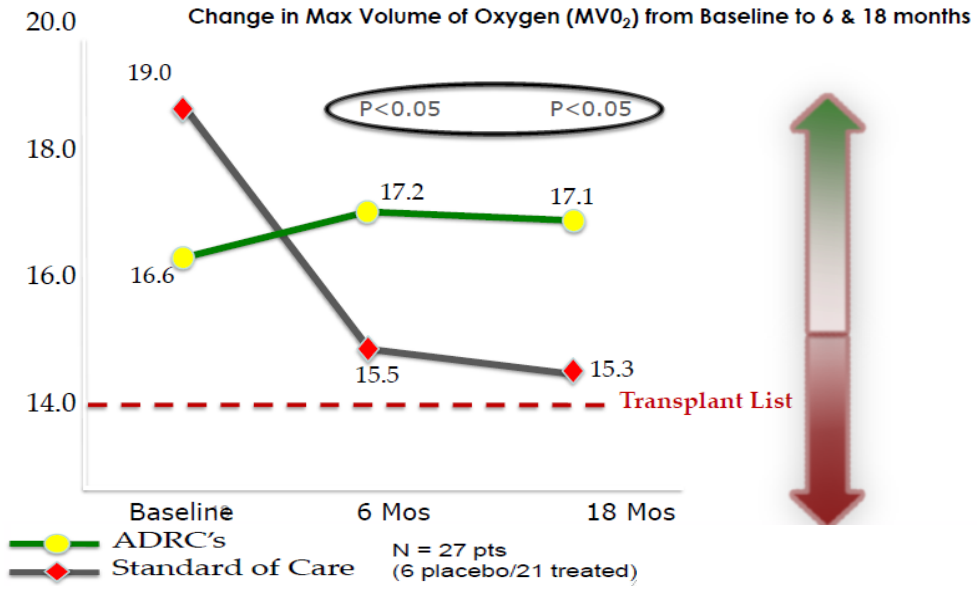
Next Step: ADVANCE (a PIII registrational quality study along the "notified body" pathway). This is a prospective, randomized, double-blind, European heart attack trial in up to 216 patients in up to 35 sites in the G5, Canada, Netherlands, and Poland. The accepted primary endpoint with regulators is reduction in infarct size, which has been shown to directly correlate with mortality benefit.

Chronic myocardial ischemia (CMI). Cytori completed the "PRECISE" trial in patients with CMI, a severe form of coronary artery disease. Primary six-month outcomes and longer-term 18-month data demonstrated safety and sustained improvement in cardiac functional capacity (MVO_2). Based on this data, in 2011 Cytori applied for approval in Europe to expand the Celution CE Mark (currently approved for general processing, breast reconstruction, and other soft tissue claims) to include patients with no-option chronic myocardial ischemia (CMI). A regulatory decision is expected this year.

In the United States, however, Cytori has enrolled the first patient in the U.S. FDA "Pilot" Phase II trial "ATHENA." Our channel checks have been very positive that enrollment is going very strong. Given the small size of the trial (N=45), we believe the rtial can complete very quickly. Guidance is for approximately 2H-2013, but we believe Cytori may be able to do better, based on the interest in the trial and the high demand. We also have been hearing that Baxter's trial may be running into multiple issues including: a) Complex treatment that requires GCSF, apheresis, manufacturing, and, as such, three patient visits versus Cytori's one visit; b) Complex protocols that may require patient self-monitoring for 30 days using iPads, presenting patient compliance issues; c) In our opinion, ultimately a very expensive high cost of goods ($10,000-$15,000) versus Cytori ($200-$300) or lower. Baxter is hoping to complete two large pivotal studies. Cytori may be able to catch Baxter if, through the device pathway, it can demonstrate a p-value on primary endpoint in one small study.

Exhibit 10. Data from Phase 1 CMI Trial : A few key points. MVO_2 as a primary endpoint has been shown to correlate with survival. We reference Mancini et al, Circulation Vol 83, No 3, March 1991, "*Value of Peak Exercise Oxygen Consumption for Optimal Timing of Cardiac Transplantation in Ambulatory Patients with Heart Failure"* and "*Peak $V0_2$, A simple yet Enduring Standard"* also by Mancini, Circulation, 2000; 101:1080-1082. These data validate that MVO_2 is a widely accepted measure for cardiac function in CMI patients.

The data below shows an improvement in MVO_2 in the treated group versus a deterioration in the control group.



Source: Cytori

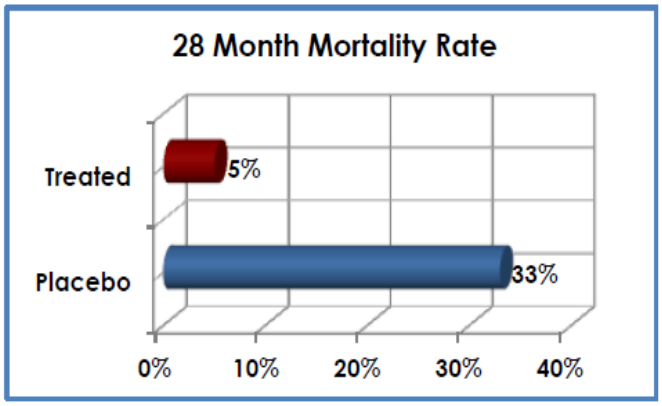
Exhibit 11. Correlation of Survival (Treated vs. Control)

MVO_2: significant change at 18 months
- MVO_2 correlates to improved survival
- $MVO_2 \leq 14$ = 47% 1 yr survival rate

METS: significant change at 18 months

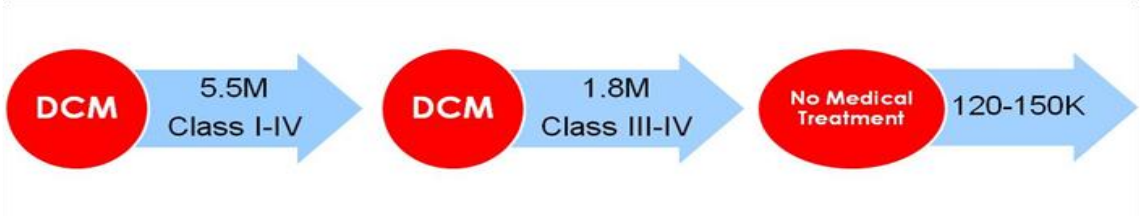
Cytori procedure safe and feasible through 18-months

Lower cardiac mortality rate:
- At avg. follow-up of 28 months:
  - 2/6 placebo
  - 1/21 treated



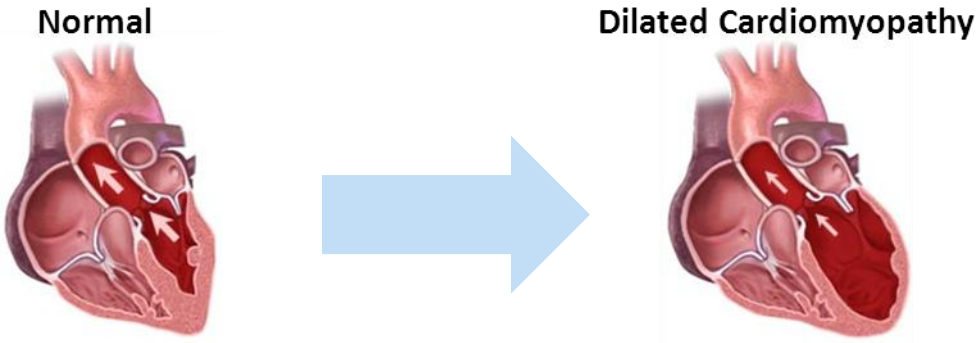
Source: Cytori

Exhibit 12. Aastrom's Target Market: Dilated Cardiomyopathy



Source: AHA 2008

Exhibit 13. What is Dilated Cardiomyopathy (DCM)?



Source: Aastrom

Phase II IMPACT-DCM results: Data from this trial were presented in September 2011. Results demonstrated that ixmyelocel-T was well tolerated, and there were trends in efficacy. The trial was based on a small group of 40, consisting of 20 ischemic and 20 non-ischemic patients across five U.S. clinical sites. Patients were randomized three to one to either a single administration of ixmyelocel-T or standard of care; they were followed for 12 months. Other criteria included the New York Heart Association's functional classification level III/IV. Level III, moderate, is characterized as limited physical activity, comfortable at rest. Level IV, severe, is defined as unable to engage in any physical activity without increased discomfort, mostly bedbound patients. Further, patients must have a left ventricular ejection fraction (LVEF) – fraction of blood pumped out of the ventricles with each heartbeat of less than or equal to 30%. Ixmyelocel-T was delivered through either direct injection via thoracotomy or minimally invasive thoracoscopy. Patients were followed for 12 months post treatment.

The data results are encouraging. The trial suggests that a proof-of-principle in ischemic DCM patients exists. Specifically 21 one of the 25 (84%) ixmyelocel-T patients completed the 12-month visit. Seven of 15 (47%) of the control patients completed the 12-month visit, while an additional five of 15 (33%) of the control patients enrolled into the extension phase of the study and received ixmyelocel-T treatment.

- Results showed no difference in adverse events in treatment and control group patients after the initial post-operative period.
- ICM patients treated with ixmyelocel-T showed improved outcomes compared to the control.
- Efficacy observations related to structural and functional end points, including major adverse cardiovascular events (MACE), New York Heart Association (NYHA) functional classification, six-minute walk distance, and septal wall thickening, were consistent with improved function of impaired myocardium.

Point to watch: The start and progress of the Phase IIb study in DCM patients.

In summary: cardiovascular and related indications: We believe the applications of cell therapy in heart disease may represent one of the greatest opportunities in medicine and in our society as a way to preserve life and create economic value. There are now multiple late-stage trials underway. These include trials from Baxter, Aastrom, Mesoblast, and Cytori. All are in or about to start their pivotal march towards the finish line.

- **Osiris**: Allogeneic: A phase II trial of Prochymal for the repair of heart tissue following a heart attack. Prochymal is an allogeneic, bone-marrow-derived mesenchymal stem cell population. We note that prochymal was approved in Canada in May of this year for GvHD. Currently Osiris does not appear focused on cardiology.

- **Mesoblast:** Allogeneic: A phase III trial (n=1,700) is expected this year in CHF. In a phase II trial, Revascor was delivered via coronary artery infusion using a standard catheter, after angioplasty and/or stent implantation following a heart attack. Revascor consists of allogeneic mesenchymal **precursor** cells, which secrete trophic factors that promote healing. Mesoblast believes these cells are much more potent than MSCs found later in the lineage, such as CD34+ cells. The trial data showed no deaths in the treated arm out to three years and significant P values between the active and control arms. Teva has now openly stated that it will support the Mesoblast trial.

- **Aastrom**: Autologous: A phase III trial, "REVIVE," in critical limb ischemia patients is being enrolled. This trial will assess the efficacy and safety of ixmyelocel-T. Ixmyelocel-T is a 50 cc marrow derived product in which specific cells in the population mix are expanded and others reduced to provide what Aastrom believes is the optimum mix. REVIVE is being conducted in the United States across 80 sites and is targeting an enrollment of just under 600 no-option CLI patients. REVIVE represents the largest randomized, double-blind, placebo-controlled, multi-center study ever conducted in patients with CLI.

- **Baxter**: We understand that Baxter is in a large phase III trial in CMI. Baxter uses GCSF to mobile stem cells into the peripheral blood, where they are then sent to the factory for processing and enrichment for CD 34+ content. Cost of goods is high and, as such, we are concerned that if an equivalent but cheaper product (such as a Cytori or Mesoblast product) works, it has the potential to make the Baxter product obsolete. Our channel checks on this trial have been very

negative. The trial has been difficult to enroll and physicians have concerns about using GcSF in these patients.

- **NeoStem**: Autologous: A phase II trial in AMI. Cells are harvested during days 4-6, if patients' ejection fraction has not recovered; 300cc of marrow are collected, processed, and enriched for CD34+ cells. Like Baxter, the cost of goods is high, and the harvest of cells (>300 cc bone marrow) may be problematic for many patients. As such, we are concerned that if an equivalent but cheaper product (such as a Cytori or Mesoblast product) works (and is less invasive), it has the potential to make an expensive, long-time-to-process, and non-patient-friendly treatment (multiple bone marrow needle sticks) obsolete. Our channel checks have been negative how management implied to us that the trial may be approaching the half way mark in terms of enrollment.

- **Athersys:** Allogeneic: A phase I trial of MultiStem is completed, and the company is ready to start a phase II trial (based on funding). The cells in the phase I study were delivered via catheter directly into the damaged region of the heart following percutaneous coronary intervention in patients post AMI. The data showed encouraging improvements in all metrics.

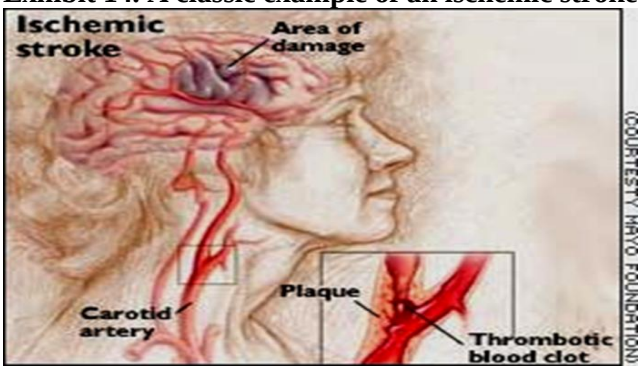
- **Pluristem:** Allogeneic: A phase II/III registrational trial of the company's placental derived stem cells in patients with critical limb ischemia is planned for next year. Patients will receive intramuscular injections in up to 50 locations in the affected limb. In the phase I study, the treatment appeared safe and reduced the need for amputations.

- **Cytori (CYTX)**: Autologous: The "ADVANCE" trial is now enrolling. It is an EU pivotal trial, investigating the Celution System for AMI. In addition, the company has begun enrollment in the "ATHENA" trial. ATHENA will investigate the use of the Celution System to treat chronic myocardial ischemia (CMI). Our channel checks are positive and enrollment is ahead of schedule.

Stroke: An unmet medical need and a blockbuster opportunity. We review the Athersys stroke program as we believe this represents one of the critical events for the cell therapy space in 2013.

The leading cause of serious disabilities and the third leading cause of mortality in both the United States and globally is stroke. Approximately 800,000 people are victims of stroke annually in United States, and 15 million globally. The majority of these strokes (~85%) are ischemic strokes. According to Athersys, the economic impact of both direct and indirect costs of stroke on the United States are estimated at ~$73 billion annually (based on 2009 data). There is no argument that stroke represents a tremendous unmet need. The only approved viable therapy today is recombinant tissue plasminogen activator (rtPA). It has limitations as it must be administered within three to four hours of the initial ischemic stroke. As such, it is only actually used on ~5% to 8% of treatable patients. With an aging population, the clinical need and commercial opportunity is expected to increase dramatically between 2010 and 2030 (and beyond).

Exhibit 14. A classic example of an ischemic stroke



Source: Athersys and Mayo Foundation

Market opportunity in stroke. In the United States, over 600,000 patients suffered an ischemic stroke in 2012. The only FDA-approved drug for the treatment of stroke is tPA (tissue plasminogen activator), a clot-dissolving drug that has to be administered to patients within three hours of stroke; otherwise patients risk significant bleeding into the brain. For this reason, only 5% of patients currently receive treatment with tPA. Despite significant efforts directed toward developing new treatments for stroke, there have been no new drugs approved by the FDA in the recent past.

Athersys program preclinical data. In preclinical studies conducted to date, Athersys' MultiStem has been well tolerated and has not required immunosuppression. MultiStem has also demonstrated impressive activity in rodent models of ischemic stroke. In a rat middle cerebral artery occlusion model of ischemic stroke, animals received IV delivery of MultiStem one day, two days, and seven days post-occlusion. The extent of neurological deficit post-experimentally-induced stroke was evaluated according to the Bederson Composite Score. Data presented at the 2006 American Academy of Neurology meeting demonstrated that the administration of a single dose of MultiStem one week after an experimentally-induced stroke led to substantial and durable therapeutic benefits across nearly all measures of neurological function, including mobility, strength, and fine motor skills. MultiStem is thought to achieve this through reduction of inflammation and immune system modulation at the ischemic site, as well as the protection and rescue of injured neurons.

A note on animal work. One area where Athersys as a company shines in the quality of the science. We discussed some of the animal work and learned that scientists at Athersys determined that MultiStem only functions in animals when delivers post infarct. If delivered before or simultaneously, there was no effect. The hypothesis is that the cells act on an inflammatory response—so if there is nothing to act on, the cells do nothing. In animal models, the company was able to see the expression profiles of the cells as they react to the environment.

How does MultiStem work? Athersys believes that, beyond the initial ischemic event, a host of secondary events cascade through the body. These include maturing T-cells that migrate to the damaged areas of the body (in this case, the brain). This process takes several days (thus there is a longer therapeutic window). As a result, the body seems to create scar tissue, which effectively walls off the area of the stroke. It becomes impossible then for neurons (which have retracted) to penetrate this wall. As noted earlier, the inflammatory response and the role of the spleen is a key part of the disease mechanism. In fact, the over-production of immune cells often leaves patients vulnerable to infection, which is a major post-stroke complication. The administration of MultiStem appears to play a significant role in preserving spleen function then, by both down regulating the initial inflammatory response and allowing the spleen to later fight infection-related complications that may have occurred as a result of the initial trauma or traumatic brain injury (such as car accident, explosion) that caused the event.

Specifics on mechanism of action include:

- Reduction of inflammatory activity of activated immune cells (e.g. T cells, Mf)
- Reduction of infiltration of activated immune cells to site of damage
- Reduction of hyperinflammatory cascade emanating from spleen
- Neuroprotective, neurotrophic activity (e.g. increase neuronal survival)
- Angiogenic and vasculogenic activity
- Enhanced repair of blood-brain barrier

Current phase II study in stroke. Athersys is conducting a placebo-controlled trial for ischemic stroke. The trial began in 4Q11 and is currently in multiple active U.S. sites (a total of 25 are planned). The trial (based on DSMB findings) is now focusing on the high dose group. Entry criteria for patients will be those who have suffered an ischemic stroke (who have suffered a moderate to moderately severe stroke, as defined by a National Institutes of Health Stroke Scale (NIHSS) score of 8 to 20), within the prior one to two days. Patients will receive MultiStem intravenously versus the control (placebo). The study is double blinded (blind to both doctors and patients).

Trial Update: The independent safety committee reviewed data from these patients, finding that both of the doses initially evaluated were safe and well tolerated, and therefore, recommended proceeding with high dose administration to patients for the remainder of the trial.

The first part of the Phase 2 study included two cohorts, with each cohort including a placebo group and a treatment group—a low dose of MultiStem in the first cohort and a higher dose in the second cohort. The third cohort has a placebo group and treatment group, randomized 1 to 1. The study is expected to enroll approximately 136 patients in total. We also note that, unlike its peers, Athersys in the competitive environment is able to deliver a very large dose (we speculate > 1 billion cells) because of the efficiency, scalability, and cost effectiveness of the MultiStem process. We believe this is a major differentiator in the competitive landscape.

A note on dose: We believe that Athersys is in a unique position. The company has invested many years in perfecting manufacturing process behind MultiStem and is able to cost effectively manufacture high therapeutic dose levels (> 1 billion cells), which is just not feasible for autologous competition. Here is where we see the critical intersection of dose, with manufacturing and indication (systemic or local). Athersys is not concerned about pursuing high-dose, systemic indications, because it has the manufacturing capability and capacity to do so in place today. Athersys is working with Lonza.

Primary safety endpoints for the trial include measuring acute infusional reactions over the first 7 days following treatment. Primary efficacy measures include determining the proportion of patients with a modified Rankin Scale of 0 to 2 (which represents patients capable of independent living) at day 90 in the MultiStem treatment group compared to subjects in the placebo treatment group. Secondary endpoints include functional outcome as determined by a NIHSS score and the Barthel Index. The study includes additional exploratory endpoints, such as measuring stroke infarct size and blood marker changes between the MultiStem and placebo treatment groups.

Competitive landscape. The pharmaceutical industry has tried and failed with multiple small molecule approaches for stroke. TPA is limited in its efficacy (it must be used within two to three hours of the event). Cytomedix acquired Aldagen (private) and is currently in a similar stroke trial using its ALDH-br cells; however, the product is being administered approximately three weeks after the stroke occurred (post-acute). ReNeuron is developing a stem cell product (ReN001) for the treatment of patients left disabled by stroke (chronic). The company intends to treat stroke patients several months after the initial event with neural cells that they believe will upregulate the activity of the healthy remaining cells.

Neuralstem has been talking about launching a stroke trial offshore in China. We do not yet understand what the scientific basis is behind the use of Neuralstem's product in stroke and as such we are very skeptical.

We do believe that each of these "other" approaches have multiple problems in comparison to Athersys which include dosing, production capacity, cost of goods sold, and timing of administration.

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