EnteroMedics' Late Stage Treatment Takes on Obesity Epidemic

The Associated Press

Our focus turns to EnteroMedics, which offers a new treatment approach currently in Phase III clinical trials, designed to help morbidly obese people lose weight.

EnteroMedics' approach may be a better solution for people who see little or no benefit from current treatments on the market. If the device proves successful, the company could end up being a very good investment.

The treatment device, currently in Phase III trials, acts similar to a pacemaker, but in this case for the vagal nerve. The system periodically inhibits the delivery of the message from the stomach to the brain which informs the brain, "I'm hungry." Instead, it sends a message that no more food is needed, suppressing excess appetite. This fully eliminates the need for gastric bypass surgery, diet pills, and weight loss shakes.

We asked my friend, Dr. Dung Trinh, Clinical Assistant Professor of Medicine, University of California-Irvine (UCI) to give us a summary of the current obesity problem we are facing in today's world, and to go over the current treatments being offered in the market.

Author, Scott Matusow: Obesity seems to be a growing health and appearance issue these days. Can you please explain to us the current scope and magnitude of this problem for us?

Dr. Trinh: Obesity is a huge problem in the United States. Two thirds of Americans fit the definition of overweight or obese. Obesity is associated with a multitude of healthcare problems we see in the office on a daily basis; diabetes (1 in 3 adults in the US have prediabetes), heart disease, stroke, and cancer. Some blame obesity on genetics, the food industry, proximity of McDonald's to elementary schools, large sizes of soda drinks in New York City, and the lack of adequate exercise.

If our out-of-control healthcare spending and rising insurance premiums are ever going to be manageable, we need to focus on prevention of disease (obesity) rather than putting out burning fires related to obesity (diabetes, heart disease, hypertension, etc). Our strategy needs to be focused on maintaining wellness rather than fighting Illness.

Our approach to fight obesity comes from multiple fronts. From a regulatory stand point, last year the FDA approved two weight loss medications. Politically, New York City banned soft drinks over a certain size (I'm not sure how that would circumvent

someone from drinking multiple smaller sodas). Surgeons are shrinking stomach sizes with invasive gastric bypass, gastric banding, and other surgical techniques.

Matusow: Dr. Trinh, what are the current methods people can choose to help them with severe weight issues?

Dr. Trinh: In addition to caloric burning exercise, the most basic approach to weight loss is simply to cut caloric intake by eating less. Here is a quick review of our current weight loss approaches:

The surgical approach to weight loss:

Treatments such as gastric bypass surgery, gastric banding, etc lead to a smaller stomach. Having a smaller stomach leads to the mental sensation of "being full" earlier with a smaller meal content. This sense of fullness (satiety) is driven by the vagal nerve that provides communication between the stomach and the brain. The vagal nerve is the information highway between the stomach and the brain. When the vagal nerve is "inhibited," it tells the brain "hey I am full now, stop eating." Having a smaller stomach through surgery means the stomach is distended by a smaller amount of food (less caloric intake), which in turns tells the vagal nerve to inform the brain that you are full. The downside of anatomically changing the stomach through surgery includes possible problems with digestion and malaborption as well as possible need for repeat surgeries in the future.

Prescription Weight loss medications:

Two weight loss drugs were approved by the FDA last year; Qsymia by VIVUS, Inc. and Belviq by Arena Pharmaceuticals, Inc. Both medications have documented weight loss benefits as well as side effects. The approvals come after a 13-year dry spell of any new weight loss medications due to issues with safety with previous weight loss medications (i.e. "fen-phen").

Vivus patients on average lose 10% of their weight after a year of treatment while Arena's patients lose 5% of their weight. Qsymia has potential risk of birth defects and has a fairly strict prescribing label. Arna's Belviq appears safer than Qsymia but achieves only modest weight loss of 5% in clinical trials. Neither drug is meant to be taken "forever."

There is also a company named Orexigen Therapeutics, Inc. that is currently testing an obesity drug in clinical trials called Contrave. Contrave is a combination of two medications already on the market for many years, bupropion SR and naltrexone SR. Bupropion is currently FDA approved for depression and naltrexone used primarily for the management of alcohol dependence. Bupropion's side effect profile includes "weight loss" and naltrexone's common potential side effects include non-specific GI complaints (nausea, abdominal cramping, etc). Apparently the documented side effect profiles of these two medications lead to the weight loss indication Orexigen is seeking approval for. Orexigen may have an advantage over both Qsymia and Belviq which were approved a few months ago. Both Qsymia and Belviq are currently tightly controlled by the FDA (requiring "special prescriptions")

whereas Contrave's medications used are not as highly regulated, allowing easier access to prescribing and refills at local pharmacies.

Weight loss Programs:

Over the years many types of weight loss programs have come and gone. We've been exposed to many of the weight loss programs and diets out there through the experiences of my patients; Weight Watchers, Jenny Craig, Slim Fast shakes, Lendora, Adkins diet, Zone diet, South Beach diet, etc. The shakes and meal plans all have the same underlying goal: Reduce caloric intake with the attempt to "not feel hungry." These diet plans again rely on the vagus nerve physiologic function by eating low caloric foods while expanding the stomach and inhibiting the vagus nerve (connects stomach to brain). This sends a message to the brain, "I'm no longer hungry, stop eating."

Matusow: As I recall the other day, we spoke about the drawbacks of drug treatments. Can we cover that again for the readers?

Dr. Trinh: Sure, although most patients do lose weight during their active participation in these programs, from my experience the results are usually not long term. The problem I've witnessed is a lack of long term behavioral changes in exercise and good eating habits. When the diet plan ends, we tend to revert back to our original habits that caused weight gain in the first place. As a result, the pounds come back.

The age long belief that preventing obesity boils down to simple exercise and healthy diet remains true, but the facts point out that teaching diet and exercise alone have been ineffective. If it was effective, we would not see a continuous rise of obesity in our culture. This article would not exist. It's obvious that something different needs to be done in order to reverse this trend.

Up to now there hasn't been a very good option at tackling weight loss. Surgeries are invasive, diet pills have systemic side effects and not long term, and weight loss plans come and go without consistency.

Now, let's take a further look at EnteroMedics and its flagship treatment and device, The Maestro System.

Unlike gastric bypass, the placement of this device is not done through invasive surgery, but rather laproscopically. The device attaches with two leads which innervates the vagal nerve. Despite how dangerous it may sound, no significant safety issues have been reported to date. The device also preserves normal digestive system anatomy and the may be adjusted, deactivated, reactivated, or entirely removed at any given point in time.

The EMPOWER study:

The EMPOWER study was a randomized, double-blind, controlled study of 252 patients designed to test the safety and efficacy of the company's first generation

Maestro RF System. Both groups were implanted the Maestro Rechargable System but only the treatment group the system was activated to inhibit the vagus nerve on an intermittent basis.

The Detailed Preliminary Results reported in November 2009 showed that the Maestro system did meet its safety endpoint but failed to meet the primary and secondary endpoints for efficacy. Such results significantly impacted the company as the stock saw significant losses to the downside.
Patients who met or exceeded the prescribed nine hours of daily device use (n=128, 51% of evaluated patients) averaged 10.9 hours of daily use and experienced an average excess weight loss (EWL) of 23.1% from implant by BMI method (18.3% from treatment initiation by Met Life method) in the treatment arm and 22.6% (BMI) from implant, (17.8% from initiation, Met Life) in the control arm at 12 months. Patients that did not meet the prescribed nine hours of daily device use (n=125) averaged 6.9 hours of daily use and experienced a mean EWL of 10.5% from implant in the treatment arm (6.4% from initiation, Met Life) and 8.6% in the control arm (4.6% from initiation, Met Life) at 12 months. For all patients (n=253), the average EWL at 12 months was 16.6% EWL from implant (12.1% from initiation, MetLife) for the treatment arm and 16.4% EWL from implant (12.0% from initiation, MetLife) for the control arm. For those patients with a diagnosis of hypertension (n=110), a statistically significant reduction of systolic and diastolic blood pressure from baseline was observed, a result that will require follow-up study.
Also from the detailed review, the company stated:

"Based on the analysis to date, the control arm of the trial, which was intended to be inactive, apparently provided a low-intensity blocking signal that introduced VBLOC Therapy in human subjects.

"Our interpretation of this statement is that the control arm somehow had VBLOC treatment as well which would explain the statistically indistinguishable results between both arms -- both groups lost weight."

President and CEO Mark Knudson stated:

"The apparent control arm effect, while unexpected, may be a scientifically important addition to our understanding of neuromodulation."

As we began to dig deeper into our due diligence, we found another pr dated November 8th, 2010 on the company's website that seems to back up my interpretation of the company's statements from the detailed November, 2009 report.

In the Australian cohort, a total of 83 subjects were enrolled at two centers, with 61 subjects implanted. Main outcome measures were morbidity, mortality and excess weight loss at 12 months. Results include:
Mean 12-month excess weight loss was 25% for the treatment group and 17% for the control group; Weight loss was linearly related to hours of device use; subjects with greater than or equal to 9 hours/day use achieved 37% and 21% mean EWL (treated versus control, p = .02); No therapy-related serious adverse events or

deaths were reported across the entire study population.
Based on the data above, it appears my understanding of the company's original suspicion was correct, the control arm of the EMPOWER study was receiving some form of treatment, when they should not have been.

The newly designed Recharge Study:

More often than not, drug companies, after realizing a failure in a late stage clinical study, meet with the FDA to determine the best path forward on how to re-design a study that is acceptable to the organization in order to gain eventual approval of a drug and/or a device. Also, more often than not, companies find success in a re-designed study.

In September 2009, ACADIA Pharmaceuticals Inc. drug Pimavanserin failed to meet its endpoints in the treatment of PSP on its initial Phase III study.

Uli Hacksell, Ph.D., Chief Executive Officer of ACADIA remarked at the time:

While we obviously are disappointed with the results of this Phase III study, we continue to believe in the potential of Pimavanserin based on our clinical experience to date. We will thoroughly analyze these data along with the data on other secondary and exploratory endpoints over the next month to better understand the outcome of this study. Meanwhile, we are continuing with the second Phase III PDP trial with Pimavanserin.

After engaging in a thorough analysis of the failed first Phase III trial for Pimavanserin, the company obviously got it right the second time around. On November 27, 2012, ACADIA announced successful top-line results from its pivotal Phase III trial.

ACADIA shows here how a re-designed study can produce drastically different results from a former failed one.

In Pimavanserin's 2009 failure, the placebo effect was high from patients in India/Europe who had higher healthcare standards than what is normal for the region. In the Re-designed study, only North American patients were part of the trial, to get more consistent and equal results.

After the newly found positive results for Pimavanserin, the stock has had an incredible rally, trading from a range of the mid-$1 range to where it currently trades today -- $6.19 a share.

Study design matters, and more than most people might think. In this case, ACADIA management saw the issue and corrected it to give the trial a better shot at success.

EnteroMedics launched its newly designed Phase III ReCharge clinical trial in 2011. The trial consists of 234 patients that were randomized and placed in double-blind treatment control group. This time around, the study design was adapted to

accommodate for the potential "low-dose treatment effect" of the control arm. Inclusion criteria included not only obese patients (BMI > 40 or > 35 with one or more co-morbid condition), but also patients with well controlled Type 2 diabetes, which is yet another possible benefit from the device in addition to treating morbid obesity.

The primary endpoint efficacy objective in the new trial is to observe a 10% greater excess weight loss with the treatment group compared to the control group based on BMI method and to observe meaningful weight loss of 20% and 25% EWL at 12 months for the treatment arm (not statistically based).

Major Near term catalyst:

According to company press releases, conference calls, and my correspondence with investor relations for the company, Phase III data from the Recharge study is due to be released around mid Q1, which would be mid to late February. Based on the new trial design and the apparent control group issue that caused the first failure, I expect positive data to be revealed this time around.

Key fundamental information for ETRM:

Shares Outstanding:	41.70M
Float:	26.90M
% Held by Insiders:	29.34%
% Held by Institutions:	56.20%
Shares Short (as of Dec 31, 2012):	1.53M
Short Ratio (as of Dec 31, 2012):	7.10
Short % of Float (as of Dec 31, 2012):	5.90%
Shares Short (prior month):	1.30M

Total Cash (mrq):	27.21M
Total Cash Per Share (mrq):	0.65
Market Cap (intraday):	112.59M
Operating Cash Flow (TTM):	-22.41M

Source: Yahoo! Finance

The stock has a very low number of shares outstanding, and even a smaller float with a low market cap. What we like about the share structure above is the healthy but not exaggerated number of shorts in the stock. Additionally, both insiders and institutions hold a significant amount of shares in the company. EnteroMedics has been burning about $5M a quarter which gives it over a year of cash to operate on. However, since the trial is now complete, we expect its Q1 cash burn to be somewhat less than last year's Q1.

Considering the vast potential in the obesity space among its peers, it becomes evident that a market cap for EnteroMedics of $112M is grossly undervalued at this time, especially comparing this to Orexigen Therapeutics, which has a market cap of just over $470M.

In comparison, VBLOC has shown efficacy much greater than Orexigen's Contrave, which has efficacy of 4.2% over placebo, while VBLOC has shown to be well into the double digits in efficacy (based on Australian cohort) with minimal side effects. If EnteroMedics shows the kind of success I believe it will from its current trial design, the stock should have no issues being valued equal to or greater than Orexigen, which would place it over $11 a share based on the 40M shares outstanding.

Conclusion:

We believe the company is correct in its assessment about the control arm receiving a low dose of the actual treatment and the current ReCharge study design should accommodate for this.

Positive results from the ReCharge study bring into play an obesity treatment option that does not require anatomically changing surgery, prescription medication weight loss pills, or diet plans that fail once the diet is over with. Additionally, the company has reported positive results in treating obesity related hypertension, and is studying the device for the treatment of diabetes related from obesity as well.

The obesity problem in The United States alone costs insurance companies billions

of dollars annually, with a good deal of the money shelled out to cover a variety of obesity related diseases. If EnteroMedic's VBLOC therapy proves to be successful, which we predict it will, this could be a huge game changer in treating morbid obesity, and potentially could save billions of dollars in expenses.

Insurance companies would gladly shell out the cost to cover an effective device that can treat a variety of life threatening diseases, and save them a ton of money in the process which is why EnteroMedics is definitely a company to watch in 2013.

Disclosure: Author Scott Matusow is Long ETRM. His full report can be found at:

http://www.biomedreports.com/20130129120698/enteromedics-late-stage-treatment-takes-on-obesity-epidemic.html

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