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Life Sciences – Biomedical Devices and Services

Obesity, the Next Big Thing in Medical Devices

*Coming back for seconds, an update to
our 2009 report*

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Eighty-four million adults in the US struggle with obesity: The prevalence of obesity as a percentage of the US adult population in the last 25 years has grown to 35% (approximately one in three), or 84M people, from approximately 23% or 40M people. Globally, there are over 500M obese adults.

Near-term \$1B+ US market opportunity: Using what we believe to be an *extremely* conservative average ASP of \$2,000 per device, we derive a \$1.3B US market estimate for obesity devices in 2025. We assume increasing procedure volumes driven by new, safer, less invasive options combined with improving reimbursement.

US regulatory environment for obesity companies – a truly positive situation: Our conversations with industry (executives and physicians) lead us to believe that FDA is very supportive of advancing new technologies to the commercial markets for obesity-related devices/procedures. We would also point to FDA's actions with the formation and publication of a guidance document in December 2012, "Benefit-risk paradigm for clinical trial design of obesity devices: FDA proposal."

Improving acceptance of obesity as a medical issue: Obesity was officially classified as a disease by CMS in 2004 and the AMA in 2013, thus removing a major barrier to access to medical treatment for obese patients. In 2006, and again in 2012, CMS expanded coverage to include more types of devices and procedures, further improving patient access to care. While CMS pays for only 20% of bariatric procedures for obesity, it sets the bar for insurers to follow.

Multiple technologies on the cusp of US FDA PMA approval – positions the market for significant growth: We believe there will be more than one winner in the obesity space as different devices/procedures achieve weight loss by different mechanisms of action. From a timing perspective, we highlight that there are three PMA devices that have been submitted within the past 12 months, and four more companies with products in US pivotal trials. Given the plethora of new devices on the near-term horizon (next two years), unmet clinical need in the market today, and low penetration of existing products/procedures, we believe the obesity market is poised for significant growth.

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The recommendations and opinions expressed in this research report accurately reflect the Investment Analyst's personal, independent and objective views about any and all the Designated Investments and Relevant Issuers discussed herein. For important information, please see the Important Disclosures section in the appendix of this document.

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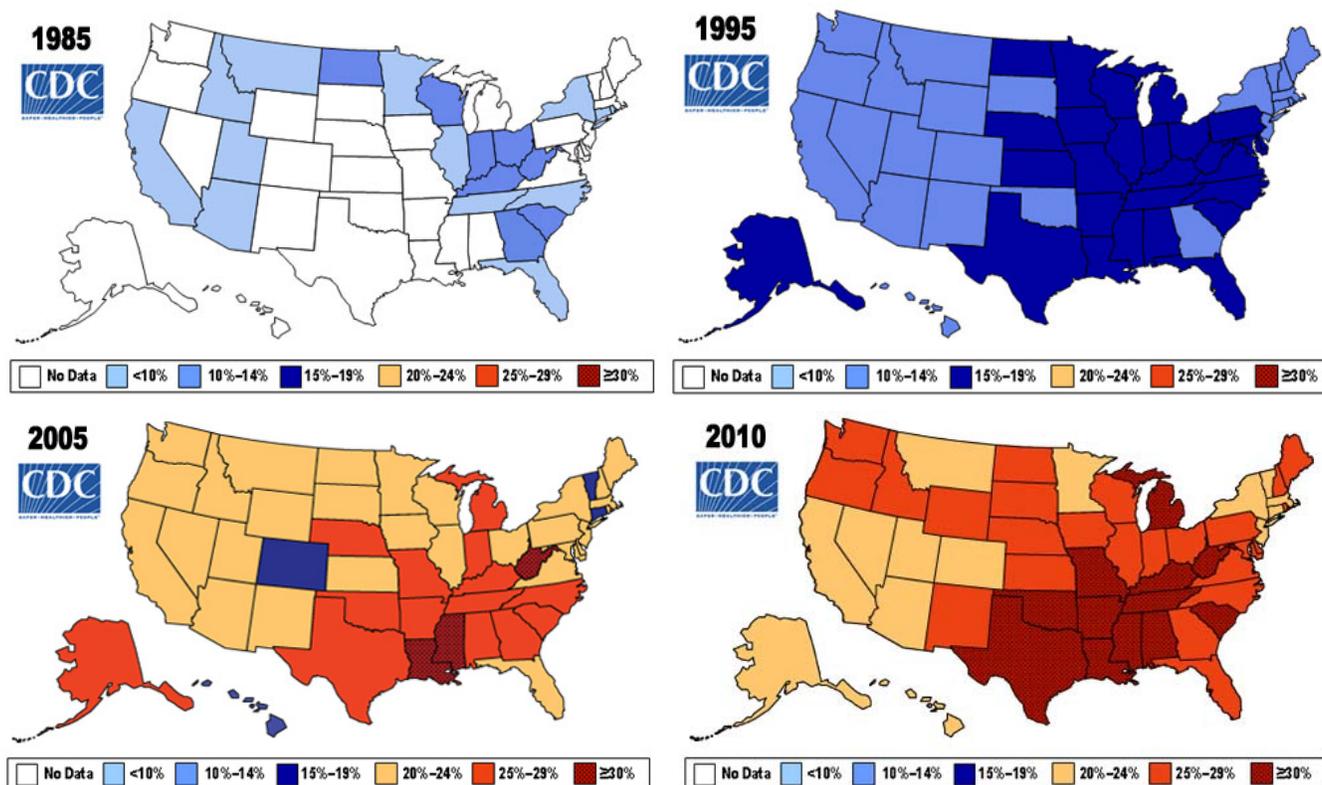
INVESTMENT THESIS – REPORT HIGHLIGHTS

Understanding the prevalence of obesity

One in three US adults are obese, and nearly one in five children are obese

Obesity is a growing problem with no end in sight. The prevalence of obesity as a percentage of the US adult population has grown over the past 25+ years to 35%, or 84M people, from approximately 23%, or 40M people. Globally, there are over 500M obese adults. We have included a well-known chart from the US Centers for Disease Control (CDC) highlighting changes that have taken place in the US population over the past 30 years. Furthermore, the trends become even more frightening when we see the prevalence of overweight children in the US rising to 17% in 2011-2012 from 5% in 1980.

Figure 1: Percent of obese (BMI>30) US adults



Source: Centers for Disease Control

The rapidly increasing prevalence of obesity, coupled with the poor long-term efficacy and tolerability of weight loss drugs, has created an amazing opportunity for device makers. Figure 2 shows the prevalence data for the morbidly obese, increasing from 2.9% in 1994 to 6.4% as of 2012. Lastly, based on the data provided by the CDC, it becomes apparent that the significant jump in prevalence took place in the 1990s, particularly in the obese and morbidly obese populations, and have held relatively steady over the past 10+ years.

Figure 2: Prevalence of BMIs > 25, 30, and 40 in American adults

	Overweight (BMI 25-30)	Obesity (BMI 30-40)	Severe Obesity (BMI ≥ 40)
1976 to 1980	31.60%	14.40%	No data
1988 to 1994	35.90%	20.10%	2.90%
1999 to 2000	34.00%	25.80%	4.70%
2001 to 2002	35.10%	25.50%	5.10%
2003 to 2004	34.10%	27.40%	4.80%
2005 to 2006	32.70%	28.40%	5.90%
2007 to 2008	34.20%	28.10%	5.70%
2009 to 2010	33.10%	29.40%	6.40%
2011 to 2012	33.40%	28.70%	6.40%

Source: CDC, National Center for Health Statistics, National Health and Nutrition Examination Survey

Drivers for the expanding prevalence of obesity include larger, fatty meals combined with a more sedentary lifestyle. In addition, obesity in childhood leads to physiological changes that predispose adults to become obese. Diet and exercise are not effective for a lion's share of the afflicted population. Drug results have been sub-par with only 3%-8% weight loss (not percentage excess weight loss, or %EWL, traditionally a common measure of obesity treatment success) and major side effects such as nausea, headaches, and oily stools. While current surgical options have proven effective with EWL as high as 70%, they carry complications including nutrition deficiencies, chronic anemia, dumping syndrome, and the potential need for a revision in later years.

Figure 3: US overweight & obese addressable market

	2000	2005	2010	2014	2015	2016	2017	2018	2019	2020	2025	2030
Total US Population	282,171,957	295,753,151	309,326,295	318,892,000	321,363,000	323,849,000	326,348,000	328,857,000	331,375,000	333,896,000	346,407,000	358,471,000
Addressable age group (20-64)	166,522,163	176,976,709	185,668,966	198,555,868	199,150,000	199,670,867	200,193,097	200,716,692	201,241,657	201,768,000	203,166,000	205,349,000
Overweight & Obese (BMI > 25)	107,406,795	117,954,977	127,740,249	136,010,770	136,417,750	136,774,544	137,132,271	137,490,934	137,850,535	138,211,080	139,168,710	140,664,065
% of total US population	64.5%	66.7%	68.8%	68.5%	68.5%	68.5%	68.5%	68.5%	68.5%	68.5%	68.5%	68.5%
Overweight (25 > BMI < 29.9)	56,617,535	59,110,221	61,456,428	66,714,772	66,914,400	67,089,411	67,264,881	67,440,809	67,617,197	67,794,048	68,263,776	68,997,264
% of total US population	34.0%	33.4%	33.1%	33.6%	33.6%	33.6%	33.6%	33.6%	33.6%	33.6%	33.6%	33.6%
Obese (BMI > 30.0)	50,789,260	58,844,756	66,283,821	69,295,998	69,503,350	69,685,133	69,867,391	70,050,126	70,233,338	70,417,032	70,904,934	71,666,801
% of total US population	30.5%	33.3%	35.7%	34.9%	34.9%	34.9%	34.9%	34.9%	34.9%	34.9%	34.9%	34.9%
Obese (30.0 > BMI < 34.9)	-	-	37,690,800	40,505,397	40,626,600	40,732,857	40,839,392	40,946,205	41,053,298	41,160,672	41,445,864	41,891,196
% of total US population	-	-	20.3%	20%	20%	20%	20%	20%	20%	20%	20%	20.4%
Clinically Obese (35.0 > BMI < 39.9)	-	-	16,895,876	16,083,025	16,131,150	16,173,340	16,215,641	16,258,052	16,300,574	16,343,208	16,456,446	16,633,269
% of total US population	-	-	9.1%	8%	8%	8%	8%	8%	8%	8%	8%	8.1%
Morbidly Obese (BMI > 40)	7,826,542	9,468,254	11,882,814	12,707,576	12,745,600	12,778,936	12,812,358	12,845,868	12,879,466	12,913,152	13,002,624	13,142,336
% of total US population	4.7%	5.4%	6.4%	6.4%	6.4%	6.4%	6.4%	6.4%	6.4%	6.4%	6.4%	6.4%

Source: Canaccord Genuity estimates

Sizing the current and future market opportunity

We estimate current bariatric surgical options are penetrating <1% of the applicable population

The market opportunity for the surgical treatment of obesity is enormous, but remains under-penetrated. In 2014 we estimate more than 136 million Americans (aged 20-64) are considered overweight or obese (BMI > 25). Of that number, more than 69M people qualify as obese (BMI > 30), including ~16M clinically obese (35.0 > BMI < 39.9) and ~13M morbidly obese (BMI > 40). These two groups with BMIs > 35 have historically been identified as the clear-cut candidates for bariatric treatment. That said, we believe the large pipeline of new/safer/less invasive treatment options will further broaden the addressable market to include patients with BMIs in the range of 27+.

The surgical/procedural penetration is miniscule compared to the addressable market. Specifically, in 2014 we estimate that only 179,000 procedures will be performed. That is a penetration rate of only 1.4% of the morbidly obese population, 1.1% of clinically obese population, and 0.3% of the total addressable obese patient population. Based on the incidence data from the CDC, our forward model conservatively assumes prevalence rates to stay at current levels – growing only at the rate of the broader population demographics. That said, we feel the current procedures/devices on the market have only scratched the surface – and therefore believe there is significant opportunity to drive market growth by 1) increasing penetration into the existing market, and 2) introducing new/safer/less invasive devices/procedures to expand the addressable market.

We estimate new/safer/less invasive procedural options and improving reimbursement will drive penetration of the applicable obese population to 0.5% by 2020 and 3% by 2030

We project the surgical/procedural market for obesity to reach 1.9M procedures and equate to ~\$3B by 2030. In Figure 4, we use a 29% CAGR estimate for procedure volumes per year through 2030, leading to a forecast of 25% CAGR in revenues over the next 16 years. While at first glance these metrics may appear aggressive, we note that our model does not include robust assumptions for penetration into the addressable market – specifically our estimates max out at 1.9M procedures in 2030, which equates to only 14% penetration in the morbidly obese, 3% in obese, and 1% in the obese+overweight market segments. This, compared against our conservative assumption for flat growth in the underlying patient population, highlights our expectation for increased procedural penetration driven by broader patient awareness and new procedures and device introductions. The typical indication for traditional bariatric surgical procedures is: 1) BMI>40 or 2) BMI>35 with at least one co-morbid condition (i.e. diabetes, cardiovascular disease). Further, we believe the introduction of temporary and less-invasive devices over the next five years will expand the addressable market to include BMIs > 27. Lastly, it is also important to note that we estimate penetration rates will increase as risks applicable to bariatric surgery decrease, reimbursement improves, and new products are launched starting in 2015.

Figure 4: Estimated procedure volume and market penetration rates

Bariatric Procedures	37,603	135,139	154,301	179,000	180,530	190,172	204,796	232,998	275,302	338,757	812,448	1,881,920
% of Obese Population	0.07%	0.23%	0.23%	0.26%	0.26%	0.27%	0.29%	0.33%	0.39%	0.48%	1.15%	2.63%
Y/Y Growth	nm	nm	nm	nm	0.86%	5.34%	7.69%	13.77%	18.16%	23.05%	139.83%	131.64%
Bariatric Procedures - General	37,603	101,867	95,153	148,391	148,391	148,391	148,391	148,391	148,391	148,391	148,391	148,391
% Mix	100%	75%	62%	83%	82%	78%	72%	64%	54%	44%	18%	8%
Y/Y Growth	nm	nm	nm	nm	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%
Bariatric Procedures - Device	0	33,272	59,148	30,609	32,139	41,781	56,405	84,607	126,911	190,366	664,057	1,733,529
% Mix	0%	25%	38%	17%	18%	22%	28%	36%	46%	56%	82%	92%
Y/Y Growth	nm	nm	nm	nm	5%	30%	35%	50%	50%	50%	249%	161%
Bariatric Device Market	nm	\$99,817,143	\$177,443,490	\$91,827,000	\$98,989,506	\$117,363,630	\$139,206,885	\$194,680,942	\$281,741,650	\$415,902,074	\$1,336,415,627	\$3,082,647,279
ASP per procedure	nm	\$3,000	\$3,000	\$3,000	\$3,080	\$2,809	\$2,468	\$2,301	\$2,220	\$2,185	\$2,013	\$1,778
Y/Y Growth	nm	nm	nm	nm	8%	19%	19%	40%	45%	48%	221%	131%
Bariatric Procedure Penetration												
Overweight & Obese (BMI > 25)	nm	0.11%	0.12%	0.13%	0.13%	0.14%	0.15%	0.17%	0.20%	0.25%	0.58%	1.34%
Obese (BMI > 30.0)	nm	0.23%	0.23%	0.26%	0.26%	0.27%	0.29%	0.33%	0.39%	0.48%	1.15%	2.63%
Morbidly Obese (BMI > 40)	nm	1.43%	1.30%	1.41%	1.42%	1.49%	1.60%	1.81%	2.14%	2.62%	6.25%	14.32%
Bariatric Device Penetration												
Overweight & Obese (BMI > 25)	nm	0.03%	0.05%	0.02%	0.02%	0.03%	0.04%	0.06%	0.09%	0.14%	0.48%	1.23%
Obese (BMI > 30.0)	nm	0.06%	0.09%	0.04%	0.05%	0.06%	0.08%	0.12%	0.18%	0.27%	0.94%	2.42%
Morbidly Obese (BMI > 40)	nm	0.35%	0.50%	0.24%	0.25%	0.33%	0.44%	0.66%	0.99%	1.47%	5.11%	13.19%
Catalysts					ETRM commercializes Q1/15 , Apollo and ReShape Enter Q3/15	GI Dynamics, Scientific Intake Q1, Aspire, Obalon Q2	Endosphere					

Source: Canaccord Genuity estimates

US regulatory environment for obesity companies – a truly positive situation

Rarely do the words “US Food and Drug Administration (FDA)” and “positive environment” for companies come together in the same sentence. However, we feel that the Obesity space within medical devices is experiencing something every executive and investor in medical devices dreams – a truly positive regulatory environment. Our belief is supported by not only commentary from medical device company executives in the obesity space, but also by FDA’s actions.

FDA “guidance” document on obesity – both words and actions. We point to the publication in the *Journal of Surgical Endoscopy* in December 2012, *Benefit-risk paradigm for clinical trial design of obesity devices: FDA proposal*. The paper was authored by H. Lerner, J. Whang and R. Nipper, all employees of the Federal Drug Administration and involved with the Center for Devices and Radiological Health, Office of Device Evaluation at the time of publication. As stated in the paper, “the purpose of the paper was to propose a new paradigm for devices intended to treat obesity, based on a benefit-risk determination, with the hope to provide sponsors an a priori tool for systematic assessment of the risk associated with the devices intended for treatment of obesity and to suggest appropriate levels of benefit for devices with different risk levels.” It was also noted that “the paradigm is NOT intended to determine the class of a device from a regulatory perspective.” (We added the emphasis on the word NOT.) The approach was conceived at an FDA co-sponsored workshop in October 2011 and formally presented to an FDA advisory panel for discussion in May 2012.

FDA mapped out the general risk-benefit paradigm for obesity devices/procedures. In the FDA guidance document, four risk levels are based on percentage of patients experiencing expected and unexpected events during one year after device placement, defined by category. The published tables are provided below in Figure 5 for additional clarity. In summary, for each level of risk, there is a suggested observed mean Total Body Loss (TBL) and timeframe “targeted.” In addition, the probability of a patient experiencing a benefit was included. As expected, TBL (benefit) and time (duration of study) both need to increase with higher risk levels. The importance of this document is that it provided the first “guidelines” for companies in the obesity space. Prior to publication, it was generally perceived that regardless of risk, a new device needed to clear the performance hurdle similar to existing procedures.

FDA employees spearheaded the effort to develop a guidance document for obesity devices in 2012.

For each level of risk, there is a suggested observed mean TBL and timeframe targeted.

Figure 5: Benefit-risk paradigm for clinical trial design of obesity devices; FDA proposal

Table 1 Definition of risk levels based on percentage of patients experiencing expected and unexpected events during 1 year after device placement, defined by category

Adverse event category	Level 1	Level 2	Level 3	Level 4	Examples of events
A: Discomfort that does not require prescription drugs or other medical intervention but may need over-the-counter medications	≤100 %	≤100 %	≤100 %	Any % higher than those listed for level 3 places the device into level 4	Nausea, vomiting, pain, constipation, burping, bloating, gas, cramps, dyspepsia, diarrhea, dehydration
B: Scheduled visit to physician	≤100 %	≤100 %	≤100 %		Band adjustment
C: Unscheduled visit to physician	<10 %	<50 %	≤100 %		Band adjustments due to dysphagia, administration of IV fluids
D: Problems that can be managed with prescription drugs or diet, or topical care or mild interventions	<5 %	<50 %	≤100 %		Nausea, vomiting, pain, infection, dehydration, cutaneous bleeding, GERD, esophagitis, gastritis, nonhemorrhagic anemia, dysphagia, inflammation, depression requiring medication
E: Scheduled endoscopy	<2 %	≤100 %	≤100 %		Device removal, device adjustments, diagnostic evaluation
F: Unscheduled endoscopy	<2 %	<10 %	<20 %		Device removal, device adjustments, diagnostic evaluation or therapeutic intervention (e.g., due to dysphagia or bleeding)
G: Health consequences of malabsorption/malnutrition	<2 %	<10 %	<20 %		Nutritional deficiencies (e.g., anemia, iron deficiency, electrolyte imbalances) or effect on medication levels, development of an eating disorder
H: Substantial discomfort not managed even with drugs	<0.1 %	<20 %	<50 %		Severe nausea, vomiting, bloating, GERD
I: Tissue damage requiring therapy other than an operation	<0.1 %	<10 %	<20 %		Erosion, ulcer, GI or esophageal mucosal bleeding
J: Hospitalization, no operation	<0.1 %	<5 %	<5 %		Visit to the ER, IV antibiotics for infection, IV medication for severe pain, severe anemia with or without need for blood transfusion, pneumonia, need for anticoagulation for pulmonary embolism, severe depression
K: Hospitalization, with operation	<0.1 %	<1 %	<1 %		GI or esophageal perforation, gallbladder removal, obstruction (all etiologies), unscheduled device removal due to severe pain or other symptoms
L: Death	<0.1 %	<0.1 %	<0.1 %		

IV intravenous, GERD gastroesophageal reflux disease, GI gastrointestinal, ER emergency room

Table 2 Target effectiveness levels: % of total body loss (%TBL)

Level 1	Level 2	Level 3	Level 4
5 % observed mean TBL and statistical superiority to diet and exercise control	8 % observed mean TBL over sham and 50 % patients with 5 % TBL in treatment group	10 % observed mean TBL over sham and 50 % patients with 7 % TBL in treatment group	13 % observed mean TBL over sham and 50 % patients with 10 % TBL in treatment group
Measured at 6 months	Measured at 1 year	Measured at 2 years	Measured at 3 years

Source: Lerner Et Al, Journal of Surgical Endoscopy (2013)

“Over the past few years, the growing body of medical literature has identified obesity with its associated metabolic and cardiovascular comorbidities as one of the major public health problems facing our nation.”

FDA CDRH, 2012

Clinical data about obesity related co-morbidities heightens governmental interest in obesity. As to why the FDA would stomach a change for obesity companies, we only need to read the above-mentioned document, which states that the link between obesity and other diseases (especially diabetes and hypertension, with a sprinkling of cancer) has become standard knowledge over the past five years. More importantly, there is a lack of options available for patients. Specifically, it was stated that “over the past few years, the growing body of medical literature has identified obesity with its associated metabolic and cardiovascular comorbidities as one of the major public health problems facing our nation. The primary treatments for obesity have ranged from diet and exercise, with and without counseling and behavior modification, to prescription drugs and surgical procedures. The use of medical devices also has played a role in the treatment of

obesity.” Finally, the report goes on to state that only three medical devices have been FDA approved for the treatment of obesity (two of which were bands and are still sold today by Apollo EndoSurgery and Johnson & Johnson Ethicon EndoSurgery), and the Garren-Edwards Gastric Bubble, which was voluntarily withdrawn from the US market in 1992.

We believe FDA is a help, not a hindrance. It is our belief that the sheer magnitude of the obesity pandemic and the related co-morbidities has driven governmental focus on the issue. Furthermore, given the lack of options available and eventual cost to the healthcare system, we believe a decision was made by the US government (Specifically CMS and FDA) to address the problem. That said, our conversations with industry (executives and physicians) lead us to believe that FDA is very supportive of advancing new technologies to the commercial markets to address the obesity pandemic.

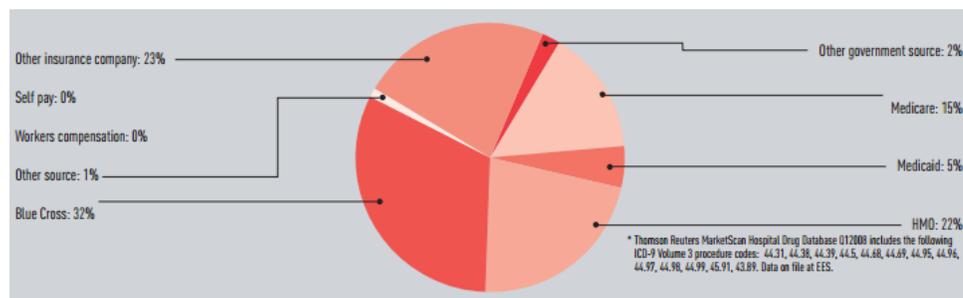
Improving acceptance of obesity as a medical issue – one step closer

The first step in resolution of any problem is first to recognize, and then accept that there is a problem. CMS officially designated obesity as a disease in 2004, and the AMA followed suit in 2013. Officially classifying obesity as a disease has drastically changed the way scientists, medical professionals, and payers think about obesity.

CMS took the first step in 2004. The turning point for the medical device industry occurred in 2004 when CMS eliminated language stating that “obesity is not an illness and therefore is not covered for treatment under the agency’s official guidelines.” The deleted section said that for a surgery to be covered it had to “correct an illness which caused the obesity or was aggravated by the obesity.” With this wording in place, beneficiaries could not even begin requesting approval or appeal a denial because obesity was not even considered a disease.

In 2006 and 2012, CMS coverage was expanded to include devices and more types of procedures (gastric banding). Specifically, a Medicare Coverage Advisory Committee (MCAC) subsequently concluded that there was enough clinical evidence supporting the safety and efficacy of both open and laparoscopic bariatric surgery in treating morbid conditions associated with obesity. Up until then, almost all of the charges related to bariatric surgery were related to gastric bypass procedures, hospital stays, and complications due to gastric bypass. In the new 2006 policy, laparoscopic adjustable gastric banding procedures, along with open and laparoscopic biliopancreatic and duodenal switch surgeries, were added to coverage on top of gastric bypass. In June 2012, CMS released a decision on coverage for laparoscopic sleeve gastrectomy, expanding treatment options one step further.

CMS sets the tone for commercial insurance companies. It is important to note that only about 20% of the bariatric procedures related to obesity are for the CMS (Medicare and Medicaid) population as most seniors do not meet the health requirements for a bariatric procedure. However, we believe the broader impact of the 2004 and 2006 CMS changes has been at the commercial payer level, since insurance companies typically follow Medicare policies closely.

Figure 6: Estimated bariatric surgery reimbursement distribution 2011

Source: Ethicon EndoSurgery

Government payers accounted for 22%, while commercial payers accounted for 77% of bariatric procedures in 2011

United States Affordable Care Act (ACA) has been neutral thus far, but is an incremental positive. One of the main goals of the ACA (which was implemented Jan 1, 2014) outside of providing insurance coverage for the un-insured was to re-shift our country's healthcare focus to preventative care, away from higher acuity services along the healthcare continuum. Health plans, as of 2014, must cover obesity screening and counseling at no cost to the patients. Medicare has provided this as a benefit to its recipients since 2011, but few patients actually take advantage of it. Provisions of the ACA also prohibit insurance denials based on pre-existing conditions and lifetime caps on healthcare-related costs for patients.

All is not perfect as access is still limited. The ACA selectively left out coverage for bariatric surgery and gave state insurance exchanges broad discretion as to whether they would cover the service. Thus far, only 22 states have elected to include obesity treatments such as metabolic and bariatric surgery as part of their health benefits. Net, net the ACA is positive for bariatric surgery. However, we do note that employers have scaled back on health plan coverage (two-thirds of which do not provide coverage on bariatric procedures anyway), and multiple states have elected not to cover bariatric surgery as an option, access to bariatric procedures continues to be restricted. However, we believe as new lower-cost technologies are commercialized and more data on economic costs/benefit becomes available, we believe access could improve, driving significant market penetration rates.

Mechanisms of action for obesity devices: FARMS

E – Flow Control

A – Appetite Suppression

R – Restriction

M – Malabsorption

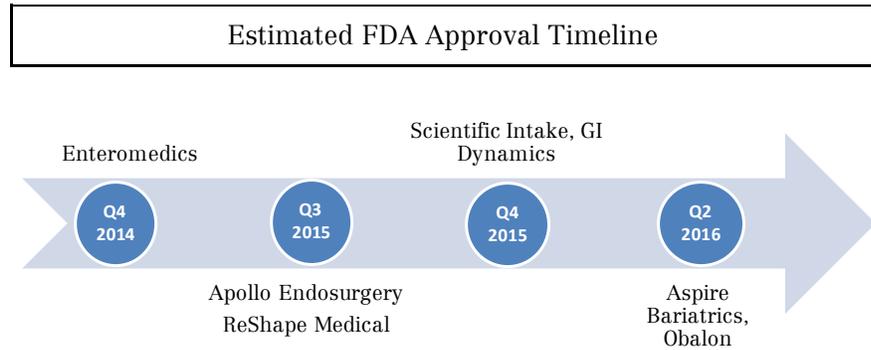
S – Space Occupation/Filler

Multiple technologies on the cusp of US FDA PMA approval – new, lower-cost options

We believe there will be more than one winner in the obesity space. Our thesis stems from the fact that there are several mechanisms of action upon which a device/procedure can be effective. We have provided our categorization for the mechanisms of action. FARMS is the acronym we use to outline which category a device falls into: **F**low control, **A**ppetite suppression, **R**estriction, **M**alabsorption, and **S**pace occupation/filler. We note that a device may work targeting more than one mechanism of action. Furthermore, we note that the different devices and approaches are targeted toward different BMI levels ranging from 27 to 50+. Lastly, we also note that the devices/approaches being developed are at a range of price points from \$1,000-\$25,000. As a result of the multiple risk/reward options, quality of life impacts, and price points, we believe patient choice will be a significant factor on commercial success. Thus, we believe given the low penetration rate for obesity device/bariatric procedures of <1%, or 179,000 procedures

out of potential patient population of 69M+ in the US alone, we believe there is a huge opportunity for success by multiple types of products as the market is penetrated.

Figure 7: Estimated FDA approval timeline



Source: Canaccord Genuity Estimates

The flood gates are about to burst – three PMAs are at FDA. From a timing perspective, we highlight that there are four PMA devices that have been submitted within the past 12 months. Specifically, we note the Maestro System (vagal nerve blocking) from EnteroMedics (ETRM), the Obera (space occupier/filler) from Apollo EndoSurgery, and the ReShape Duo (space occupier/filler) from ReShape Medical. We also note there are a few other companies with products in US Pivotal trials including the Aspire Assist (malabsorption) from Aspire Bariatrics, Endobarrier (malabsorption) from GI Dynamics, the Obalon balloon (space occupier/filler) from Obalon, and the SMART device (restriction) from Scientific Intake. We have provided a timeline (Figure 7) for when we project FDA approval and subsequent commercialization over the next two years. Given the plethora of new devices on the near-term horizon, unmet clinical need in the market, and low penetration rate of existing products/procedures, we believe the obesity market is poised for significant growth.

OBESITY: BEYOND AN EPIDEMIC

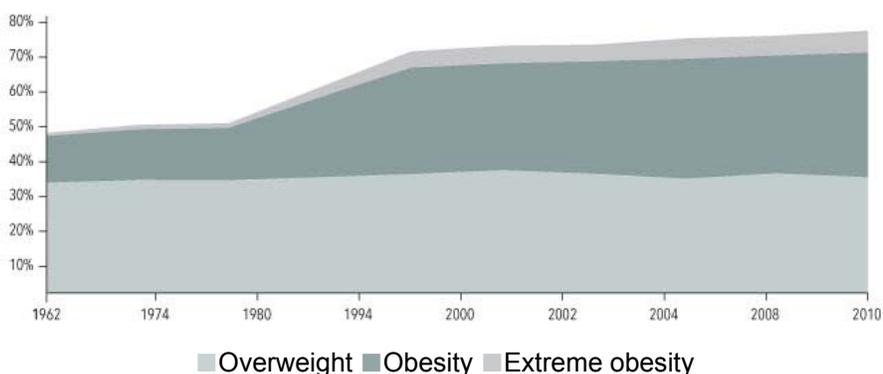
WHO estimates 500 million obese adults worldwide, with 17% (84 million people) residing in United States

35% of adult Americans are obese and 69% are categorized as overweight or obese

500 million obese adults worldwide and growing. In recent decades, the consequences of obesity have shifted drastically from a social and cosmetic issue to a serious epidemiological and clinical concern. The World Health Organization (WHO) estimates that approximately 11% of the world's adult population is obese (at least 500 million people), with almost 17% of this population (84 million people) residing in the United States. If present trends continue, the obese population could exceed 1.12 billion people globally by 2030.

~84 million obese adults in the US today (approximately one in three adult Americans). The United States has seen a dramatic rise in the prevalence of obesity over the past 30 years. In 1980, a National Health and Nutrition Examination Survey (NHANES) estimated that 14% of US adults were obese. As of 2012 the same survey showed that 35% of adult Americans suffer from obesity, with 69% adult Americans being categorized as either overweight or obese, figures that are only expected to get larger. Specifically, forecasts predict a 33% increase in the prevalence of obesity among Americans by the year 2030.

Figure 8: Obesity growth in the United States 1962-2010



Source: National Institute of Health

Prevalence of obese children in the United States has risen to 17% in 2011-2012 from 5% in 1980

Childhood obesity is a severe health challenge. The trends become more alarming when focusing specifically on children and adolescents. Specifically, the prevalence of childhood obesity (18 years old and under) rose from 5% in 1980 to 17% in 2011-2012 (NHANES 2011-2012). Today, 32%, or one in three children are overweight or obese, with rates as high as 40% in the African American and Hispanic demographics.

Obese children are predisposed to remain obese. Overweight and obesity in childhood lead to physiological changes that cause children to become or remain obese as adults.

According to a study published in the Journal of the American Medical Association, JAMA, in 2010 (JAMA, The. Vol. 304, No. 18. Nov. 10, 2010), obese adolescents are 16 times more likely to become severely obese adults than overweight and normal adolescents. Further, black male obese teenagers are 29 times more likely to become severely obese adults and Hispanic male obese teenagers are 28 times more likely to become severely obese adults.

Figure 9 displays the changes in obesity rates among youths in the US from 1971 to 2012. Although we can see modest improvement in childhood obesity rates for children ages 2

through 5 and ages 6 through 11 between 2003-2004 and 2011-2012, these rates are still significantly higher today than they were in the 1970s and 1980s, especially for youths ages 12 through 19. While any improvement in obesity rates, however small, is a step in the right direction, simply delaying the age at which children become overweight or obese will not do much good in the long run.

Figure 9: Obesity rates for youths (ages 2-19) in the United States 1971-2012

	NHANES I	NHANES II	NHANES III	NHANES	NHANES
	1971-1974	1976-1980	1988-1994	2003-2004	2011-2012
Ages 2 through 5	5.00%	5.00%	7.20%	13.90%	8.40%
Ages 6 through 11	4.00%	6.50%	11.30%	18.80%	17.70%
Ages 12 through 19	6.10%	5.00%	10.50%	17.40%	20.50%

Source: National Health and Nutrition Examination Survey (NHANES)

Obesity will have a significant burden on our healthcare system. Larger, fattier meals and excessive amounts of sugary drinks combined with a more sedentary lifestyle are poised to produce damaging and potentially deadly effects. Those who are overweight and obese carry higher risks for serious co-morbidities, such as type 2 diabetes, heart disease, stroke, hypertension, cancer, and osteoarthritis. The complications associated with weight gain highlight the colossal burden being placed on the healthcare system. The direct and indirect annual cost of obesity to the US healthcare system is already in excess of \$182 billion. According to a report commissioned by the United Health Foundation and the American Public Health Association and Partnership for Prevention, this figure is expected to increase to \$344 billion, or 21% of total US healthcare expenditures, in 2018 if the obesity rate continues to rise at its current level.

Defining the obese patient

The most common formula used in classifying a person as obese or overweight is the Body Mass Index (BMI), which is weight/height² (kg/m²). The clinical guidelines are as follows:

- **Underweight:** BMI < 18.5
- **Normal:** BMI between 18.5 - 24.9
- **Overweight:** BMI between 25.0 - 29.9
- **Obesity, Class 1:** BMI between 30.0 - 34.9
- **Obesity, Class 2 or Clinically Obese:** BMI between 35.0 - 39.9
- **Obesity, Class 3 or Morbidly Obese:** BMI between > 40
- **Obesity, Class 4 or Super Obese:** BMI > 50

Figure 10: BMI calculation

WEIGHT lbs	100	105	110	115	120	125	130	135	140	145	150	155	160	165	170	175	180	185	190	195	200	205	210	215
kgs	45.5	47.7	50.0	52.3	54.5	56.8	59.1	61.4	63.6	65.9	68.2	70.5	72.7	75.0	77.3	79.5	81.8	84.1	86.4	88.6	90.9	93.2	95.5	97.7
HEIGHT in/cm	Underweight					Healthy					Overweight					Obese			Extremely obese					
5'0" - 152.4	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42
5'1" - 154.9	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	
5'2" - 157.4	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39		
5'3" - 160.0	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38		
5'4" - 162.5	17	18	18	19	20	21	22	23	24	25	26	27	28	29	30	31	31	32	33	34	35	36	37	
5'5" - 165.1	16	17	18	19	20	20	21	22	23	24	25	25	26	27	28	29	30	30	31	32	33	34	35	35
5'6" - 167.6	16	17	17	18	19	20	21	21	22	23	24	25	25	26	27	28	29	29	30	31	32	33	34	34
5'7" - 170.1	15	16	17	18	18	19	20	21	22	22	23	24	25	25	26	27	28	29	29	30	31	32	33	33
5'8" - 172.7	15	16	16	17	18	19	19	20	21	22	22	23	24	25	25	26	27	28	29	29	30	31	32	32
5'9" - 175.2	14	15	16	17	17	18	19	20	20	21	22	22	23	24	25	25	26	27	28	28	29	30	31	31
5'10" - 177.8	14	15	15	16	17	18	18	19	20	20	21	22	23	23	24	25	25	26	27	28	28	29	30	30
5'11" - 180.3	14	14	15	16	16	17	18	18	19	20	21	21	22	23	23	24	25	25	26	27	28	28	29	30
6'0" - 182.8	13	14	14	15	16	17	17	18	19	19	20	21	21	22	23	23	24	25	25	26	27	27	28	29
6'1" - 185.4	13	13	14	15	15	16	17	17	18	19	19	20	21	21	22	23	23	24	25	25	26	27	27	28
6'2" - 187.9	12	13	14	14	15	16	16	17	18	18	19	19	20	21	21	22	23	23	24	25	25	26	27	27
6'3" - 190.5	12	13	13	14	15	15	16	16	17	18	18	19	20	20	21	21	22	23	23	24	25	25	26	26
6'4" - 193.0	12	12	13	14	14	15	16	16	17	17	18	18	19	20	20	21	22	22	23	23	24	25	25	26

Source: National Institute of Health

Four classes of obesity: obese, clinically obese, morbidly obese, and super obese

The four different classes of obesity (obese, clinically obese, morbidly obese, and super obese) provide healthcare professionals with specific treatment options and protocols to address the varying risks for developing co-morbidities.

BMI as a measure for assessing optimal weight and overall health dates back to the 1800s.

According to an article published in *IMS Magazine* (a publication of the Institute of Medical Science at the University of Toronto) in 2011 (Pekar, Tatyana. Body Mass Index. *IMS Magazine*, Summer 2011: p. 21-22), the concept of BMI was introduced by the Belgian mathematician Adolphe Quetelet, who made the observation in the 1830s that an individual’s weight is approximately proportional to the square of their height. BMI did not gain popularity, however, until 1972, when Ancel Keys published a paper in the *Journal of Chronic Diseases*, which included the finding that BMI was the best measure of adiposity, or body fat percentage, at varying ratios of heights and weights for a population as a whole.

BMI is not perfect; BMI was designed for populations, not individuals to classify patients.

BMI is not perfect, but it is the best yardstick we have. While BMI has proven to be the best way to classify patients, it still has some flaws, as it does not directly measure fat. Because of this, it does not differentiate between body fat and lean body mass, nor does it account for factors such as gender, age, and ethnicity. For example, women have, on average, more body fat than men, and Asians have more body fat than Caucasians. In fact, Ancel Keys himself noted that BMI is a good way of assessing adiposity among populations, but that it is inappropriate for individual diagnoses. However, because of its simplicity, it has become the standard for individual diagnoses of overweight and obesity.

Benchmarking patient progress

There are multiple ways to measure weight loss. The most basic and the most common method is body mass index (BMI). It is easily calculated based on height and weight. Waist circumference is a common measurement for abdominal obesity. It is defined as the circumference of the abdomen, measured at the waist, usually from the belly button (umbilicus). The downside to waist circumference as a measure of health is that there are variations in patient anatomy and it can become difficult to measure with patients who have a BMI of 35 or higher. Another method, Skinfold Thickness, uses a special caliper to measure the thickness of a “pinch” of skin and the fat under specific areas of the body.

Success is measured differently for devices and drugs, but that is changing. In order for researchers and patients to effectively compare results of different fat reduction therapies, there are a couple of metrics used for comparison:

The benchmark for device success was previously excess weight loss (%EWL), but the FDA is now shifting to total body weight loss (%TBL) as its primary metric

- **Percentage excess weight loss (%EWL)** reduction has traditionally been a common benchmark for surgical procedures and medical devices. The calculation is (weight loss) / (excess weight) x 100. Excess weight is defined as the difference between the actual weight and the “ideal weight,” which is based on an individual’s height and the weight that they would need to have in order to yield a BMI of 25. For example, a 6’ person weighing 300lbs would have a BMI of 41 (morbidly obese) and be carrying approximately an extra 115 pounds. Weight loss of 60 pounds would result in a %EWL of 52% (60/115).
- **Percentage weight loss or total body weight loss (%TBL)** is traditionally a metric used more commonly for diet, exercise, and drug therapies. It is calculated as (weight loss) / (original weight) x 100. Using this metric, the same 6’ person weighing 300lbs and losing 60lbs would be reported as having achieved 20% TBL.

That all said, we would note that the FDA is migrating device companies toward total body weight loss (%TBL) as a primary metric. This makes the comparison of drug and device companies significantly easier and more accurate.

UP CLOSE AND PERSONAL: FAT AT THE CELLULAR LEVEL

Adipose tissue, or body fat, can be stored either subcutaneously (under the skin) or viscerally (surrounding the internal organs). The location on the body where fat is stored varies depending on gender, race, and genetics. For instance, during times of weight gain, women tend to store fat around the hips and thighs, while men typically deposit fat around the middle of their bodies. The broad generalization is that women resemble “pears” and men resemble “apples.” Besides the external/cosmetic result, the internal/clinical ramifications of fat storage depend on the location as well.

Adipocytes, or fat cells, make up adipose tissue and play a critical role in energy regulation and homeostasis. During infancy, adipocytes are brown in color and function completely opposite to the white adipocytes found in adults. Brown adipose tissue utilizes energy to generate heat, which keeps infants warm. As a child grows, the body produces mitochondrial uncoupling proteins that convert the brown adipocytes into the white adipocytes, which function as energy storage facilities.

As energy intake exceeds energy consumption, these white adipocytes will store this extra energy as triglycerides. During starvation, the body depends on the adipocytes to release excess energy stores in the form of free fatty acids. However, if the body is in a constant state of excess energy, the adipocytes steadily enlarge. Once an adipocyte reaches its maximum capacity, the cell divides (also known as hyperplasia) leaving the body with additional repositories for energy reserves.

The body’s ability to create new adipocytes all but diminishes after puberty. Only in extreme cases does adipocyte hyperplasia occur in adulthood. Excess fat early in life can lay the foundation for a lifetime struggle with obesity. **Weight gain as an adult is mainly achieved through adipocyte enlargement or hypertrophy.**

Fat deposition varies based on gender, race, and genetics

Adipocytes enlarge when body is in a constant state of excess energy

Adipose tissue releases adipokines (fat hormones) believed to be involved in the side-effects/co-morbidities of obesity

During hypertrophy, the adipocyte secretes various molecules known as adipocytokines. These adipocytokines act as signaling messengers and are believed to be involved in some of the harmful side effects and co-morbidities associated with obesity. The key concept is that adipose tissue is a highly active metabolic and endocrine organ and can lead to serious consequences if increased significantly by weight and by size. For a listing of adipocytokines and their respective functions, please see Figure 11 below.

Figure 11: Adipocytokines and their functions

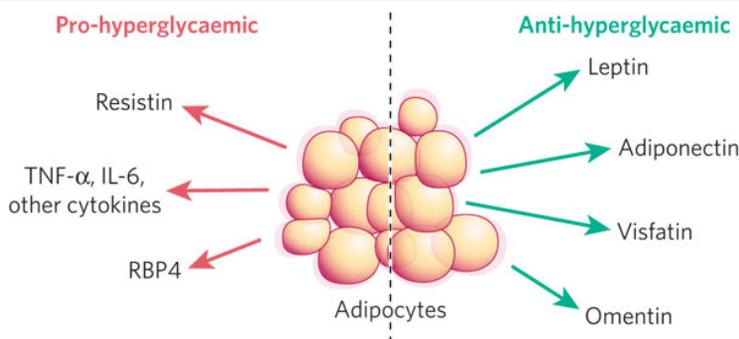
Adipocytokine	Full name	Effects on
Leptin	Leptin	Food intake, fat mass
Adiponectin	Adiponectin	Insulin resistance, inflammation
Resistin	Resistin	Insulin resistance, inflammation
Visfatin	Visfatin	Insulin resistance
Omentin	Omentin	Insulin resistance
Vaspin	Visceral adipose tissue-derived serpin	Insulin resistance
Apelin	Apelin	Vasodilatation
CETP	Cholesteryl ester transfer protein	Lipid metabolism
LPL	Lipoprotein lipase	Lipid metabolism
HSL	Hormone sensitive lipase	Lipid metabolism
A-FABP 4 (aP2)	Adipocyte fatty acid-binding protein 4	Lipid metabolism
Perilipin	Perilipin	Lipid metabolism
RBP ⁴	Retinol-binding protein ⁴	Lipid metabolism
ASP	Acylation stimulating protein	Lipid metabolism
AT II	Angiotensin II	Blood pressure
ACE	Angiotensin converting enzyme	Blood pressure
AGT	Angiotensinogen	Blood pressure
TNF- α	Tumour necrosis factor- α	Inflammation
IL-6	Interleukin-6	Inflammation
CRP	C-reactive protein	Inflammation
Adipsin	Adipocyte trypsin/complement factor D	Inflammation
MCP-1	Macrophage chemo attractant protein-1	Macrophage attraction
ICAM-1	Intercellular adhesion molecule-1	Macrophage activation
PAI-1	Plasminogen activator inhibitor-1	Fibrinolysis

Source: European Society of Cardiology

Leptin prevents the obese patient from feeling full through a circular signal mechanism

Weight gain makes it more difficult to feel full. Leptin is one of the hormones secreted, and it acts as a circulating signal to reduce appetite. Obese individuals are subject to high concentrations of leptin, which can develop into a resistance to the hormone in the muscle, liver, and hunger-related neurological pathways. Due to the leptin signal resistance, obese individuals have difficulty feeling satiated during or after a meal.

Figure 12: Understanding the adipocyte



Source: www.nature.com

TNF- α , IL-6, and FFAs are associated with insulin resistance

Adipocyte secretions are involved in metabolism and the onset of type 2 diabetes. Adipose tissue was previously thought of as a storage site for fatty acids; however, numerous recent studies suggest adipose tissue plays a much larger role in lipid and glucose metabolism than previously thought. As more adipocytes secrete cytokines such as TNF- α , IL-6, and FFAs (free fatty acids), an additional protein (insulin receptor substrate-1) is induced, which causes insulin receptors to be blocked. In turn, the pancreas produces more insulin, but with insulin resistance increased and the inability to adopt it, diabetes ensues. Additionally, as fat mass increases, TNF (tumor necrosis factor)- α increases. TNF- α negatively impacts blood sugar absorption by the liver and muscle and signifies another potential cause of insulin resistance.

More fat can lead to heart disease and even cancer. In addition to insulin resistance, adipocytes lead to atherosclerosis and elevated cancer risks. It has long been known that higher concentrations of fat increase the likelihood of heart disease-related events, but we have learned that at a cellular level, excess fat also causes plaque build-up in the vasculature. Increased adipocytokines block the plaque-clearing mechanisms that prevent build-up. Adipose tissue also releases oestrogen, which, when unchecked by the necessary countering hormones (progesterone or estradiol), can increase the risk of cancer.

THE GI TRACT: UNDERSTANDING THE BASIC PLUMBING

The gastrointestinal tract (GI) is responsible for processing food for absorption and expelling excess waste. Digestion first starts in the mouth where food is mechanically broken down and mixed with saliva, which begins the chemical breakdown process. The stomach is an extremely acidic environment where large molecules are broken down into smaller particles that will be easily absorbed by the small intestine.

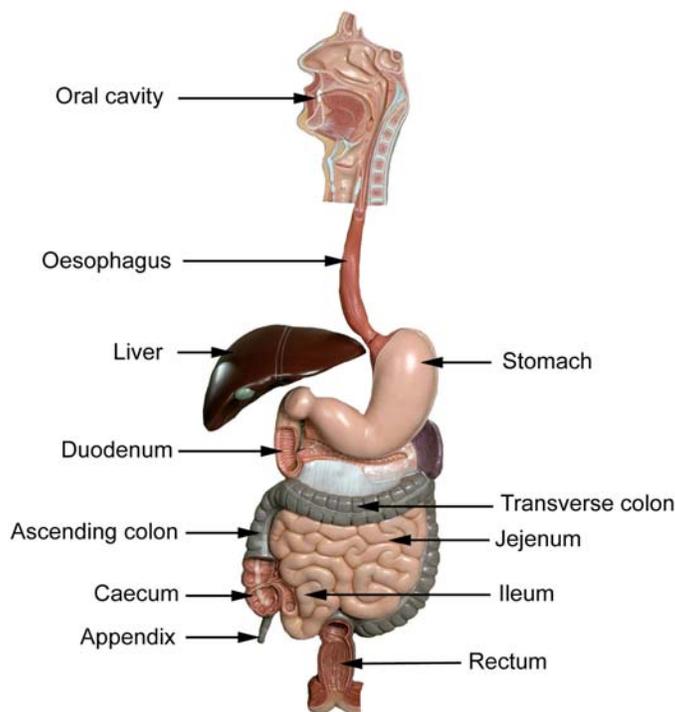
The small intestine is the primary site of fat, carbohydrate, and protein absorption

The small intestine is the site for a great deal of chemical digestion as well as the primary segment of the GI tract for absorption. The small intestine walls are covered with structures called microvilli which allow for the absorption of 98% of all digestible carbohydrates, 95% of all fat, and 92% of all protein consumed.

The first section of the small intestine is the duodenum, which is also the shortest section, measuring 10-12 inches in length. This is the primary location for chemical digestion and is responsible for regulating gastric emptying. Once gastric chyme (the food post-digestion in the stomach) enters the duodenum, secretin and cholecystokinin are released, triggering the release of bile from the liver and gallbladder, along with enzymes from the pancreas.

The middle section of the small intestine, the jejunum, is approximately 36 inches long and is the location of the final chemical digestion process. Afterwards, nutrients and bile are absorbed in the final segment of the small intestine, called the ileum, which is approximately 72 inches long.

The large intestine is 60 inches long and completes the remaining digestive processes. Over 12-25 hours, any remaining minerals will be absorbed, along with water. The chyme is then packed into feces.

Figure 13: Gastrointestinal tract diagram

Source: www.Oxford174.com

GENETIC PREDISPOSITION TO OBESITY COMES FROM MULTIPLE GENES

It was initially thought that there was a single obesity gene that predisposed individuals to become obese. Monogenic forms of obesity were verified in a number of genetic studies as genetic testing become more prevalent. Twin and adoption studies demonstrated that genetic factors do play a role in determining which individuals are more susceptible to becoming obese in response to a particular environment. A 2007 study published in *Science* (Science, Fayling, April 12, 2007) identified one specific gene that carries higher obesity risk and also found a link between the gene and increased incidence of diabetes. The study involved over 38,750 participants and focused on the FTO gene region on chromosome 16; it showed that the presence of a certain variant (rs9939609) was highly correlated with an increased BMI from childhood to old age. In particular, 16% of adults who carried two copies of the gene variant weighed approximately 3 kg (6.6lb) more and had a 67% increased risk of type 2 diabetes.

A 2008 study published in the *New England Journal of Medicine* (NEJM, Cecil, Vol. 359, No. 24, Dec. 11, 2008) involving 2,726 children ages 4-10 showed similar weight gain and BMI increase in children with the gene variant. Children were isolated for either expressing or not expressing the A allele of rs9939609. Results found there was no significant difference between the two groups in the rate of metabolism, energy expenditure, or weight of the food ingested by the children. This led to the conclusion that the gene variant likely leads to consumption of high-calorie, energy-dense foods.

Researchers have concluded that variants of gene rs9939609 results in a predisposition to consuming high-calorie, energy-dense foods

These findings coincide with the NIDDK's research of the Pima Indians and the "thrifty gene." The concept was proposed in the 1960s to explain why the Pima has such a high incidence of obesity. According to the theory, for thousands of years in southern Arizona and Mexico, the Pima relied on farming, hunting, and fishing for food. This "thrifty gene" would have evolved to enable them to survive the alternating periods of feast and famine. The body would store energy as fat at a higher rate when food was plentiful in order to help the Pima survive periods of starvation. However, now that the Pima have adjusted to the high-fat, Western diet, the trait has become detrimental to their health. The study found that 95% of the Arizona Pima were obese and approximately 50% had diabetes. In contrast, the Mexican Pima, who still live the traditional lifestyle of their ancestors, showed no incidence of obesity and only 9% had diabetes.

Since those studies concluded, there has been further meta-analysis of GWAS (genome wide association studies) pertaining to obesity and diabetes. Those studies identified additional polygenic variants. As of December 2009, 17 polygenic variants have been confirmed. These meta-analyses show that obesity isn't due to one single factor but an amalgamation of multiple alleles, each one having a small impact on the propensity for obesity in childhood and adulthood.

Epigenetics are chemical tags that can change gene expression without altering the genetic code. Environmental factors can create genetic responses to obesity.

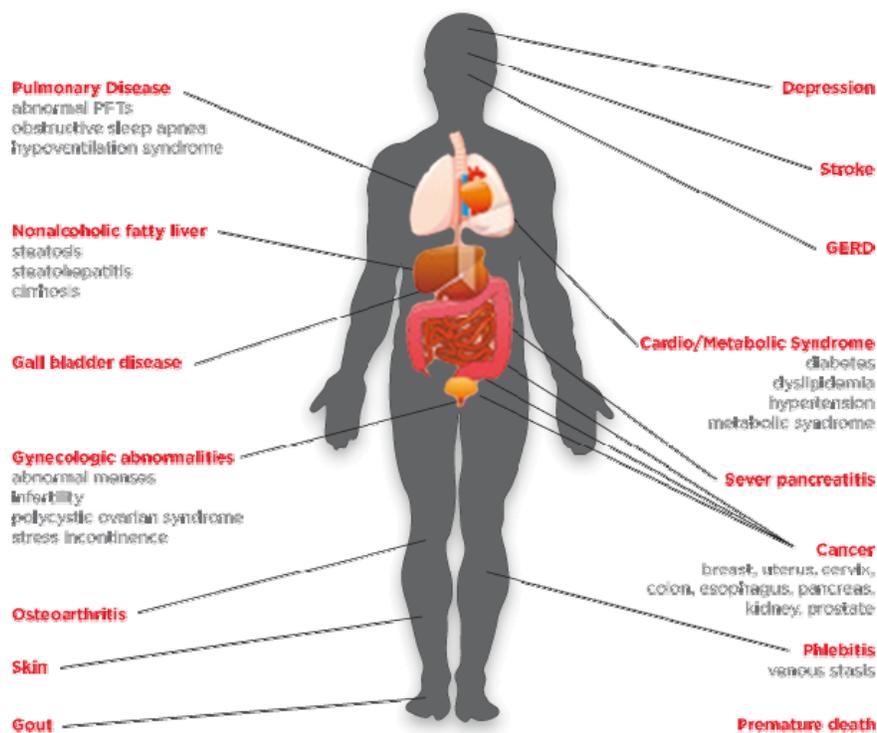
That said, genetics alone do not cause obesity. The interaction between genetics and environment shapes obesity. Epigenetics, the chemical tags that can change gene expression without altering the genetic code, create genetic responses to environmental factors that drive obesity. Studies have shown that epigenetic factors can be inherited in subsequent generations. Many environmental factors such as chemicals, starvation, or disease can influence the propensity for obesity risk. There is still much to be studied in the field of obesity epigenetics, as environmental factors are widespread. Additionally, as human genome sequencing becomes more personalized, smaller, less common alleles will be identified at an individual level. GWAS identifies polygenic variants that are more commonly seen in larger proportions of the population due to their large study sizes.

CLINICAL COMPLICATIONS: OBESITY'S EFFECTS ON THE REST OF THE BODY

CMS officially designated obesity as a disease in 2004, and the AMA followed suit in 2013. Officially classifying the condition as a disease has drastically changed the way scientists and medical professionals think about obesity. By changing the treatment algorithms and researching the interconnectivity between different diseases, researchers and physicians are now starting to fully understand just how impactful obesity is to comorbidities that patients suffer from in addition to their primary medical condition.

Adipose tissue impacts the body on a chemical and mechanical level

The long list of health consequences associated with being obese is the result of two independent factors: 1) the increase in the mass of the adipose tissue or number of fat cells and 2) the secretion of pathogenic products or metabolic effects from the enlargement of fat cells. Figure 14 highlights the various and numerous risks associated with obesity.

Figure 14: Medical complications of obesity

Source: www.Ethicon.com

Problems linked to the increased mass of fat cells***Obstructive sleep apnea***

The respiratory complications clinically linked to excess abdominal and upper body fat focus on sleep disorders and breathing. Airway passages and lungs become constricted by excess adipose tissue temporarily blocking the passage of air, making it difficult to breathe. Obstructive sleep apnea (OSA) is defined as episodes of cessation in breathing lasting for at least 10 seconds during sleep.

70% of sleep apnea sufferers are overweight or obese

Typically the symptoms include fatigue, irritability, snoring, and morning headache. The lack of REM (rapid eye movement) sleep can lead to emotional and behavioral problems, including overeating, which exacerbates the problem.

Complications due to OSA mostly lie within the cardiovascular system. When the bloodstream is deprived of oxygen (oxygen desaturation), patients will typically become hypertensive. This low-oxygen, high-blood-pressure state can bring on cardiac events, especially in cases where there is preexisting heart disease.

Psychological disorders; a vicious downward spiral.

Overweight individuals suffer 25% increased risk of developing major depressive disorder

Obesity carries a devastating social stigma and often leads to many psychological disorders. Long-term depression is a common byproduct of obesity and can perpetuate overeating as patients try to alleviate depression symptoms. Research reported in the July 2006 *Archives of General Psychiatry* (*Archives of General Psychiatry*, July 2006, Volume

63, page 824) showed a 25% increased risk of major depression, bipolar disorder, panic disorder, and agoraphobia (a fear of being in public places).

Depression and other psychotic disorders are typically treated using psychotherapy and/or medication. One main obstacle is that many antidepressants and antipsychotic pharmaceuticals on the market induce weight gain and cause cravings for specific food groups such as carbohydrates.

Binge eating disorder is estimated to occur in approximately 1-5% of the general population.

Compulsive and binge eating are also much more prevalent in obese patients. These are forms of food addiction, a behavior presented by a loss of control over the amount of food consumed. Patients can be both regular compulsive eaters and/or binge eaters. According to the National Eating Disorder Association, compulsive and binge eating disorders are estimated to affect approximately 1-5% of the general population and are independently associated with symptoms of depression.

Osteoarthritis: the joints are suffering from the added strain

10 lbs. of excess weight translates to 30-60 pounds of added force to the knee joint

With the additional load placed on the joints in the body, it is intuitive that obese patients have a higher risk of facing mobility issues. Osteoarthritis (OA), or degenerative joint disease, is the most common form of arthritis and occurs when cartilage in the joints wears down over time. This wear and tear becomes much more rapid with increased stress and loading. It is easy to understand how being just 10 pounds overweight, which increases the *force* on the knee by 30-60 pounds with each step, can have a damaging effect on the body's joints.

Jiang et al., a meta-analysis in 2012 in the *Journal of Joint, Bone, and Spine*, showed that even a 5-unit increase in body mass index was associated with a 35% increased risk of knee OA and an even higher risk for women than men.

Excess weight can lead to osteoarthritis in both large joints and non-weight bearing joints

While it does make sense that healthcare providers are seeing higher incidences of OA in knees and hips, they are also seeing increased osteoarthritis in non-weight-bearing joints such as the hands and wrists. This evidence points to the possibility that there could also be some cross-over systemic effects from the enlargement of fat cells as well. Researchers have found a high correlation between OA and the pro-inflammatory molecule leptin, which is secreted by hypertrophic adipocytes.

At present time, there is no cure for osteoarthritis. Typically, physicians will first recommend therapies to reduce stress on the joint and to relieve pain and stiffness. The initial common treatment options include diet, exercise, NSAIDs taken orally, and (or) lifestyle modifications. Secondly, patients may elect to receive corticosteroid and (or) hyaluronic acid injections into their joints to reduce pain, inflammation, and swelling. In very severe cases, patients may be required to undergo surgical intervention, arthroscopic surgery and even partial or total joint replacement.

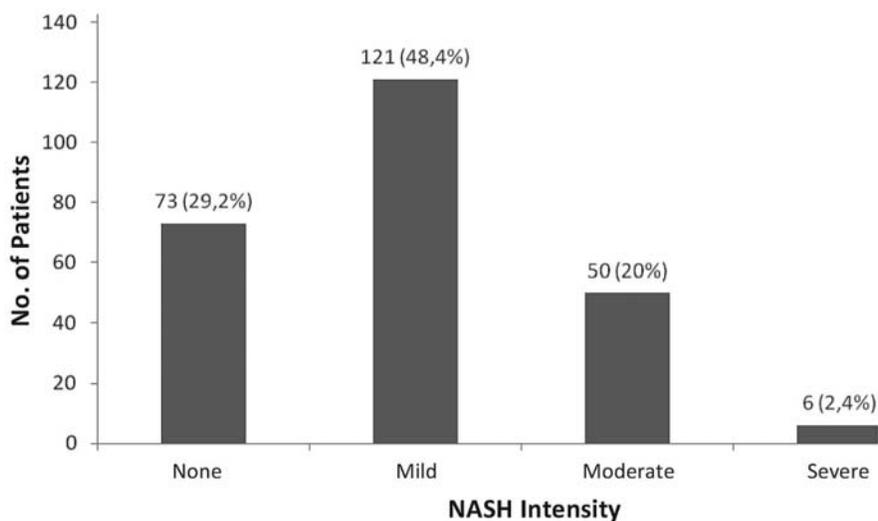
Liver disease

Obesity is a risk factor for liver disease, specifically nonalcoholic steatohepatitis (NASH). NASH, referred to as "fatty liver," results from the accumulation of triglycerides in the liver. If untreated, NASH can progress into cirrhosis.

According to a study on non-alcoholic fatty liver disease published in the Brazilian journal *Arquivos de Gastroenterologia (Arq. Gastroenterol.*, Losekann et al. 2013 Oct-Dec; 50(4): 285-9), 90.4% of the study's 250 morbidly obese subjects presented with steatosis (also known as fatty change, fatty degeneration, and adipose degeneration; defined as abnormal cellular retention of lipids, which can cause cells to burst if left untreated). Additionally,

70.4% of subjects presented with nonalcoholic steatohepatitis (NASH). These results demonstrate the strong correlation between obesity and liver abnormalities. While mild steatosis and NASH are not extremely harmful, these conditions can progress into severe liver disease and even death. Figure 15 depicts the data collected regarding the presence and severity of NASH among the 250 morbidly obese subjects of this study.

Figure 15: Distribution of presence and severity of NASH among morbidly obese patients



Source: Arq. Gastroenterol., Losekann et al. 2013 Oct-Dec; 50(4): 285-9.

According to the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), a division of the National Institutes of Health (NIH), the only confirmed method of treating NASH is lifestyle change (losing weight, improving diet, increasing physical activity, avoid alcohol, and avoiding unnecessary medications). The NIH is currently conducting research regarding the extent to which weight loss improves NASH severity and whether this improvement last over time.

Several other possible treatments for NASH are currently being investigated, including the administration of antioxidants, such as vitamin E, selenium, and betaine, which may reduce the oxidative stress that often appears in NASH patients, and the use of new antidiabetic medications, even in patients without diabetes, that may increase insulin sensitivity and reduce the incidence of liver injury in NASH patients. The efficacy of these treatments is currently being evaluated by the NIH, and results of their clinical studies should be available in the next few years.

High concentrations of visceral fat linked to increased risk of heart disease, stroke, and hypertension, also known as “metabolic syndrome”

Problems linked to the release of pathogenic agents with the enlargement of fat cells *Cardiovascular disease and metabolic syndrome*

The hypertrophy (increase in size) of the adipocytes (fat cells) and the addition of visceral fat can be a dreaded combination that accelerates metabolic and immune responses, which promote type 2 diabetes, hypertension, and dyslipidemia. All three of these afflictions are major risk factors for cardiovascular disease. The severity and prevalence of having any combination of the three diseases led to the coining of the term “metabolic syndrome.” Greater cardiac output is required to treat excess adipose tissue through increased blood flow.

Visceral fat poses a higher risk for heart disease than subcutaneous fat.

There is also a very strong link between central obesity and metabolic syndrome. The collection of intra-abdominal visceral fat that surrounds the organs poses a much higher risk of heart disease than subcutaneous fat. Visceral fat is darker in color, much denser, and more difficult to lose because it is deeply embedded in the body’s tissue. The visceral fat is metabolized by the liver and converted into harmful low-density lipoprotein (LDL), which accumulates as plaque on artery walls. As such, individuals with high levels of visceral fat are at an increased risk of developing heart disease, stroke, and hypertension.

Recent research shows that obesity has become the top risk factor for heart disease, overtaking smoking, diabetes, high cholesterol, and uncontrolled high blood pressure.

Cancer: excess weight leads to increased risk

Perhaps even more disturbing are the current trends linking obesity to at least 20 different types of cancer. Leading experts in public health are even predicting that obesity will soon replace smoking as the primary cause of cancer in the developed world. The Harvard School of Public Health has estimated that 15%-20% of cancer cases are associated with obesity, a high number considering tobacco is responsible for 30% of cancer cases.

A study by the British Medical Association published in *Lancet* in Feb. 2008 reviewed 280,000 cases from 141 studies following both subjects of normal weight and overweight over a 9- to 15-year period. For men who had over 33 pounds of excess fat, there were increased risks of esophageal cancer by 52%, thyroid cancer by 33%, and both colon and kidney cancers by 24%. Women had similar results, with greater than 29 pounds of excess fat linked to increased risks of esophageal cancer by 51%, kidney cancer by 34%, colon cancer by 9%, and both uterine and gallbladder cancers by 59%. These statistics are displayed below in Figure 16.

Obesity is now linked with 20 types of cancer and the cause of 20% of all cancer cases

Figure 16: Increased risk of cancer after a 5kg/m² increase in BMI

	Excess Weight	Esophageal	Endometrial	Thyroid	Gallbladder	Renal	Colon
Men	>33 lbs.	52%	N/A	33%	N/M	24%	24%
Women	>29 lbs.	51%	59%	14%	59%	34%	9%

Source: Lancet, Feb 2008

Studies have also found that obese women are 30% more likely to develop post-menopausal breast cancer than women with BMIs in the normal range. Additionally, putting on just 5-20 pounds after menopause can increase breast cancer risk by an additional 30%. In contrast, in 2005, researchers found that losing 20 or more pounds after menopause and keeping the weight off can cut breast cancer risk in half for overweight and obese women. In a study published in the *British Journal of Cancer* in 2011, researchers estimated that obesity causes 11-14% of bowel cancer cases, 20% of esophageal adenocarcinoma (a form of esophageal cancer) cases, and close to 25% of gallbladder and kidney cancer cases.

While there are multiple proposed mechanisms for the pathogenesis of cancers stemming from obesity, it is not fully clear if there is one single factor that promotes carcinoma cell growth, as each cancer type varies in location and hormonal trigger. However, all of the evidence seems to point to the systemic effects of the hormonal imbalance that results from enlarged adipocytes.

60%-90% of type 2 diabetes cases are related to obesity or weight gain

Type 2 diabetes + obesity = diabetes

According to data from the Center for Disease Control and our calculations, there are approximately 21 million diagnosed type 2 diabetics in the US, of whom 85% are overweight or obese. When we include the additional estimated 8 million undiagnosed type 2 diabetics in the US, we calculate that there are approximately 29 million overweight and obese type 2 diabetics in the country (both diagnosed and undiagnosed). These 29 million people represent roughly 15% of the 185 million overweight and obese in this country. A 2008 review published in the *Journal of the American College of Nutrition* performed a meta-analysis of clinical studies that suggested that 60%-90% of type 2 diabetes cases are related to obesity or weight gain, and the CDC estimates that as many as 1 in 3 Americans will have diabetes by the year 2050. There is such a strong correlation between the diseases that the combination of the two is often referred to as “diabetesity.”

At the cellular level, adipocytes experiencing hypertrophy (growth) are known to release increased levels of the hormone resistin (named for its resistance to insulin). As resistin levels go up, insulin becomes ineffective at helping cells absorb glucose as an energy source. Many researchers have found a strong correlation between levels of resistin and insulin resistance. Additionally, as fat mass increases, TNF (tumor necrosis factor)-alpha increases. TNF-alpha negatively impacts blood sugar absorption by the liver and muscle and signifies another potential cause of insulin resistance.

There is also compelling data showing that a 10% reduction in initial body weight in obese patients dramatically improves glycemic control along with reducing cardiovascular-related risks. Furthermore, obese patients who undergo bariatric surgery and experience substantial excess weight loss are known to experience remission of their type 2 diabetes.

Asthma: breathing only makes it worse.

While it was previously thought that asthma was caused by excess fat pushing onto the lungs and airway, new research suggests that obesity inflames asthma symptoms through genetic expression. The research has shown that obese individuals produced higher amounts of inflammatory molecules through a much higher concentration of leptin in the body. As the leptin, an obesity genetic product, increases, production of inflammatory mediators such as tumor necrosis factor (TNF)-alpha, interleukin (IL)-6, and interferon (IFN)-gamma are stimulated. These mediators lead to tissue inflammation and airway obstruction exacerbating asthma symptoms in obese patients.

QUANTIFYING THE PREVALENCE AND RISK OF OBESITY CO-MORBIDITIES

Figure 17 shows the prevalence of co-morbidities in men and women of varying BMI ranges. Notice that for men with a BMI from 30-34.9, the prevalence of heart disease is 16.1%. This is nearly twice that of the healthy BMI group, which had a prevalence of 8.8%. A nearly 3x increase in prevalence was seen in women with BMIs greater than 40, having a prevalence of 19.2% relative to 6.9% of the 18.5-24.9 BMI group.

Figure 17: Prevalence of obesity co-morbidities

Prevalence of Medical Conditions by Body Mass Index (BMI) for Men				
Medical Condition	Body Mass Index			
	18.5 to 24.9	25 to 29.9	30 to 34.9	>40
	Prevalence Ratio (%)			
Type 2 Diabetes	2.03	4.93	10.1	10.65
Coronary Heart Disease	8.84	9.6	16.01	13.97
High Blood Pressure	23.47	34.16	48.95	64.53
Osteoarthritis	2.59	4.55	4.66	10.04

Prevalence of Medical Conditions by Body Mass Index (BMI) for Women				
Medical Condition	Body Mass Index			
	18.5 to 24.9	25 to 29.9	30 to 34.9	>40
	Prevalence Ratio (%)			
Type 2 Diabetes	2.38	7.12	7.24	19.89
Coronary Heart Disease	6.87	11.13	12.56	19.22
High Blood Pressure	23.26	38.77	47.95	63.16
Osteoarthritis	5.22	8.51	9.94	17.19

Source: NHANES III, 1988-1994

Additionally, with obesity comes an increased risk for a number of co-morbidities, as seen in Figure 18. We can see that the risk for type 2 diabetes is 6x greater in those with extreme obesity (BMI > 35) relative to a person with healthy weight. Furthermore, diseases with high mortality rates such as hypertension, stroke, and heart disease see an almost two-fold risk increase.

Figure 18: Increased co-morbidity risk with increasing BMI

Increased Risk of Obesity Related Co-Morbidities with Higher BMI				
Disease	BMI <25	BMI 25-29	BMI 30-35	BMI >35
Arthritis	1.00	1.56	1.87	2.39
Heart Disease	1.00	1.39	1.86	1.97
Diabetes Type 2	1.00	2.42	3.35	6.16
Gallstones	1.00	1.97	3.3	5.48
Hypertension	1.00	1.92	2.82	3.77
Stroke	1.00	1.53	1.59	1.75

Source: Centers for Disease Control, NHANES III. Analysis by The Lewin Group, 1999.

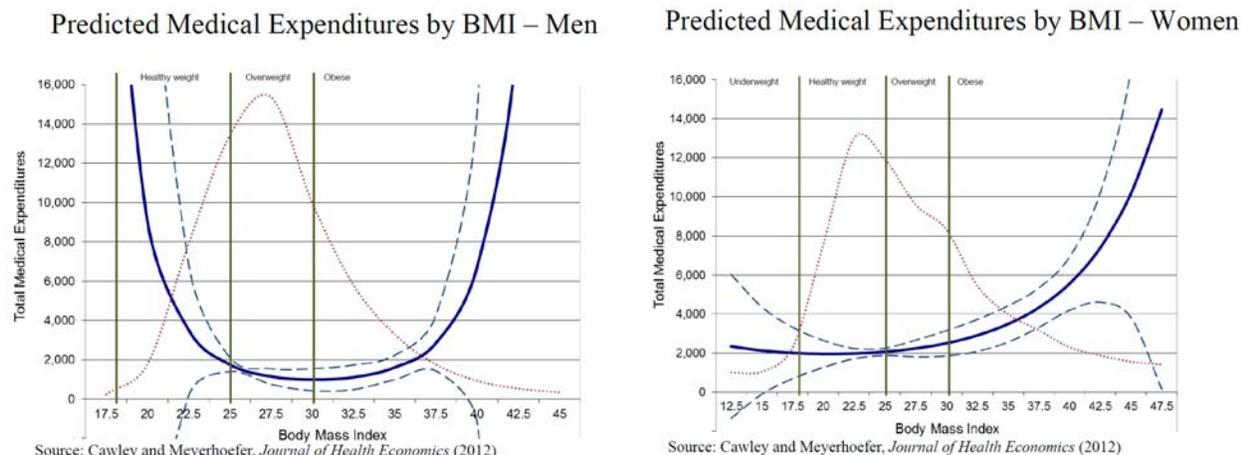
ECONOMIC IMPACT

Direct and indirect costs to the system associated with obesity are in excess of \$182 billion annually

Who pays for the obesity epidemic? Whether the non-obese know it or not, they are paying a high price for this epidemic through taxes and higher commercial insurance bills. In 2009, the total US expenditures, both direct, and indirect, resulting from the overweight and obese were estimated to be \$182 billion (George Washington School of Public Health). The \$152 billion in direct health care costs resulted from physician visits, hospital stays, diagnostic testing, and treatment. The indirect costs of approximately \$30 billion are associated with loss in productivity, insurance premiums, absence from work, and foregoing the value of future earnings due to premature death. A report from the American Public Health Association in November 2009 estimated that if obesity levels continue to rise, \$344 billion in healthcare costs would be attributable to obesity (either directly or indirectly) by 2018.

The expected lifetime medical costs are almost double for obese males versus normal BMI males per each age group. Figure 19 displays the medical expenditures associated with an increase in BMI by gender. Dashed lines represent the 90% confidence intervals, medical expenditures are denoted in the solid blue line, and the dotted line indicates the population proportions by BMI. (Cawley and Meyerhoefer, *Journal of Health Economics*, 2012).

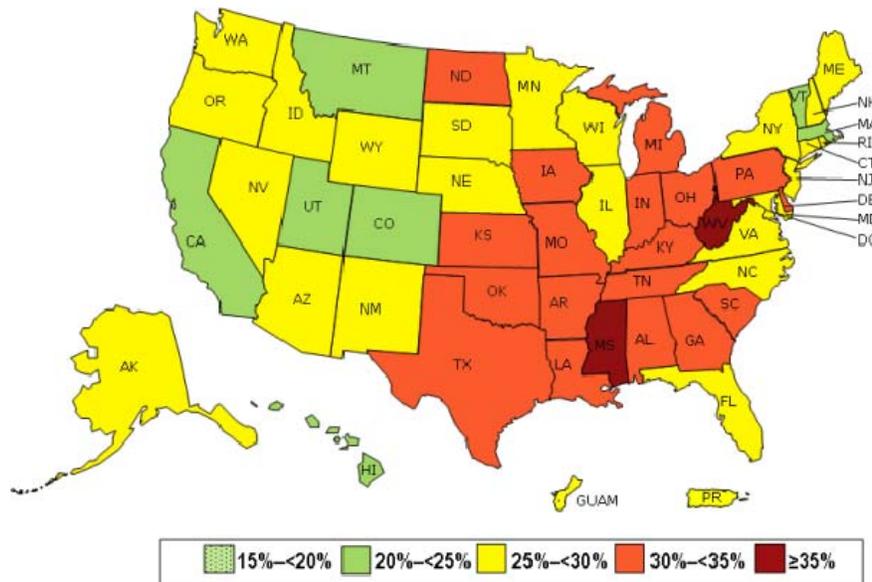
Figure 19: Effect of obesity on expected lifetime medical care costs in men and women



Source: Cawley et al, *Journal of Health Economics*, 2012

Obesity rates vary widely state-to-state. Data from the CDC collected in 2013 revealed that Colorado had the lowest obesity rate at 21.3%, while Mississippi had the highest rate at 35.1%. Figure 20 displays the obesity rates for each of the 50 states, as of 2013.

Figure 20: Prevalence of self-reported obesity among US adults by state in 2013



Source: Centers for Disease Control

The expenses attributable to treating the obese also vary depending on the state. The percentage of total Medicare expenditures related to obesity was 8.5% across all states (ranging from 5.2% in Hawaii to 10.2% in Ohio). The percentage of total Medicaid expenditures related to obesity was slightly higher, at 11.8% nationwide (ranging from 6.5% in Kansas to 18.8% in Oregon). Figure 21 below shows a more detailed state-by-state breakdown and displays the large disparity.

Figure 21: State expenditures related to obesity as a % of total expenditures

Top 5 States for Medicare Expenditures		Top 5 States for Medicaid Expenditures	
	Percentage		Percentage
Ohio	10.20%	Oregon	18.80%
Michigan	10.00%	Arizona	17.00%
West Virginia	9.90%	Rhode Island	16.30%
Nebreska	9.80%	DC	16.20%
South Carolina	9.70%	Colorado	16.20%
Bottom 5 States for Medicare Expenditures		Bottom 5 States for Medicaid Expenditures	
	Percentage		Percentage
Hawaii	5.20%	Kansas	6.50%
Arizona	6.20%	Virginia	6.80%
New Mexico	6.60%	North Dakota	7.50%
Montana	6.90%	Iowa	8.10%
Colorado	7.30%	Texas	9.40%

Source: Trogdon et al. Obesity 2012

The link between obesity and poverty forces states and the federal government to pay through Medicaid. While this is a nationwide and worldwide economic burden, some communities are hit worse than others, and subsequently certain states are more burdened than others as well. A strong correlation has been found between obesity and poverty. It is not a coincidence that the five poorest states in the United States also have the highest

obesity rates. Low-income, poorly educated communities historically have serious problems with obesity and type 2 diabetes. Food pricing and marketing, work schedules, and transportation/access to grocery stores (i.e. “food deserts”) all are factors behind this trend. As obesity rates continue to rise, Medicaid will continue to take the brunt of the healthcare-related costs of these individuals.

REIMBURSEMENT TRENDS

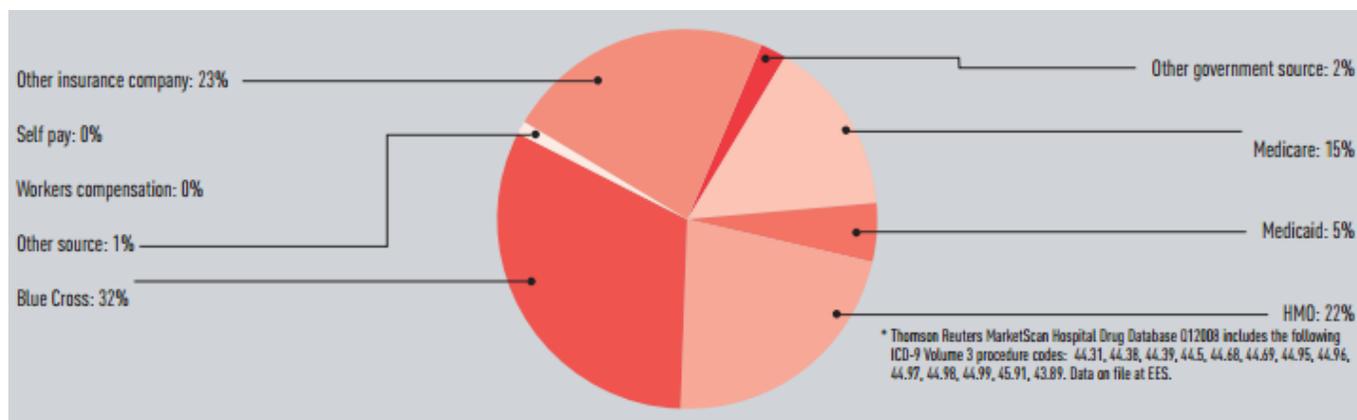
The payer mix historically has been much more commercial insurance focused. Figure 22 shows the breakdown of hospital billings for bariatric surgery from 1996 to 2002. As the overall charges increased 900% over those seven years, private insurers took more and more of the load, while CMS took proportionately less and less. Specifically, CMS picked up 13% of the patients in 2002 versus 19% in 1996, while private insurers increased their load to 82% in 2002 from 75% in 1996. In 2011, CMS was back to paying for 20% of the procedures, while private insurers picked up 77% of the tab (see Figure 23 below).

Figure 22: US hospital billings for bariatric surgery (\$ Millions)

	Medicare		Medicaid		Private		Overall
1996	\$ 23	11%	\$ 16	8%	\$ 152	75%	\$ 204
1997	\$ 37	15%	\$ 17	7%	\$ 167	66%	\$ 252
1998	\$ 31	9%	\$ 22	7%	\$ 246	75%	\$ 327
1999	\$ 54	9%	\$ 42	7%	\$ 444	76%	\$ 588
2000	\$ 59	8%	\$ 66	9%	\$ 589	78%	\$ 753
2001	\$ 99	7%	\$ 65	4%	\$ 1,165	80%	\$ 1,453
2002	\$ 132	7%	\$ 115	6%	\$ 1,662	82%	\$ 2,016

Source: Source Davis et al. National Trends in Bariatric Surgery, 1996-2002. *Archives of Surgery*, Vol. 141, Jan 2006

Figure 23: Estimated bariatric surgery reimbursement distribution 2011



Source: www.ethiconendo.com

CMS defined obesity as an illness in 2004 – and the floodgates opened. The turning point for the medical device industry occurred in 2004, when CMS eliminated language stating that obesity was not an illness and therefore was not covered for treatment under the agency’s official guidelines. The deleted section said that for a surgery to be covered, it had to “correct an illness which caused the obesity or was aggravated by the obesity.” With this

CMS removed obstacles in 2004, defined obesity as an illness.

wording in place, beneficiaries could not even begin requesting approval or appeal a denial because it was not even considered a disease. Subsequently, a Medicare Coverage Advisory Committee concluded that there was enough clinical evidence supporting the safety and efficacy of both open and laparoscopic Roux-en-Y gastric bypass surgery in treating morbid conditions associated with obesity.

CMS expanded services covered for obesity surgery in 2006 and again in 2012, expanding the market again. Two years after CMS acknowledged that obesity was an illness covered for treatment, it expanded coverage even more. Up until then, almost all of the charges related to bariatric surgery were related to gastric bypass procedures, hospital stays, and complications due to gastric bypass. In the 2006 policy, laparoscopic adjustable gastric banding and both open and laparoscopic biliopancreatic and duodenal switch surgeries were added to coverage on top of gastric bypass. More recently, in June of 2012, CMS released a decision on coverage for laparoscopic sleeve gastrectomy, expanding treatment options a step further. We note that the expanded coverage for sleeve gastrectomy was a major negative for banding.

CMS set the tone for commercial insurance companies. One might look at this trend and think, “Are there really that many seniors (65 and older) having bariatric surgery?” In reality, most seniors do not meet the health requirements for bariatric surgery. However, an eye-popping 90% of obese Medicaid beneficiaries are under 65 and are categorized as disabled. To be medically approved for disability, a patient must be either unable to work or earning under \$1,070 gross per month for two years (www.SSA.gov). The broader impact of the 2004 and 2006 CMS changes has been at the commercial payer level, since the insurance companies typically follow Medicare policies closely. Much like CMS’ prior stance, commercial insurance policies had always been adamant about not paying for these procedures. Once the categorization changed, insurance companies began to provide coverage, but did not make it easy for the patient to qualify.

More recently, the American Medical Association officially recognized obesity as a disease. In June 2013, AMA delegates at the annual meeting overrode a recommendation against classification by a committee commissioned to study the matter. The intent of this classification was significant in the physician community. Prospectively, recognition should help the medical community bring awareness to such a large public health pandemic and allow physicians to more accurately treat it. While the actual definition of when a person becomes obese varies and is immaterial to the treatment protocol, it will push physicians to take obesity more seriously. It also helps companies in the obesity space by lending credence to a problem they have been trying to solve for years.

Rarely do the words “US Food and Drug Administration (FDA)” and “positive regulatory environment” come together in the same sentence. However, we feel that the obesity space within medical devices is experiencing something every executive and investor in medical devices dreams – a truly positive regulatory environment. Our belief is supported by not only commentary from medical device company executives in the obesity space, but also by FDA’s actions.

FDA “guidance” document on obesity – both words and actions. We point to the publication in the *Journal of Surgical Endoscopy* in December 2012, *Benefit-risk paradigm for clinical trial design of obesity devices: FDA proposal*. The paper was authored by H. Lerner, J. Whang, & R. Nipper, all employees of the Federal Drug Administration and involved with the Center for Devices and Radiological Health, Office of Device Evaluation at the time of publication. As stated in the paper, “the purpose of the paper was to propose a

In 2006, CMS added more types of procedures as coverable for obesity. In 2012, sleeve gastrectomy became a covered procedure.

FDA employees spearheaded the effort to develop a guidance document for obesity devices in 2012.

new paradigm for devices intended to treat obesity, based on a benefit-risk determination, with the hope to provide sponsors an a priori tool for systematic assessment of the risk associated with the devices intended for treatment of obesity and to suggest appropriate levels of benefit for devices with different risk levels.” It was also noted that “the paradigm is NOT intended to determine the class of a device from a regulatory perspective.” (We added the emphasis on the word “not.”) The approach was conceived at an FDA co-sponsored workshop in October 2011 and formally presented to an FDA advisory panel for discussion in May 2012.

For each level of risk, there is a suggested observed mean TBL and timeframe targeted.

FDA mapped out the general risk-benefit paradigm for obesity devices/procedures. In the FDA guidance document, four risk levels are based on percentage of patients experiencing expected and unexpected events during one year after device placement, defined by category. The published tables are provided below in Figure 24 for additional clarity. In summary, for each level of risk, there is a suggested observed mean Total Body Loss (TBL) and timeframe “targeted.” In addition, the probability of a patient experiencing a benefit was included. As expected, TBL (benefit) and time (duration of study) both need to increase with higher risk levels. The importance of this document is that it provided the first “guidelines” for companies in the obesity space. Prior to publication, it was generally perceived that regardless of risk a new device needed to clear the performance hurdle similar to existing procedures.

Figure 24: Benefit risk paradigm for clinical trial design of obesity devices; FDA proposal

Table 1 Definition of risk levels based on percentage of patients experiencing expected and unexpected events during 1 year after device placement, defined by category

Adverse event category	Level 1	Level 2	Level 3	Level 4	Examples of events
A: Discomfort that does not require prescription drugs or other medical intervention but may need over-the-counter medications	≤100 %	≤100 %	≤100 %	Any % higher than those listed for level 3 places the device into level 4	Nausea, vomiting, pain, constipation, burping, bloating, gas, cramps, dyspepsia, diarrhea, dehydration
B: Scheduled visit to physician	≤100 %	≤100 %	≤100 %		Band adjustment
C: Unscheduled visit to physician	<10 %	<50 %	≤100 %		Band adjustments due to dysphagia, administration of IV fluids
D: Problems that can be managed with prescription drugs or diet, or topical care or mild interventions	<5 %	<50 %	≤100 %		Nausea, vomiting, pain, infection, dehydration, cutaneous bleeding, GERD, esophagitis, gastritis, nonhemorrhagic anemia, dysphagia, inflammation, depression requiring medication
E: Scheduled endoscopy	<2 %	≤100 %	≤100 %		Device removal, device adjustments, diagnostic evaluation
F: Unscheduled endoscopy	<2 %	<10 %	<20 %		Device removal, device adjustments, diagnostic evaluation or therapeutic intervention (e.g., due to dysphagia or bleeding)
G: Health consequences of malabsorption/malnutrition	<2 %	<10 %	<20 %		Nutritional deficiencies (e.g., anemia, iron deficiency, electrolyte imbalances) or effect on medication levels, development of an eating disorder
H: Substantial discomfort not managed even with drugs	<0.1 %	<20 %	<50 %		Severe nausea, vomiting, bloating, GERD
I: Tissue damage requiring therapy other than an operation	<0.1 %	<10 %	<20 %		Erosion, ulcer, GI or esophageal mucosal bleeding
J: Hospitalization, no operation	<0.1 %	<5 %	<5 %		Visit to the ER, IV antibiotics for infection, IV medication for severe pain, severe anemia with or without need for blood transfusion, pneumonia, need for anticoagulation for pulmonary embolism, severe depression
K: Hospitalization, with operation	<0.1 %	<1 %	<1 %		GI or esophageal perforation, gallbladder removal, obstruction (all etiologies), unscheduled device removal due to severe pain or other symptoms
L: Death	<0.1 %	<0.1 %	<0.1 %		

IV intravenous, GERD gastroesophageal reflux disease, GI gastrointestinal, ER emergency room

Table 2 Target effectiveness levels: % of total body loss (%TBL)

Level 1	Level 2	Level 3	Level 4
5 % observed mean TBL and statistical superiority to diet and exercise control	8 % observed mean TBL over sham and 50 % patients with 5 % TBL in treatment group	10 % observed mean TBL over sham and 50 % patients with 7 % TBL in treatment group	13 % observed mean TBL over sham and 50 % patients with 10 % TBL in treatment group
Measured at 6 months	Measured at 1 year	Measured at 2 years	Measured at 3 years

Source: Lerner et al, Journal of Surgical Endoscopy (2013)

“Over the past few years, the growing body of medical literature has identified obesity with its associated metabolic and cardiovascular comorbidities as one of the major public health problems facing our nation.”

FDA CDRH, 2012

Clinical data about obesity related co-morbidities heightens governmental interest in obesity. As to the why did FDA stomach a change for obesity companies, we only need to read the above mentioned document, which states that the link between obesity and other diseases (especially diabetes and hypertension, with a sprinkling of cancer) has become standard knowledge over the past five years. More importantly there is a lack of options available for patients. Specifically, it was stated that “over the past few years, the growing body of medical literature has identified obesity with its associated metabolic and cardiovascular comorbidities as one of the major public health problems facing our nation. The primary treatments for obesity have ranged from diet and exercise, with and without counseling and behavior modification, to prescription drugs and surgical procedures. The use of medical devices also has played a role in the treatment of obesity.” Finally, the report goes on to state that only three medical devices have been FDA approved for the

treatment of obesity (two of which were bands and are still sold today by Apollo EndoSurgery and Johnson & Johnson Ethicon EndoSurgery, as well as the Garren-Edwards Gastric Bubble, which was voluntarily withdrawn from the US market in 1992.)

Obesity coding will become more specific to each treatment type. Bariatric surgery, in an inpatient setting, will be impacted by the implementation of the ICD-10 classification system. ICD-9 is a 30 year old classification system that does not provide enough information and data to CMS about a patient's conditions and procedures. ICD-10 provides more specificity and exactness in describing a patient's diagnosis and procedure. The ICD-10 conversion, which is expected to occur on October 1, 2015, does not impact outpatient CPT codes or physician services. Providers looking to capitalize on this change will need to ensure their documentation specificity in order to fully capture their full reimbursement. For example what was previously an ICD-9 code for laparoscopic sleeve gastrectomy (43.82) will now be split into four coding options, offering laparoscopic, natural orifice, open, and open vertical coding options. Additionally, the provider has the choice to also allocate sub-codes for bypass of the stomach to the jejunum, ileum, and the duodenum to the ileum; each with open or percutaneous approach options. Many hospitals and health systems have been preparing for this change, but it will be critical for both providers and medical technology companies to fully understand them in order to receive appropriate reimbursement for their products and services.

Figure 25: ICD-10 procedure and diagnosis codes for bariatric surgery

Code	Procedure Description
0DP60CZ	Removal of extraluminal device from stomach, open approach
0DP64CZ	Removal of extraluminal device from stomach, percutaneous endoscopic approach
0DV60CZ	Restriction of stomach with extraluminal device, open approach
0DV64CZ	Restriction of stomach with extraluminal device, percutaneous endoscopic approach
0DV60ZZ	Restriction of stomach, open approach
0DV64ZZ	Restriction of stomach, percutaneous endoscopic approach
0DW60CZ	Revision of extraluminal device in stomach, open approach
0DW64CZ	Revision of extraluminal device in stomach, percutaneous endoscopic approach
0D160ZA	Bypass stomach to jejunum, open approach
0D160ZB	Bypass stomach to ileum, open approach
0D164ZA	Bypass stomach to jejunum, percutaneous endoscopic approach
0D164ZB	Bypass stomach to ileum, percutaneous endoscopic approach
0D190ZB	Bypass duodenum to ileum, open approach
0DB60Z3	Excision of stomach, open approach, vertical
0DB64Z3	Excision of stomach, percutaneous endoscopic approach, vertical
0DB68Z3	Excision of stomach, via natural or artificial opening endoscopic, vertical
0DB60ZZ	Excision of stomach, open approach

Source: www.anthem.com

You no longer need to be a “center of excellence” for CMS participation. In 2006 CMS added guidelines stating that it would only cover bariatric procedures performed at high-volume, low-mortality designated “centers of excellence” that are approved by the American Society of Bariatric Surgeons and the American College of Surgeons. To gain this accreditation, a hospital or center had to perform at least 125 procedures per year. A surgeon must have performed a total of at least 125 procedures and perform 50 per year. Currently, there are 750 centers of excellence in the US.

As of September 2013, CMS dropped the center of excellence designation requirement and opened up bariatric surgery to any participating hospital for payment purposes. This was a

very controversial decision in the bariatric community, as it created more competition (with the intent of lowering costs) and expanded access for many patients.

Does bariatric surgery help to reduce overall healthcare costs and the larger burden faced by society? The data to date is mixed and the debate continues. Initial data suggested bariatric surgery does lower costs, based on research that bariatric surgery offered a two year payback based on the cost of an average laparoscopic procedure in terms of reduced healthcare costs. In fact, a study in the *American Journal of Managed Care*, “A Study on the Economic Impact of Bariatric Surgery” (*Am J Manag Care*. 2008;14(9):589-596) confirmed this fact. The results showed that all costs associated with the procedure were recouped after two years with a laparoscopic procedure and four years with an open-surgery procedure.

Unfortunately, Weiner et al. looked out further post-operatively and refuted these earlier findings. “Impact of bariatric surgery on health care costs of obese persons; a six-year follow-up of surgical and comparison cohorts using health plan data” (*JAMA Surg*. 2013 Jun;148(6):555-62) showed a different take on this debate. The six-year follow-up study showed that there was no reduction in overall health care costs in the long-term between obese patients undergoing bariatric surgery and those that did not receive surgery.

New evidence furthers this discussion, as the connection between bariatric surgery and its effects on type 2 diabetes reduction becomes clearer. In one of the longest studies to date, a 15-year study in the *Journal of the American Medical Association* was published in June 2014. The study showed that in a group of 343 diabetic patients who underwent bariatric surgery 72% had diabetes remission after two years and 30% maintained reduction after 15 years. The control group, who received only routine medical care, had a 16% remission after two years and a 7% remission after 15 years. This study validates the expectations of bariatric surgery with regards to type 2 diabetes and provides significant evidence for its reduction in overall healthcare costs long-term. Diabetes has a significant impact on overall healthcare costs and overall healthcare resources used.

The American Diabetes Associates estimates that diabetes patients have, on average, \$13,700 in medical expenditures per year. Of the \$13,700, \$7,900 is diabetes related and within type 2 diabetics the average is \$6,000 per year for their annual care. Diabetes patients incur expenditures 2.3x higher than an average patient without diabetes. Approximately 28 million Americans have type 2 diabetes, with the 24 million overweight and obese American type 2 diabetics making up 17.6% of the overweight and obese population in the US.

Bariatric surgery promoted by insurance companies? It could happen. As return-on-investment studies such as these improve and as risks associated with these procedures decrease, we expect reimbursement to expand. If commercial insurers begin to see increased evidence of long-term cost benefits, especially if comorbidities are included in the cost benefit analysis, we believe they may begin to promote bariatric therapy by relaxing guidelines and increasing the reimbursement to surgeons/hospitals.

How does the Affordable Care Act impact bariatric surgical reimbursement? The Affordable Care Act (ACA) was signed by President Obama on March 23, 2010. One of its main goals, outside of providing insurance coverage for many non-covered Americans, was to re-shift our country’s healthcare focus to preventative care in the United States, away from higher acuity services along the healthcare continuum. Health plans, as of 2014, must cover obesity screening and counseling at no cost to patients. Medicare has provided this as a benefit to its recipients since 2011, but few patients actually take advantage of it. This

Bariatric surgery significantly reduced type 2 diabetes at 15 years.

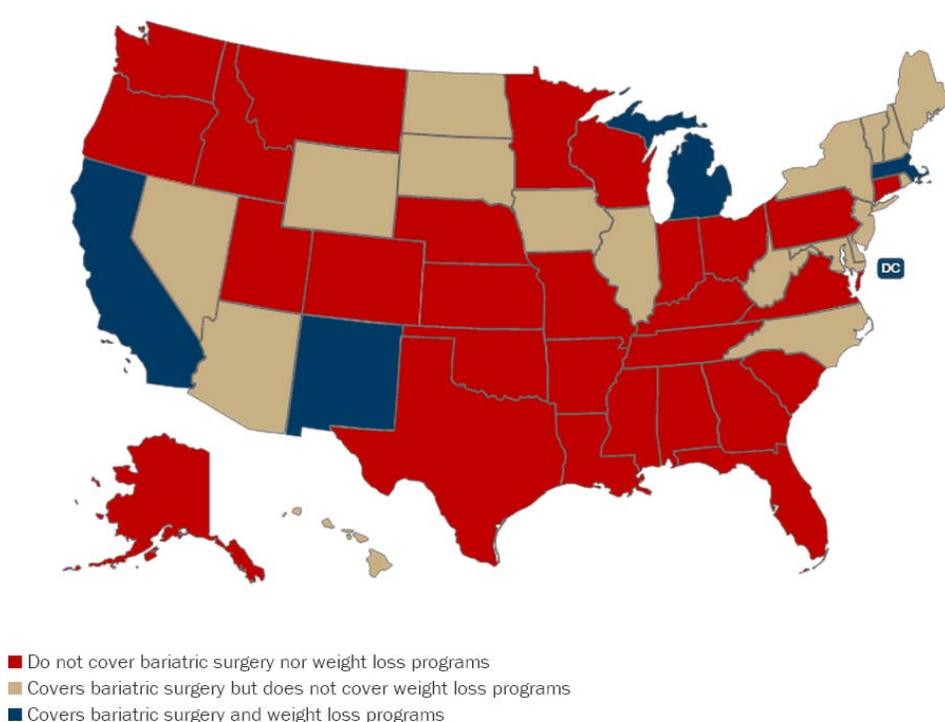
Diabetes patients incur 2.3 times higher health care expenses per year than the average patient

Reduction in risk and overall costs could drive insurers to recommend bariatric procedures

is certainly a boost to primary care physicians, fitness centers, and behavioral coaching programs (i.e., Weight Watchers, Jenny Craig, etc.) across the United States. These services, while enticing, are arduous and time consuming for obese patients, and many will elect bariatric surgical options if medically appropriate. Provisions of the ACA also prohibit insurance denials based on pre-existing conditions and prohibited lifetime caps on healthcare related costs for patients.

The ACA selectively left out coverage for bariatric surgery and gave state insurance exchanges broad discretion as to whether they would cover the service. Thus far, only 22 states have elected to include obesity treatments such as metabolic and bariatric surgery as part of their health benefits (Figure 26). Unfortunately, many of the states with the highest obesity rates have elected not to include the coverage. There are approximately 3.8 million additional American adults who will enter the exchanges in states covering bariatric surgery, and a large proportion will be candidates for the surgery. Net, net the ACA is positive for bariatric surgery, but as employers scale back health plan coverage and more than half the states elect not to cover bariatric surgery as an option, there will likely be a bottleneck to access existing providers in the near term.

Figure 26: State by state analysis of bariatric surgery coverage under ACA health exchanges



Source: ASMBS

Both the AMA and ASMBS have passed resolutions regarding “Patient Access to Evidence-Based Obesity Services.” Currently, only 22 of 50 states have bariatric surgery listed as a covered benefit within the Affordable Care Act (ACA). The specific exclusion of obesity treatment in the ACA state health exchanges is unusual and in conflict with the ACA’s own stated statute that the state health exchanges may not exclude treatment on the basis of a health condition. This type of mixed legislation significantly bottlenecks the market growth of bariatric surgery, at least in the near term.

Another limiting factor is the growth of employer-sponsored health plans. Nearly two-thirds of health plans sponsored by employers do not cover weight loss surgery, forcing many patients to now pay out of pocket for the procedure (Mercer Consulting). Charge estimates for bariatric surgery can range from \$15,000 to \$40,000. However, as new lower cost technologies are commercialized we should expect market penetration rate to increase.

The referral process

It starts with the primary care physician (PCP). With the number of patients fitting the indication for treatment increasing, it is important to examine how these patients make their way to the surgical table or the physician's office and what possible obstacles lie in between. For the average morbidly obese patient, visiting the doctor is an unpleasant experience. It is no surprise that these patients typically do not visit their primary care physician (PCP) unless absolutely necessary.

At what point do PCPs refer their patients to a bariatric surgeon? PCPs navigate multiple factors such as patient health, insurance coverage, and complication risk when determining whether a patient is a good candidate for bariatric surgery. Historically, the rate at which PCPs refer candidate patients for this therapy is very low. Less than 1% of the potential bariatric population receives surgical treatment for obesity, despite as many as one-third of patients in a primary care practice being obese. Part of the limitation is a lack of knowledge by the PCP population as to the efficacy and treatment options for their bariatric patients. Additionally many PCPs may not feel comfortable referring patients to a bariatric surgeon they do not know. If the patient is taking their cues from the PCP, then it is at the discretion of the PCP to make the determination as to when surgery is an option. As a result, more patients today are deciding, on their own, to have the surgery and circumventing their PCP, thus another potential reason for the low penetration rate for surgical intervention. We believe this is a key point and believe that a successful company in the space will need to develop a referral channel to drive procedures.

Primary care physicians are likely to be the near-term gate keepers for new bariatric procedure adoption

PCPs bear the burden of the patients' decision. PCPs know better than anyone else how non-compliant morbidly obese patients can be. Referring them to an elective procedure that will require them to follow a rigorous diet afterwards bears a certain amount of risk. While the decision to not have the procedure performed has risks of its own, if surgical complications arise, the referring physician takes a large share of the responsibility.

The typical steps to surgery. The patient's first visit to the bariatric surgeon will be through a PCP or friend/family referral. The process can take up to 12 months but may go more quickly for patients with a BMI > 50.

1. Community events - Surgeons and hospitals will hold community events, screenings, and meet-and-greets so patients begin to feel comfortable with the local surgeon. The surgeon may give a talk at the local library, church, or hospital on the efficacy of the procedures and technologies.
2. Consultation - Generally, surgeons will give a free consultation to the patients, explaining their options and the details of the different procedures.
3. Physician-monitored weight loss - After patients are motivated, they will need to provide documents proving completion of a physician-monitored weight loss program.
4. Psychological testing - The patient must next undergo a psychological evaluation.

-
5. Pick a center/pre-approval – Once approval from the payer is received, a location is determined. Whether the location is formally a center of excellence or not has less bearing today than it did in 2013 and before, when CMS mandated that the procedure be done at a COE.

A bit more detail on the steps

Physician-monitored weight loss – The physician-supervised weight loss program lasts for six to 12 months, during which time patients are required to visit their PCP each month. During the visit, the PCP will document all information regarding the patient's diet, physical activity, behavioral interventions, and pharmacotherapy. In addition, the patient's weight, blood pressure, and heart rate are also recorded. Note that for patients with a BMI>50, this program can sometimes be waived.

Dietetics consultation – The intent of the consultation with a dietitian is to ensure that the patient understands and continues a lifelong weight management program through diet. The dietitian will evaluate the patient's diet history and also teach them how to conduct an 800-1200 calorie diet (versus a recommended diet of 2,000 to 2,500 calories). They will help the patient institute a meal replacement program if necessary (if the patient weighs 450 pounds or more). They will also review the postoperative diet instructions and conduct routine follow-up after surgery.

Psychological testing – The psychological evaluation must be performed as a pre-surgical assessment and requirement. Every bariatric center will have a psychologist to whom they refer patients. The evaluation is to make sure that the patients do not suffer from a mental illness or behavioral disorder that could prevent adaptation to their new lifestyle. Substance abusers and alcoholics are turned down as surgical candidates for gastric restriction and malabsorptive procedures. They are clinically screened out due to their toxicity and inability to absorb vitamins as easily as other patients. Roughly 90% will pass this psychological evaluation.

Pick a center/pre-approval – After all the pre-operative requirements are met, documentation can be sent in to the payer. If performed at a center of excellence or another bariatric center, amount negotiation is probably not required and approval can be obtained. For patients who are not covered by their insurance, cash is required upfront for the procedure and a flat rate may be determined well in advance of the procedure. Post-procedure, the patient will periodically follow up with the physician and dietician to ensure new lifestyle compliance.

BARIATRIC SURGERY TRENDS – A \$3 BILLION DOLLAR MARKET OPPORTUNITY

Market growth and increased penetration of surgical/procedural approaches creates the opportunity for an enormous growth market. We see the number of weight loss procedures performed per year climbing significantly over the next 10-15 years due to three specific trends. First, the number of patients who fit the indication is increasing. Second, we expect an increase in the number of available products that provide long-term weight loss with lower risk. There are many more minimally invasive surgical and non-surgical options in development that provide a broad spectrum of obesity care than a routine lap-band or gastric sleeve. Third, we expect improving insurance coverage for obesity given support by CMS, the AMA, and implementation of the ACA.

Undisputed growth drivers. There are a multitude of factors driving growth of the obese population. While these growth figures alone may seem very enticing to device manufacturers, this ignores the biggest obstacle in getting patients into the OR: the cost to the patient. For these expensive procedures, obtaining full reimbursement or having little to no out-of-pocket cost is a must, so patients need to fit the indication for treatment. Currently, Medicare and approximately one-third of large employer sponsored health plans cover bariatric surgery. As of 2014, 28 of 50 state insurance exchanges do NOT cover bariatric surgery. Many of the newly enrolled Obamacare recipients will have to pay out of pocket if they want to receive surgical treatments for obesity. However, we believe more coverage is likely over time given CMS's positive position and plethora of new products on the cusp of commercialization.

Defining the applicable market for surgical intervention. Bariatric surgery is currently indicated for patients who have a BMI greater than 40 kg/m² or greater than 35 kg/m² if the patient has at least one co-morbid condition (BMI>30 with co-morbidities for ADGB products), such as high blood pressure or diabetes. With the many new products potentially coming to market, indications for bariatric surgery will likely widen to a larger subset of the obese population. Specifically we believe temporary space occupying products such as intragastric balloons will open the addressable market to lower BMIs, possibly even into the overweight category of 25>BMI<29.

In 2014 we estimate more than 136 million Americans qualify as being overweight or obese (BMI > 25). Of that number, more than 69M people qualify as obese (BMI > 30), including ~16M clinically obese (35.0 > BMI < 39.9) and ~13M morbidly obese (BMI > 40). These two groups with BMIs > 35 have historically been identified as the clear-cut candidates for bariatric treatment; however, we believe the large pipeline of new treatment options broadens the addressable market to include patients with BMIs in the range of 27+.

Nevertheless, surgical/procedural penetration is miniscule compared to the addressable market. Specifically, in 2014 we estimate that only 179,000 procedures will be performed. That is a penetration rate of only 1.4% of the morbidly obese population, 1.1% of clinically obese population, and 0.4% of the total obese patient population. Based on the incidence data from the CDC our forward model conservatively assumes prevalence rates to stay at current levels – growing only at the rate of the broader population demographics. That said, we feel the current procedures and devices on the market have only scratched the

Bariatric surgery is currently indicated for individuals with a BMI > 40 or a BMI > 35 with at least one co-morbid condition

surface and therefore believe there is significant opportunity to drive market growth by 1) increasing penetration into the existing market and 2) introducing new/safer/less invasive devices/procedures to expand the addressable market.

In Figure 27, we use a 29% CAGR for procedure volumes per year through 2030, leading to a 25% CAGR in revenues over the next 16 years. While at first glance these metrics may appear aggressive, we note that our model does not include robust assumptions for penetration into the addressable market – specifically, our estimates max out at at ~1.9M devices and procedures in 2030, which equates to only 14% penetration in the morbidly obese, 3% in obese, and 1% in the obese+overweight market segments. This, compared against our conservative assumption for flat growth in the underlying patient population, highlights our expectation for increased procedural penetration driven by broader patient awareness and new procedures and device introductions. The typical indication for traditional bariatric surgical procedures is: 1) BMI>40 or 2) BMI>35 with at least one co-morbid condition (i.e., diabetes, cardiovascular disease). Further, we believe the introduction of temporary and less-invasive devices over the next five years will skew the addressable market to include BMIs > 27. Lastly, it is also important to note that we estimate penetration rates will increase as risks applicable to bariatric surgery decrease, reimbursement improves, and new products are launched starting in 2015.

Figure 27: Estimated procedure numbers and market penetration rates

US Overweight & Obese Addressable Market												
	2000	2005	2010	2014	2015	2016	2017	2018	2019	2020	2025	2030
Total US Population	282,171,957	295,753,151	309,326,295	318,892,000	321,363,000	323,849,000	326,348,000	328,857,000	331,375,000	333,896,000	346,407,000	358,471,000
Addressable age group (20-64)	166,522,163	176,976,709	185,668,966	198,555,868	199,150,000	199,670,867	200,193,097	200,716,692	201,241,657	201,768,000	203,166,000	205,349,000
Overweight & Obese (BMI > 25)	107,406,795	117,954,977	127,740,249	136,010,770	136,417,750	136,774,544	137,132,271	137,490,934	137,850,535	138,211,080	139,168,710	140,664,065
% of total US population	64.5%	66.7%	68.8%	68.5%	68.5%	68.5%	68.5%	68.5%	68.5%	68.5%	68.5%	68.5%
Overweight (25 > BMI < 29.9)	56,617,535	59,110,221	61,456,428	66,714,772	66,914,400	67,089,411	67,264,881	67,440,809	67,617,197	67,794,048	68,263,776	68,997,264
% of total US population	34.0%	33.4%	33.1%	33.6%	33.6%	33.6%	33.6%	33.6%	33.6%	33.6%	33.6%	33.6%
Obese (BMI > 30.0)	50,789,260	58,844,756	66,283,821	69,295,998	69,503,350	69,685,133	69,867,391	70,050,126	70,233,338	70,417,032	70,904,934	71,666,801
% of total US population	30.5%	33.3%	35.7%	34.9%	34.9%	34.9%	34.9%	34.9%	34.9%	34.9%	34.9%	34.9%
Obese (30.0 > BMI < 34.9)	-	-	37,690,800	40,505,397	40,626,600	40,732,857	40,839,392	40,946,205	41,053,298	41,160,672	41,445,864	41,891,196
% of total US population	-	-	20.3%	20%	20%	20%	20%	20%	20%	20%	20%	20.4%
Clinically Obese (35.0 > BMI < 39.9)	-	-	16,895,876	16,083,025	16,131,150	16,173,340	16,215,641	16,258,052	16,300,574	16,343,208	16,456,446	16,633,269
% of total US population	-	-	9.1%	8%	8%	8%	8%	8%	8%	8%	8%	8.1%
Morbidly Obese (BMI > 40)	7,826,542	9,468,254	11,882,814	12,707,576	12,745,600	12,778,936	12,812,358	12,845,868	12,879,466	12,913,152	13,002,624	13,142,336
% of total US population	4.7%	5.4%	6.4%	6.4%	6.4%	6.4%	6.4%	6.4%	6.4%	6.4%	6.4%	6.4%
Bariatric Procedures	37,603	135,139	154,301	179,000	180,530	190,172	204,796	232,998	275,302	338,757	812,448	1,881,920
% of Obese Population	0.07%	0.23%	0.23%	0.26%	0.27%	0.29%	0.33%	0.39%	0.48%	0.58%	1.15%	2.63%
Y/Y Growth	nm	nm	nm	nm	0.86%	5.34%	7.69%	13.77%	18.16%	23.05%	139.83%	131.64%
Bariatric Procedures - General	37,603	101,867	95,153	148,391	148,391	148,391	148,391	148,391	148,391	148,391	148,391	148,391
% Mx	100%	75%	62%	83%	82%	78%	72%	64%	54%	44%	18%	8%
Y/Y Growth	nm	nm	nm	nm	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%
Bariatric Procedures - Device	0	33,272	59,148	30,609	32,139	41,781	56,405	84,607	126,911	190,366	664,057	1,733,529
% Mx	0%	25%	38%	17%	18%	22%	28%	36%	46%	56%	82%	92%
Y/Y Growth	nm	nm	nm	nm	5%	20%	35%	50%	50%	50%	249%	161%
Bariatric Device Market	nm	\$99,817,143	\$177,443,490	\$91,827,000	\$98,989,506	\$117,363,630	\$139,206,885	\$194,680,942	\$281,741,650	\$415,902,074	\$1,336,415,627	\$3,082,647,279
ASP per procedure	nm	\$3,000	\$3,000	\$3,000	\$3,080	\$2,809	\$2,468	\$2,301	\$2,220	\$2,185	\$2,013	\$1,778
Y/Y Growth	nm	nm	nm	nm	8%	19%	19%	40%	45%	48%	221%	131%
Bariatric Procedure Penetration												
Overweight & Obese (BMI > 25)	nm	0.11%	0.12%	0.13%	0.13%	0.14%	0.15%	0.17%	0.20%	0.25%	0.58%	1.34%
Obese (BMI > 30.0)	nm	0.23%	0.23%	0.26%	0.27%	0.29%	0.33%	0.39%	0.48%	0.58%	1.15%	2.63%
Morbidly Obese (BMI > 40)	nm	1.43%	1.30%	1.41%	1.42%	1.49%	1.60%	1.81%	2.14%	2.62%	6.25%	14.32%
Bariatric Device Penetration												
Overweight & Obese (BMI > 25)	nm	0.03%	0.05%	0.02%	0.02%	0.03%	0.04%	0.06%	0.09%	0.14%	0.48%	1.23%
Obese (BMI > 30.0)	nm	0.06%	0.09%	0.04%	0.05%	0.06%	0.08%	0.12%	0.18%	0.27%	0.94%	2.42%
Morbidly Obese (BMI > 40)	nm	0.35%	0.50%	0.24%	0.25%	0.33%	0.44%	0.66%	0.99%	1.47%	5.11%	13.19%
Catalysts					ETRM commercializes Q1/15, Apollo and ReShape Enter Q3/15	GI Dynamics, Scientific Intake Q1, Aspire, Obalon Q2	Endosphere					

Source: Census.gov, NIH and Canaccord Genuity estimates

Hospitals on average bill \$22,000 per bariatric surgical procedure. This lump sum includes inflated costs that include the nursing fees, anesthesia, equipment, overhead, and materials. Surgeons' professional fees may or may not be included, depending on whether the surgeon is employed by the hospital or not. When launching a product into this space, device manufacturers typically work backwards to find a competitive list price.

Conservative estimate of bariatric surgery market opportunity of ~\$3 billion

Our analysis of the industry shows significant variation in device ASPs across technologies. The wide spectrum is attributed to both device complexity and the time a device will be in use (i.e., permanent vs. temporary). For example we expect permanent devices like the Maestro vagal nerve stimulator (EnteroMedics) will capture ASPs of \$10,000+ whereas we expect temporary balloon products garner prices in the range of \$1,000-\$2,000. That said we are using a weighted average of the available device products in our model which results in a \$3,000 ASP in 2014. Lastly our model calls the weighted ASPs to contract over time, from ~\$3,000 in 2014 to ~\$1,800 in 2030, as new lower cost products capture (as well as drive) an increasingly large share of the procedural growth. Even with declining price mix our model still results in a \$400M+ bariatric device market revenues in 2020, \$1.3B in 2025, and a \$3.1B in 2030.

Less invasiveness and more experience has driven market growth. The decision to go under the knife has always been a risk-versus-reward dilemma for both physicians and patients. As gastric bypass has changed from mostly open surgery to being performed laparoscopically over the past few years and now through natural orifice or robotics, the risk of complication has decreased. We believe the penetration of this market appears set to increase as:

- More options become available
- risk decreases with new therapies
- there are more highly skilled physicians performing the procedures
- reimbursement improves
- physicians and patients start understanding the seriousness of the disease
- surgical treatment of obesity becomes more common

The melding of devices into the cosmetic market. Many of the products that were initially discussed in this paper in 2009 were in early development stages. Over the past five years, we have seen a change in the overall landscape. Some have failed to take off, while others are early in commercialization outside the US. Many of the products are being designed for temporary placement for three to twelve months, after which the device is removed. These products broaden the spectrum of what was traditionally part of the bariatric surgery space. They offer super obese and morbidly obese patients a “bridge to surgery” option if they cannot qualify initially for surgery. Additionally, companies are finding applications for their products in the cosmetic market with patients looking for a more temporary treatment to achieve a lower BMI patient. We believe that these individuals will represent a cash-paying contingent looking to achieve rapid, short-term weight loss. We believe that this cosmetic application represents the potential for additional upside to our current estimates from a procedure penetration rate standpoint.

CURRENT NON-SURGICAL/NON-PROCEDURAL TREATMENT OPTIONS

People throughout modern history have always paid particular focus to weight loss treatments and options. Lord Byron in the late 1800s suggested people drink water mixed with apple cider vinegar to lose excess pounds. There have been a slew of diet options in the past century that millions have tried (and failed), but many have profited. Whichever way you choose to lose weight, there are treatment options for each person, from diet and exercise to pills, procedures, or surgery.

Diet programs: America's \$60 billion fight against the fat

Dieting is the most common therapy used to lose weight, and it is a huge market (just ask Richard Simmons, Jenny Craig, and Dr. Atkins). Unfortunately for dieters, from a clinical standpoint diets are not effective. Despite the fact that Americans spent in excess of \$60 billion on diet-related programs and goods in 2012 and the market is expected to grow an average of 2.7% annually until at least 2016, the problem with most diets is that they fail to compel patients to make permanent lifestyle changes. As a result, even if dieters successfully achieve short-term results, they will usually gain back the weight over time. An NIH study showed that approximately 98% will gain any lost weight back and 90% will gain more than they originally lost. It has also been noted that dieting may reduce muscles, as well as fat, which results in lower caloric metabolism at the same "weight" in subsequent cycles.

NIH found 98% of dieters regain lost weight with 90% gaining more weight than originally lost

We list the most common diets below.

- Low-carbohydrate diets have been popular due to programs such as the South Beach, Zone, Paleo, and Atkins diets. These replace a person's consumption of carbohydrates with protein and fat. Instead of eating breads, pastas, rice, and other starchy food, dieters will eat meats and soy products. These regimens typically show good results from a weight standpoint but studies have shown an increase in possible future cardiac events due to the diet.
- Low-calorie (LCD) and very low-calorie (VLCD) diets generally target caloric intake. A LCD has a range of 1,000-1,500 calories per day, while the VLCD is 400-1,000. Since a VLCD produces the same effects as starvation (diminished appetite after five days), it requires protein and vitamin supplements. This is most common diet prescribed to the morbidly obese and can yield a three- to five-pound loss per week.
- Low-fat diets are good at lowering cholesterol as well as weight. By avoiding foods that are high in fat, patients can also see a reduction in calorie consumption.
- Gluten-free diets remove the protein gluten found in wheat, barley, rye, and triticale. Originally created to help treat celiac disease it has gained popularity in recent years and is often interpreted by novice practitioners as a low-carb diet. Recently published research calls into question the validity that gluten intolerance exists but that has not stopped the growth of a \$15B gluten-free food products market to develop in the past 10 years.
- Vegetarian-based diets exclude meat, poultry, or fish and can be based on different levels of exclusion such as lacto-vegetarian (eggs excluded but dairy products included) to the more extreme vegan where no animal byproducts are included.

Daily physical activity has the potential to prevent obesity, even in individuals genetically prone to obesity

Exercise

Regular exercise provides numerous benefits to one's health, especially when it comes to weight loss. The best results can be seen by utilizing the large muscles in the legs that require a lot of energy to do work. For the obese, running and riding a bike are often not an option, so low-impact exercise such as walking, swimming, and general physical activity are prescribed.

Aside from the direct calorie burn during exercise, physical activity can lead to increased energy expenditure even during times of rest. Additional lean muscle mass will increase metabolism because muscle tissue has a higher metabolic weight than adipose tissue. Even intense aerobic exercises such as swimming or running can speed up metabolism for four to eight hours after the workout.

Research published in the *Journal of Endocrinology* from 2012 highlighted an even more important reason why the obese population should attempt to exercise even at a moderate level. Over the past decade, skeletal muscle has been identified as a secretory organ. Cytokines and peptides are released from muscle tissue and have an autocrine, paracrine, or endocrine effect on other organs such as the liver, pancreas, bones, and brain. These proteins are secreted by muscle contraction. If people are not physically active, they develop an altered myokine response which has been shown to lead to chronic illness and potentially cancer cell development.

Currently marketed anti-obesity drugs

Everyone is searching for the magic pill that lets them lose weight while still eating excessively and leading a sedentary life. Unfortunately, it's not that easy. In the past decade, there have been a number of drugs that either produce minimal to no long-term results or have serious adverse effects. The pharmaceutical compounds currently on the market operate by one of two mechanisms :hunger suppression or fat absorption reduction.

- Hunger suppression* –**Phentermine** (highly genericized) has been on the market since 1959 and lowers weight by about 3.8-4.4% at 6 months. It has seen a recent surge in Rx volume that we think is due to off-label combination use with Belviq as well as topiramate since Qysmia's launch has raised awareness of the utility of the combo of phentermine and topiramate. **Qysmia** (a combination of phentermine and topiramate sold by Vivus) and **Belviq** (lorcaserin developed by Arena and partnered with Eisai) are two recently approved drugs that are doing OK commercially, but they too have limited efficacy. In addition, managed care has only provided limited reimbursement for the two products. Qysmia lowered weight by 6.6-8.6% over 12 months in clinical trials. Belviq showed only a 3-3.3% weight loss at 12 months. Orexigen's **Contrave** (a combination of bupropion and naltrexone) was just approved on September 11, 2014. It is indicated in patients with BMI over 30 (or in patients with BMI over 27 that have at least one comorbid condition. Contrave drops weight by about 5% and will be marketed by Orexigen's partner, Takeda, in the coming weeks. **Meridia** (sibutramine) increases the feeling of satiety by increasing the level of neurotransmitters, such as serotonin. However, it was pulled off the market in 2010 due to a controversial cardiovascular risk signal, which was deemed to outweigh its limited efficacy that lowered body weight by 3-5%. **Byetta** is only approved for diabetes, but it suppresses hunger and can show weight loss, although anecdotal data suggests that weight loss is transient with a limited effect. There are also several drugs that are used off-label for weight loss purposes, like Adderall XR and topiramate.

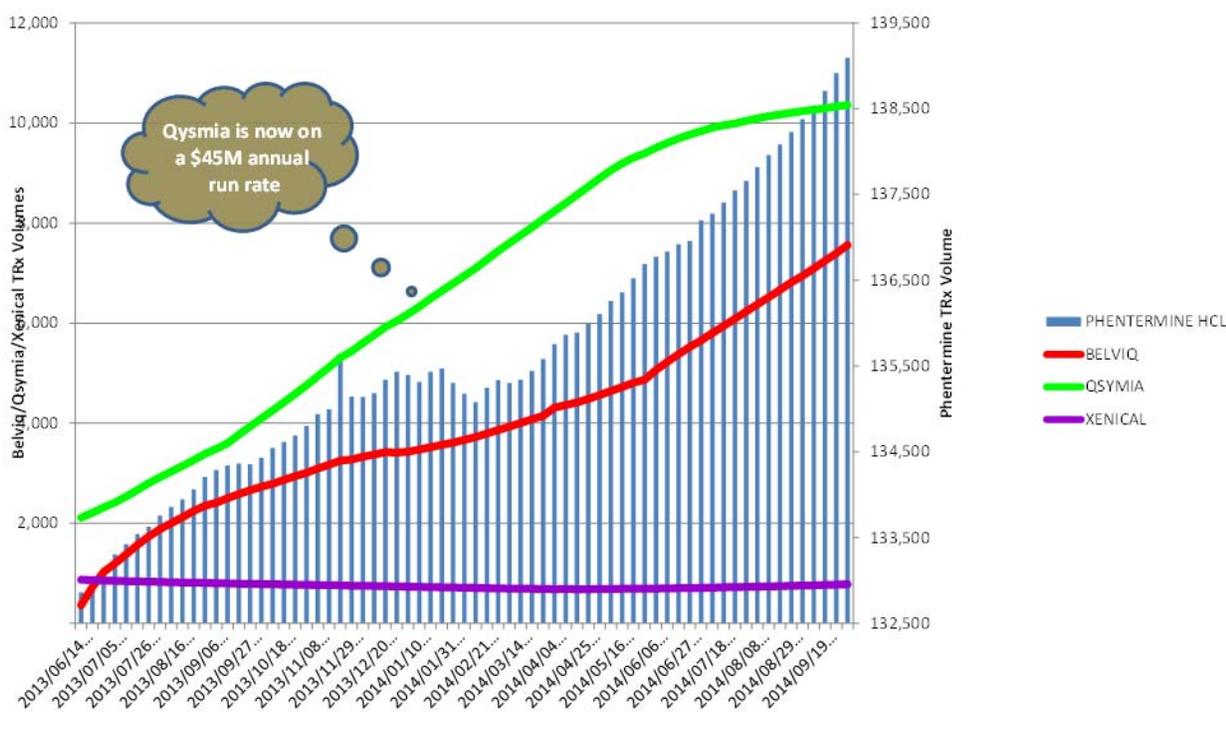
We would like to thank Corey Davis, our resident obesity drug expert at Canaccord, for his contribution of the obesity drug section of this report.

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- *Fat absorption reduction* – **Xenical** (orlistat) and **Alli** (also orlistat but over-the-counter) inhibit lipase, which is an enzyme that breaks down and digests fat in the gut. When taken with meals, it prevents 25%-30% of dietary fat from being absorbed. Patients see about a 2-5% weight loss after 12 months.

The figure below shows recent IMS prescription data trends for phentermine, Belviq, Qsymia and Xenical. Note that although the uptake rates appear robust, Qsymia is still only doing about 11,000 scripts per week (plotted on the left Y-axis) and on an annualized run rate of \$45 million (\$11 million reported by Vivus in Q2). Interestingly, despite years of flat prescription volume for phentermine, note the recent pickup in volume. It is plotted on the right Y-axis and has grown from 133,000 prescriptions per week to now close to 145,000. Our guess is that this is coming from off-label combination use with Belviq as well as with topiramate (the two active ingredients in Qsymia).

Figure 28: Qsymia and Belviq volumes are still low but climbing



Source: IMS

A table that further describes some of the attributes of the current drugs used for obesity treatment can be seen in the graphic below. This figure was recently published in the online version of the journal *Clinical Pharmacology & Therapeutics*.

Figure 29: Attributes of drugs currently being used to treat obesity

Mechanism of action	Drug	Effects and safety concerns	Efficacy	Status
Appetite suppressant. Stimulates anorexic signaling in hypothalamus or dopamine receptor in the hippocampus. Sympathomimetic agent similar to norepinephrine with central nervous system stimulatory activity	Phentermine	Appetite suppression and weight loss Side effects include dizziness, dry mouth, difficulty in sleeping, irritability, nausea, vomiting, diarrhea, or constipation. This drug has withdrawal symptoms	Weight loss greater than placebo was 3.6 kg (CI: 0.6–6.0 kg)	Approved by the FDA in 1959
	Amphetamine	Anorexia and weight loss Side effects include nervousness, restlessness, excitability, dizziness, headache, fear, anxiety, and tremor. Blood pressure and heart rate may increase. Chronic use may lead to dependence. These drugs have withdrawal symptoms	Weight loss greater than placebo was <1 kg (CI: 0.5–1.6 kg)	Off-label usage; approved for attention-deficit hyperactivity disorder
Serotonin, dopamine, and norepinephrine reuptake inhibitor that potentiates the neurotransmitter activity in the central nervous system	Lorcaserin (Belviq)	Limited weight-loss efficacy and possible increase in cancer risk Side effects include headache, infection, sinusitis, nausea, depression, anxiety, and suicidal thoughts. Possible concerns of cancer risk	Mean body weight loss: lorcaserin 5.8 ± 0.2 kg; placebo 2.2 ± 0.1 kg	Approved by the FDA in 2012
	Desvenlafaxine (Pristiq)	Anorexia, but effect on body weight is unclear Vision problems, headache, low libido, dry mouth, dizziness, insomnia, taste problems, vomiting, anxiety, sexual dysfunction, depression, high blood pressure, stomach ache, numbness and tingling, fatigue, and involuntary quivering	Mean body weight loss greater than placebo was 0.22–1.41 kg	Off-label usage; approved for depression
	Sibutramine (Meridia)	Limited weight-loss efficacy Increased risk for cardiovascular events and stroke		Approved by the FDA approval in 1997 but withdrawn in 2010 due to cardiovascular effects
Inhibits the neuronal uptake of dopamine, norepinephrine, and serotonin	Bupropion (Wellbutrin, Zyban)	Modest weight loss Nausea, vomiting, dry mouth, headache, constipation, increased sweating, joint aches, sore throat, blurred vision, strange taste in the mouth, agitation and insomnia, tremor, or dizziness may occur. Rare side effects include cardiovascular effects, hearing problems, severe headache, an increase in suicide risk, and respiratory problems	% Weight loss greater than placebo: bupropion SR 400 mg/day 5.1% (CI: 6.9–3.2%); bupropion SR 300 mg/day 2.2% (CI: 4.0–0.4%)	Off-label usage; approved for depression
Reversible inhibitor of intestinal lipases	Orlistat (Xenical)	Weight loss Increased number of bowel movements and potential changes in the bowel function and microbiota	Mean body weight loss greater than placebo was 4.2 kg	Approved by the FDA in 1999
Enhancing GABA signaling to promote anorexigenic signaling. Inhibiting voltage-gated channels and AMPA receptor in the orexigenic neurons	Topiramate (Topamax)	Appetite suppression and weight loss Fatigue, drowsiness, dizziness, loss of coordination, tingling of the hands/feet, bad taste in the mouth, and diarrhea. Mental problems such as confusion, slowed thinking, trouble concentrating or paying attention, nervousness, memory problems, or speech/language problems may also occur. Rare side effects include kidney stones, depression, suicidal thoughts/attempts, and vision loss	Weight loss greater than placebo was 6.5 kg (CI: 4.8–8.3 kg)	Off-label usage; approved for epilepsy
GLP-1 receptor agonist	Exenatide (Byetta, Bydureon)	Decreased blood glucose level and body weight Side effects include gastrointestinal symptoms, acute pancreatitis, dizziness, and headache. It might increase risks of sulfonylurea-induced hypoglycemia and thyroid cancer	Mean body weight change: exenatide –(2.49 ± 0.66) kg, placebo +(0.43 ± 0.63) kg	Off-label usage; approved for diabetes
	Liraglutide (Victoza)	Maintained normal blood glucose and body weight Increased risks of C-cell carcinoma and thyroid C-cell focal hyperplasia were observed in rats and mice	Weight loss greater than placebo was 4.4 kg (CI: 2.9–6.0 kg)	Off-label usage; approved for diabetes
Amylin analog	Pramlintide (Symlin)	Decreased blood glucose level and body weight Side effects include nausea, hypoglycemia, vomiting, headache, abdominal pain, and fatigue	% Weight loss greater than placebo was 2.2 ± 0.7%	Off-label usage; approved for diabetes
Cocktail drug	Phentermine/topiramate (Osymia)	See above effects from individual drugs	% Weight loss from baseline was placebo –2.2%, (PHEN 7.5 mg/TPM 46 mg) CR –9.3%, and (PHEN 15 mg/TPM 92 mg) CR –10.7%	Approved by the FDA in 2012

The various shades (low, medium, and high) represent FDA approval status and off-label usage of drugs.

AMPA, α -amino-3-hydroxy-5-methyl-4-isoxazole propionate; CI, confidence interval; CR, controlled release; FDA, US Food and Drug Administration; GABA, γ -aminobutyric acid; GLP-1, glucagon-like peptide 1; PHEN, phentermine; SR, sustained release; TPM, topiramate.

Source: Clinical Pharmacology & Therapeutics; VOLUME 95; NUMBER 1; January 2014

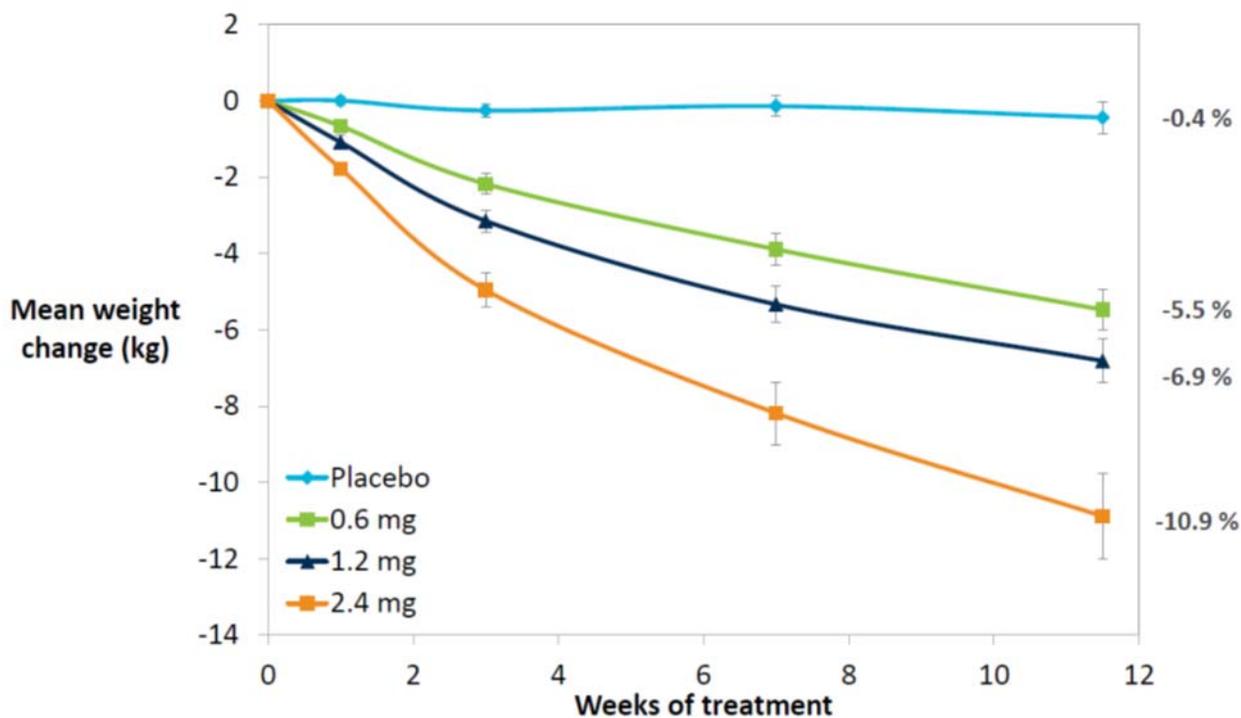
<http://www.nature.com/clpt/journal/v95/n1/full/clpt2013204a.html>

Anti-obesity drugs in the pipeline

- MetAP2 inhibition.** One of the more exciting drugs in development is Beloranib from Zafgen (ZFGN : NASDAQ : \$17.38 | BUY, covered for Canaccord Genuity by Corey Davis), which is a methionine aminopeptidase 2 (MetAP2) inhibitor. This novel mechanism works by re-establishing a balance to the ways the body packages and metabolizes fat. Inhibitors of MetAP2 reduce the production of new fatty acid molecules by the liver and help to convert stored fats into useful energy. Treatment with Beloranib results in a very fast fat catabolism and hence rapid and significant weight reduction. In a Phase 2a study in severely obese individuals, Beloranib showed an impressive and extremely rapid weight loss after only 12 weeks of 10.9% at the highest dose – see figure below. Whether patients continue to lose weight beyond 12 weeks remains to be seen in the currently planned, longer (6-12 months) studies, but the early signs as well as animal data are extremely promising. Its main drawback is that it is a twice-weekly subcutaneous injection and hence it will probably be reserved for individuals with very high BMIs (over 40 kg/m²). It is also currently enrolling patients in a Phase 3 study in Prader Willi Syndrome, a genetic disorder with Orphan status in which patients exhibit severe hyperphagia (overeating behavior).

Figure 30: Phase 2 results of beloranib in severely obese individuals

Completer population (n= 36, 34, 31, and 15, for Placebo, 0.6 mg, 1.2 mg, and 2.4 mg, respectively)



Source: Zafgen company presentation

There are also several other drugs in development for obesity with various mechanisms of action, which are shown in Figure 31 below, taken from the same publication referenced above.

Figure 31: Obesity pipeline drugs

Target	Drug	Company	Mechanism of action	Status
Central neuropeptide signaling				
Melanocortin receptor	MK-0493	Merck	Selective MC4R agonist, increases MC3R/4R signaling	Phase II completed
	RM-493	Rhythm	Selective MC4R agonist, increases MC3/4R signaling	Phase II
NPY	MK-0557	Merck	Y5 receptor antagonist, NPY blocker	Phase II completed
	Velneperit (S-2367)	Shionogi USA	Y5 receptor antagonist, NPY blocker	Phase III
Monoamine neurotransmission				
Dopamine/norepinephrine/serotonin	Contrave (bupropion/naltrexone)	Orexigen	Norepinephrine/dopamine reuptake inhibitor	Phase III completed; NDA submission
Intestinal peptide hormone signaling				
GLP-1	Liraglutide (Victoza)	Novo Nordisk	GLP-1R agonist, GLP-1 mimicking	Phase III completed; NDA submission
	Byetta (Exenatide)	Amylin	GLP-1R agonist, GLP-1 mimicking	Phase III
OXM	Oxyntomodulin (OXY-RPEG)	Prolor	GLP-1R agonist, OXM mimicking	Phase I recruiting
	TKS1225	Thiakis/Wyeth/Pfizer	GLP-1R agonist, OXM mimicking	Phase I
Pancreatic hormone signaling				
PP	PP1420	Wellcome Trust	Pancreatic polypeptide analog	Phase I completed
Amylin	Davalintide (AC2307)	Amylin	Amylin mimicking	Phase II
Adipose tissue hormone signaling				
Leptin	Metreleptin	Amylin/Takeda	Leptin receptor agonist	Phase III recruiting
Inhibition of lipase				
Pancreatic lipase	Cetlistat (ATL-962)	Alizyme/Takeda/Norgine	Pancreatic lipase inhibitor, inhibits intestinal lipid absorption	Phase III completed

GLP-1, glucagon-like peptide 1; MC3R/4R, melanocortin 3 and melanocortin 4 receptors; NDA, New Drug Application; NPY, neuropeptide Y; OXM, oxyntomodulin; PP, pancreatic polypeptide.

Source: Clinical Pharmacology & Therapeutics; VOLUME 95; NUMBER 1; January 2014

<http://www.nature.com/clpt/journal/v95/n1/full/clpt2013204a.html>

It is widely recognized that the FDA very carefully and conservatively reviews the risk/benefit profile of all new weight loss drugs in development. While drugs must prove that they are effective by inducing clinically meaningful weight loss to FDA standards, they must also show very clean safety and tolerability profiles. The FDA came under heavy criticism in the late 1990s for allowing the approval of Redux (dexfenfluramine), which was eventually found to cause heart valve damage and even death in patients. Redux was part of the notorious Fen-Phen combination (Redux + phentermine) that was very popular and widely used in the mid-1990s due to strong weight loss, often over 10%. The FDA was also very conservative and strict in reviewing Sanofi-Aventis' drug Rimonabant in the mid-2000s, which never made it to market in the US. Rimonabant was a first-in-class endocannabinoid drug, which was approved in Europe and was eventually recalled in Europe due to these same safety issues. There have been numerous recent Advisory Panels on the topic of obesity drugs, and, as referenced above, Orexigen was the only recent drug

forced to do a cardiovascular outcomes trial prior to approval. Now that that has been successfully completed, it saw a final approval on September 11, 2014.

The standards by which a drug proves clinically meaningful weight loss are clear. The drug must induce 5% mean placebo-adjusted weight loss or induce 5% body weight loss in at least 35% of drug patients (which must be about double the rate for placebo). Drugs technically only need to meet one of these hurdles for approvable efficacy. FDA standards for safety are equally as rigid, as evidenced by the lengthy CVOT trial required for Contrave. Additionally, the FDA requires that Phase 3 pivotal trials include at least 1,500 randomized to drug for one year of therapy in order to establish a large enough quantity of safety data to ensure adequate review and analysis.

BARIATRIC SURGICAL TREATMENT: A MATURING MARKET WITH PROVEN RESULTS

Individuals who approach and exceed 40% over their ideal weight seem to no longer have the physiological feedback of satiety. This makes it nearly impossible to stay on a diet, because their lifestyle revolves around eating. Medication can provide some help, but for these extreme patients there needs to be extreme results. Based on the research we've seen, we believe surgical intervention currently provides the best options for aggressive and rapid excess weight loss.

Patients have multiple treatment options, with more coming shortly

There have been many changes to the obesity landscape, both in terms of clinical treatments as well as obesity focused companies, since we published our first white paper in 2009, many companies have closed up shop while others continue to provide new and innovative solutions that challenge the existing treatment options surgically. With every product having its own strengths and weaknesses, we believe that the variety of different mechanisms used to combat the disease will allow for a customized treatment of each individual patient. Further, we believe there are four distinct groups to bucket the existing and new devices coming to market.

1. **Permanent modification** – This represents the largest and most common target market in obesity. For products competing in this space, the goal is to show superiority over the current treatment options (gastric bypass, sleeve gastrectomy, banding, etc.) for life-long resolution of obesity. This includes any surgical modifications or permanent implants designed to reduce large amounts of body weight for the morbidly obese patient.
2. **Revision surgery** – This market includes products designed to treat patients who have already had a bariatric procedure but have since regained some or all of the weight that was lost. This is fairly common following surgeries that create a small pouch, or stoma, to take the place of the older stomach. Over time, some non-compliant patients will eat more than their diet specifies and the stoma will stretch. The products targeting this patient population are mostly endoscopic suturing devices that cinch the stoma. Furthermore, endoscopic suture devices that are approved to treat GERD (gastroesophageal reflux disease) are being used off-label in bariatric revision surgery.
3. **Bridge to surgery** – Products used for this market are temporarily implanted for three to 12 months in order to bring the patient's weight down to a level where it is safe to operate. Patients with a higher BMI, such as the super obese (BMI>50 kg/m²), often carry a higher risk of complication from surgery. The bridge to surgery products that

are currently in early commercialization outside the US and development in the US are devices that are placed endoscopically. They are intended to stabilize a patient prior to surgery by reducing enough weight that the probability of a surgical complication is lowered.

4. **Cosmetic** – Currently, bariatric surgery is indicated for patients having a BMI greater than 40 kg/m², or a BMI greater than 35 kg/m² plus at least one co-morbid condition. For patients who do not fit into this indication, the treatment is considered to be cosmetic. As the safety profile for products and procedures improve and pricing per procedure decreases, we believe this market will continue to expand. We anticipate the products in this segment will derive from the “bridge to surgery” offerings. We believe that temporary products will initially fit into a cash-pay environment similar to what is seen in aesthetics (dermal fillers, body contouring, etc.) for patients looking for quick, aggressive, short-term weight loss. However as longer term data on comorbidity resolution becomes available, we would expect insurance coverage to expand.

Mechanism of action

Obesity procedures can be classified by the mechanism of action in which weight loss is achieved. **We believe current and in-development technology can best be categorized into five distinct mechanisms of action: (FARMS)**

Bariatric surgery modifies the anatomy of the GI by either:

- (a) *Flow control*
- (b) *Appetite suppression*
- (c) *Restricting consumed volume*
- (d) *Malabsorption of digested material*
- (e) *Space occupation*

- a. **Flow control:** devices that manipulate the rate of gastric emptying
- b. **Appetite suppression:** products and techniques designed to stimulate satiety and thereby reduce the volume of food consumed
- c. **Restriction:** products that limit the quantity of food that can be consumed by the individual through the physical restriction of a segment of the gastrointestinal system
- d. **Malabsorptive:** products that limit the amount of digested material that is absorbed into the body. This can be achieved by bypassing segments of the gastrointestinal tract or utilizing products to block contact between digested food and intestinal walls.
- e. **Space occupation/filler:** device that is deployed in the stomach to occupy space and in turn limit the volume of food that the stomach can hold

The developmental and currently approved procedures and devices in bariatric surgery vary in clinical results and risk of complication. It is up to the patient and doctor to perform the risk-versus-reward analysis, with the patient making the ultimate decision based on the risk profiles, lifestyle impacts, ancillary benefits and costs for each product. We believe this will create a new massive market with multiple players and varying degrees of success.

Figure 32: Risks vs. rewards in currently available bariatric procedures in the U.S.

Procedure	Product Category	%EWL @ 2 yrs	Risk	Meal restriction	Vitamin supplement (times/day)	Procedural Cost	Device Cost	Operating Time (min)	Avg. Hospital Stay (days)	Reversible	Comorbidity remission rates
Biliopancreatic Diversion (w/ Duodenal Switch)	Volume Restriction & Malabsorptive	75-80%	-Death (1%) -Bowel obstruction (5%-10%) -Night blindness (20%) -Bleeding (2%-4%)	Y	3	>\$30,000	-	178	5	No	-Type 2 diabetes (80%) -hypertension (~100%) -hypertriglyceridemia (~100%)
Gastric Bypass	Volume Restriction & Malabsorptive	55-65%	-Death (0.5%) -Staple line failure (5%-15%) -Leaking (1%-2%) -Bleeding (1%-2%) -Splenic injury (< 3%) -Pulmonary embolism (0.3%)	Y	2	\$20,000-\$30,000	-	202	4	No	-Type 2 diabetes (84%) -hypertension (88%) -hypertriglyceridemia (~100%)
Sleeve Gastrectomy	Volume Restriction	> 50%	-Death (0.5%) -Staple line failure (1%) -gallstones (1.4%) -Marginal ulcer (1.4%)	Y	1	\$20,000-\$30,000	-	50	2	No	-Type 2 diabetes (70%) -hypertension (69%) -hypertriglyceridemia (92%)
Laparoscopic Adjustable Gastric Banding	Volume Restriction	45-65%	-Death (0.05%) -Slippage (3%) -Erosion (3%)	Y	1	\$17,000-\$30,000	\$4,000-\$7,000	145	2	Yes, usually	-Type 2 diabetes (73%) -hypertension (50%) -hypertriglyceridemia (71%)
Vertical Banded Gastroplasty	Volume Restriction	40-50%	-Death (0.2%-2.0%) -Staple line failure (5%-15%) -Leaking (0.3%) -Bleeding (0.5%) -Pulmonary embolism (0.3%)	Y	1	\$20,000-\$30,000	-	141	7	No	-Type 2 diabetes (56%) -hypertension (66%) -hypertriglyceridemia (78%)

Source: www.ncbi.nlm.nih.gov

BARIATRIC SURGERY: HAS IT SHAKEN ITS PAST REPUTATION?

Weight-loss surgery has historically maintained a negative stigma due to the complications and deaths reported in a small number of cases being performed. Additionally patients do not want to modify their lifestyle post-operatively, and often times changing their diet is a major psychological hurdle patients have to overcome. Socially, bariatric surgery candidates may feel that they are taking the “quick fix” or the “easy way out” when viewed by others. Each of these factors may contribute to the low penetration rate that has kept bariatric surgery below growth expectations. Upon leaving the physician’s office, patients are left debating their options and the risks associated: 1) undergo surgery and risk **near-term** surgical complications (possibly death) or 2) no surgery and **long-term** co-morbid conditions (possibly death). Left with this choice, patients will typically opt for the long-term co-morbid conditions, thus deciding not to have surgery.

There are numerous studies that refute the poor quality and safety of the surgery, and many professional organizations, such as ASMBS, have taken steps to mitigate those misconceptions. In 1998, the in-patient mortality rate post-operation was 0.89%. More than a decade later, ASMBS showed that from a reported 60,000 cases, the mortality rates were 0.13% at 30 days after surgery. A study in the *American Journal of Family Physicians* from 2008 found that the 90-day post-operative death rate was 0.5% in a cohort of 1,465 patients undergoing laparoscopic and(or) open bariatric surgery.

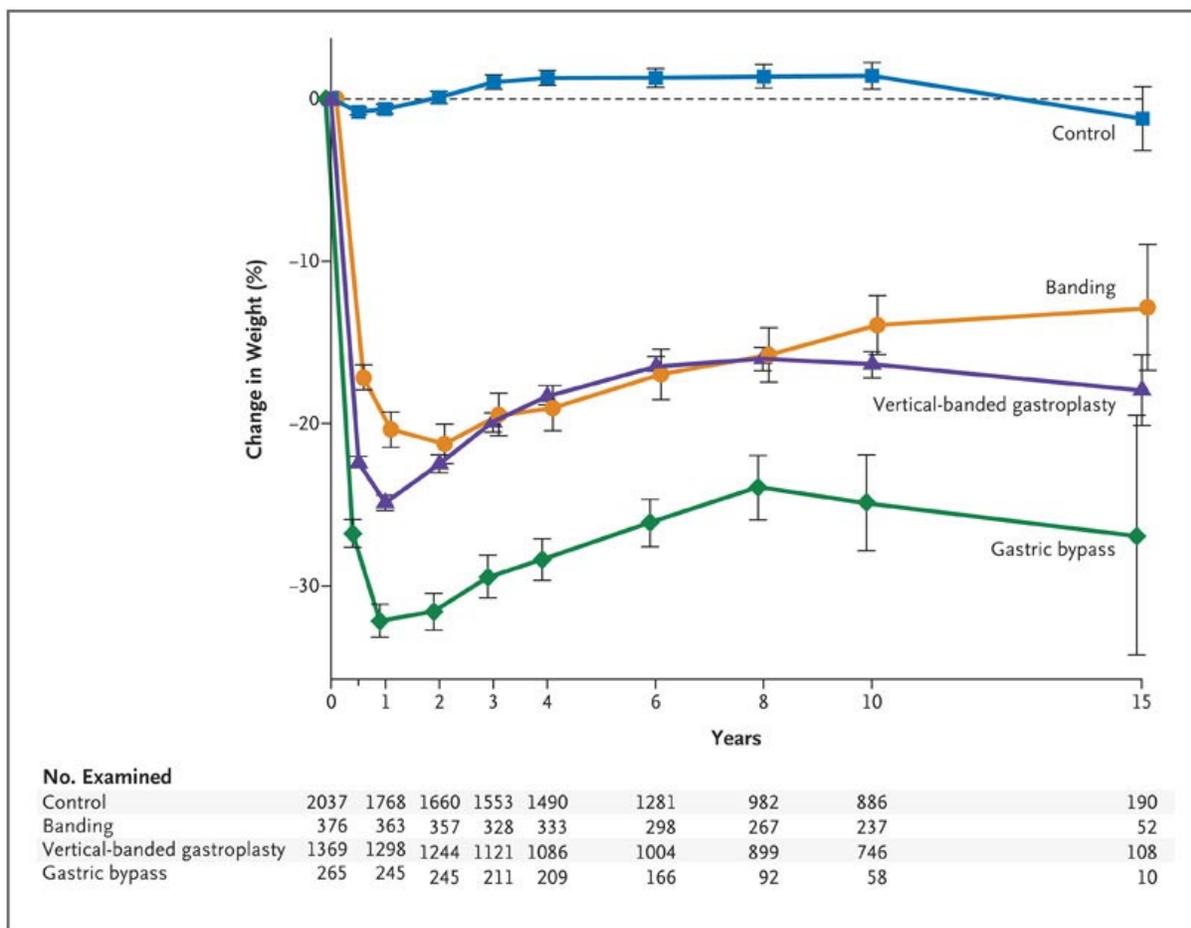
In 2007, the most irrefutable data to date was released (NEJM. 2007; 357: 741-752) from a 10-year, 4,047-patient study showing the effects of bariatric surgery on mortality in Swedish obese subjects. With 2,010 patients undergoing bariatric surgery (gastric bypass, vertical-banded gastroplasty, or adjustable gastric banding) and 2,037 using conventional treatment, the results showed that after 10 years there were 101 deaths in the surgery group compared with 129 deaths in the control group. Data from the study depicting average changes in patient body weight over a period of 15 years from when patients underwent bariatric surgery or began conventional treatment is displayed in Figure 33.

NEJM study showed surgery reduced the mortality rate in morbidly obese patients

The conclusion of the study was that bariatric surgery for morbidly obese patients is associated with long-term weight loss and a reduced mortality rate.

All this said, we believe the FDA approval of new, less invasive procedures and devices will ultimately expand the market. One topic not discussed in this report has been that PCPs and endocrinologists are the physicians burdened with caring for obesity procedure patients. Given the challenges associated with existing approaches, they have been viewed as options of last resort. With new, less burdensome procedures and device options, we believe that the non-bariatric physician community will be more open to options beyond diet, exercise, and drugs, in effect driving significant growth in the market over the next decade.

Figure 33: Results from Sjostrom’s study on Swedish obese patients



Source: www.neim.org

Bariatric surgery refinement shows marked improvements. Sleeve gastrectomy regained popularity in 2010 and has since maintained that momentum. Longitudinal studies showed that patients maintained average %EWL at two years of 75%-85% and then 68% at four years (Weiner et al.; *Summit for Sleeve Gastrectomy*, 2009). From a quality standpoint the procedure was a refinement of duodenal switch procedures performed on obese patients who initially had gastric reflux. A study released in the *Annals of Surgery* in 2013

compared sleeve gastrectomy, gastric bypass, and adjustable gastric banding for the treatment of morbid obesity. Among 8,847 patients (2,949 who received sleeve gastrectomy, 2,949 who received laparoscopic gastric bypass, and 2,949 who received laparoscopic adjustable gastric banding), researchers noted that, using 23 baseline characteristics, sleeve gastrectomy provided better weight loss than gastric banding and lower complication rates than gastric bypass (Carlin et al., *Ann Surg*, 2013).

Endoluminal procedures gaining acceptance.

Several endoluminal devices and procedures are being developed in the U.S., and we believe they will become a standard therapy for obesity. A few years ago, many companies were beginning early OUS commercialization efforts or finishing up their research and development phases in the product lifecycle. The progression to minimally invasive endoluminal devices in bariatrics mirrors the same trends that are occurring in general surgery overall, with the use of minimally invasive devices in robotics or single incision laparoscopy. The intent is to access the anatomy from a less invasive access point or use one of the body's natural orifices to reach the point of treatment. The benefit of an endoluminal approach is lower risk of complication. Invasive surgery has many downsides, such as pain, scarring, longer recovery times, increased incidence of post-surgical complications, need for general anesthesia, longer procedure times, longer hospital stays, and greater cost. If proven efficacious, products using endoluminal technology could be a resounding and overall win for the patient, physician, hospital, and device maker on most, if not all, counts, which is why we believe it will become a formidable therapy option for obese patients..

CURRENT AND PIPELINE PRODUCTS

COMBINATION VOLUME RESTRICTION AND MALABSORPTIVE PRODUCTS AND PROCEDURES:

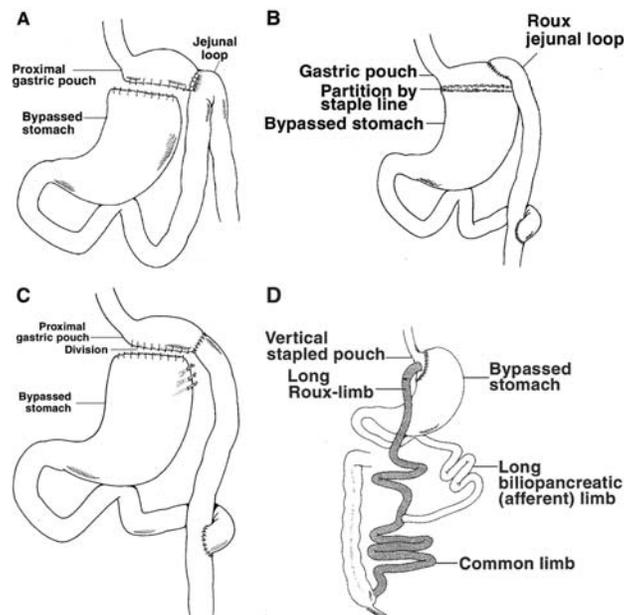
Gastric bypass: rerouting digestion

Gastric bypass was previously the darling of bariatric surgery. Since its adoption, it had maintained the top spot as the most common bariatric surgery procedure performed with 37.5% of all bariatric procedures into 2012. As of 2013, it has fallen out of favor with many bariatric surgeons who can achieve similar estimated weight loss with a sleeve gastrectomy procedure, while maintaining better post-operative outcomes. Despite this, we expect gastric bypass will still be a steadfast surgical option for moderate weight loss. Furthermore, research has shown remission of type 2 diabetes within days of the procedure.

Roux-en-Y: limits stomach capacity and re-routes drainage from the stomach directly to the lower intestine. This allows for a reduction in consumption and fat absorption.

1. **The Proximal Roux-en-Y** is the most common gastric bypass option in bariatric surgery. The procedure consists of making a very small pouch at the top of the stomach using staples, and then bringing a limb of the small intestine up to drain it. As a result, the main stomach and upper small intestine, including duodenum, are bypassed, preventing them from becoming a reservoir for food.
2. **Distal Roux-en-Y** is a variation to this procedure and is exactly same except that the “Y” connection is made farther down on the lower intestine. This is used to create a more malabsorptive effect. Since there is less of an opportunity for food to be digested, mineral and vitamin intake becomes a major problem, thus this technique is not used as much as the Proximal approach.

Figure 34: Proximal gastric bypass



Source: Journal of the American College of Nutrition, www.jacn.org

One year after surgery, patients typically see around a 50-75% EWL, and 96% of the co-morbid conditions associated with obesity are resolved after the procedure.

One year after gastric bypass surgery, patients typically experience approximately 50%-75% excess weight loss (EWL), according to various studies, and 96% of the co-morbid conditions associated with obesity are resolved after the procedure.

Even though gastric bypass surgeries are mostly performed laparoscopically, there have been significant risks associated with gastric bypass. Historically, this procedure was thought to have a 0.5% overall mortality rate, in addition to post-procedure problems of nutrition deficiencies, chronic anemia, and dumping syndrome (characterized by nausea, faintness, and diarrhea). Due to the high complication risk, possible candidates are limited and we estimate nearly 179,000 (assuming an 80% bypass/20% banding mix) procedures are performed each year.

Approved products

There are no implants (only instruments) utilized in gastric bypass procedures; it is simply a proven technique that is reimbursed for treating morbid obesity.

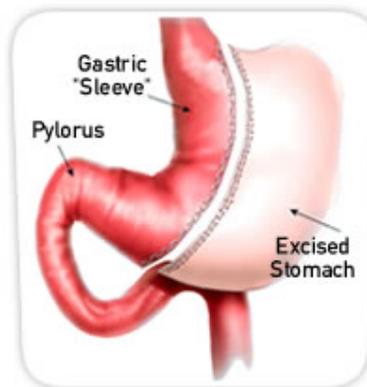
New technology

There are currently no new technologies in development to modify the gastric bypass procedure. There are multiple products in the early stages of commercialization or development that mimic gastric bypass through malabsorption and (or) hormonal blockages. Please see our discussion below for further information on these products.

Sleeve gastrectomy

Sleeve gastrectomy is currently the most common procedure performed in bariatric treatment. The procedure (mostly performed laparoscopically) removes approximately 70% to 80% of the stomach, leaving a sleeve in place. The big benefit of this approach is that even though the volume is reduced, most of the gastric nerves are left intact and the function of the stomach is not impacted. Furthermore, it is believed that with the removal of the fundus (located along the larger curve of the stomach), beneficial gastrointestinal hormones are released, such as ghrelin, which can reduce hunger. A systematic review of sleeve gastrectomies performed from 2003 to 2010 showed a mean estimated weight loss of 64.3% (with a maximum of 75%) at 12 months and a mean of 66% at 24 to 36 months (Fisher et al., Journal of Obesity Surgery). Sleeve gastrectomies were previously not covered by CMS or insurance carriers, but in 2010 three large insurance carriers initiated coverage and in 2012 CMS handed authority to regional contractors to decide whether to cover the procedure. As of February 2013, 44 of the 50 states provided coverage, although some had restrictions on the upper age limit.

Figure 35: Sleeve gastrectomy

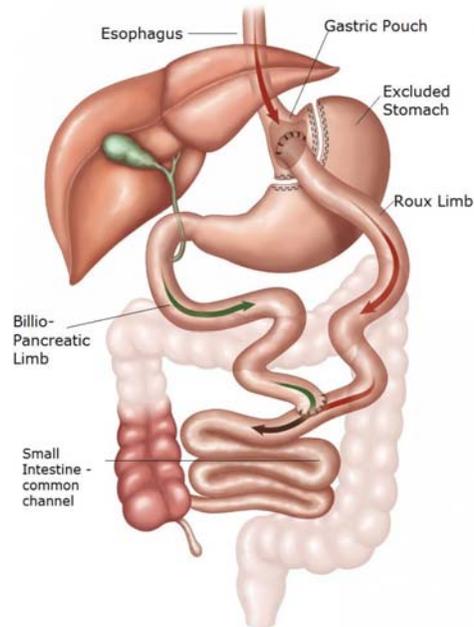


Source: www.lyassmed.com

Biliopancreatic diversion (BPD): aggressive removal, aggressive results

These procedures create the most extreme results in bariatric surgery. In this procedure, approximately 70% of the stomach is actually removed. Biliopancreatic diversions are similar to gastric bypass in that their purpose is to both restrict the volume that is able to be digested and also to create malabsorption.

1. The stomach is horizontally cut to create a six ounce pouch with the excess portion of the stomach completely removed from the body.
2. The modified stomach is connected directly to a shortened small intestine, bypassing the duodenum and jejunum, approximately 50-100 cm from the colon, allowing for malabsorption.
3. Digestive enzymes are passed from the gall bladder and pancreas through the bypassed portion of the small intestine, which is reconnected to the ileum portion of the modified small intestine.
4. When this is done with a **duodenal switch**, the stomach is cut vertically forming a tube shaped stomach which empties into a shortened duodenum. Again, the food has a shortened channel where it can be mixed with bile and pancreatic juices to be digested; however, the duodenal switch allows for improved capture of iron and calcium, which reduces nutritional deficiencies.

Figure 36: Biliopancreatic diversion with duodenal switch

Source: www.pancreaspictures.org

Biliopancreatic diversion: 70% EWL with persistent long-term weight loss

Compared to conventional gastric bypass, the %EWL outcomes are often superior with biliopancreatic diversion with a duodenal switch. Data suggests patients receiving biliopancreatic diversion achieve %EWL of up to 85% with a mean of 70% with weight loss persisting long-term (up to 18 years after the procedure was performed).

However, the intensive malabsorptive component of these procedures is so significant that patients are required to take vitamin and mineral supplements to prevent malnourishment. The adverse effect of the duodenal switch is dumping syndrome, where food is passed too quickly into the small intestine without being digested. Dumping is associated with nausea, bloating, diarrhea, and rapid heart rate after consumption of fine sugars. These risks, along with the procedure's high degree of technical difficulty, makes it a rarely utilized therapy, with only a 1% adoption rate of existing bariatric procedures.

Approved products

There are no implants utilized in biliopancreatic diversion procedures; it is simply a proven technique for treating morbid obesity.

Figure 37: Comparison of bariatric surgical procedures

	GASTRIC BAND	GASTRIC BYPASS	SLEEVE GASTRECTOMY
			
Procedure Description	The gastric band wraps around the upper part of the stomach, dividing the stomach into a small upper pouch that holds about ½ cup of food and a larger lower stomach. The degree of band tightness affects how much food you can eat and the length of time it takes for food to leave the stomach pouch.	In this procedure, the surgeon creates a small stomach pouch and attaches a section of the small intestine directly to the pouch. This allows food to bypass a portion of the small intestine.	During the sleeve gastrectomy procedure, a thin vertical sleeve of stomach is created using a stapling device. The sleeve is about the size of a banana. The rest of the stomach is removed.
How it works to help you lose weight	By creating a smaller stomach pouch, the band limits the amount of food that can be eaten at one time, so you feel full sooner and stay full longer. As you eat less food, your body will stop storing excess calories and start using its fat energy supply.	By creating a smaller stomach pouch, a gastric bypass limits the amount of food that can be eaten at one time, so you feel full sooner and stay full longer. By bypassing a portion of the small intestine, your body also absorbs fewer calories. As you eat less, your body will stop storing excess calories and start using its fat supply for energy.	By creating a smaller stomach pouch, a sleeve gastrectomy limits the amount of food that can be eaten at one time, so you feel full sooner and stay full longer. As you eat less food, your body will stop storing excess calories and start using its fat supply for energy.
How it affects digestion	Does not significantly affect normal digestion and absorption. Food passes through the digestive tract in the usual order, allowing it to be fully absorbed in the body.	Reduces the amount of calories (in the form of nutrients) that are absorbed.	Does not significantly affect normal digestion and absorption. Food passes through the digestive tract in the usual order, allowing it to be fully absorbed in the body.

Source:www.realize.com

RESTRICTION PRODUCTS AND PROCEDURES

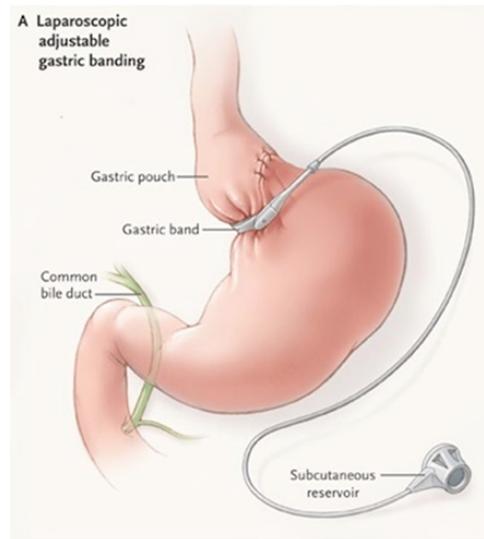
Gastric banding: first step toward minimizing trauma

Gastric banding procedures are less invasive alternatives to gastric bypass, biliopancreatic diversion, and sleeve gastrectomy. Additionally it offers patients more flexibility for long-term changes if a patient wants to remove the device or adjust the size of the band.

The LAP-BAND (laparoscopic adjustable gastric banding sold by Apollo Endosurgery, formerly sold by Allergan) and REALIZE Adjustable Gastric Band (sold by Ethicon/J&J) were approved by the FDA in 2001 and 2007, respectively. They are currently the only two gastric bands commercially available in the US and approved by the FDA on the market. A surgeon laparoscopically places an adjustable silicone band around the top portion of the stomach, forming a small pouch that will act as the new stomach. The pouch size can be adjusted through a small port placed underneath the skin where saline is injected or removed to hydraulically expand or contract the opening. As this pouch size is decreased, the sensation of fullness is increased with smaller volumes of food. Gastric banding has

fallen out of favor with many bariatric surgeons due to patient complications and remission rates post-operatively. Clinical complications and lower mortality rates made gastric banding popular, but behavior and lifestyle challenges lowered its utilization from a high of 35.4% in 2011 to just 14% of overall bariatric volume in 2013. Allergan further validated its diminishing prospects when it sold off its Lap-Band unit to Apollo Endosurgery. Sales peaked in 2008 for Allergan but fell to half the revenue by 2012 when it sold the unit.

Figure 38: Laparoscopic adjustable gastric band



Source: www.bariatricexperts.com

Gastric banding can achieve 50% EWL with post-operative hospital stays as little as 24 hours

Benefits: Patients who comply with the new lifestyle can realize approximately 50% EWL over two years. A patient can be out of the hospital in as little as 24 hours, further helping reduce costs. However, the largest advantage of this method is that it is reversible and adjustable, depending how the patient reacts to the food consumption restriction.

Downside: Risks for the procedure include possible slippage and erosion at the placement of the band, along with stretching/expansion of the stomach pouch. Additionally, obstruction at the narrow passageway is common, which causes the patient to vomit in order to clear the opening. Lastly, it is somewhat cumbersome to be required to visit the hospital or clinic for every adjustment. Approximately three or four adjustments are required per year.

Approved products

- **Apollo Endosurgery** (private). LAP-BAND has been the industry leader since its FDA approval in 2001. Inamed initially launched the product in Europe in 1994 and was then acquired by Allergan in 2006. The US pivotal study showed %EWL of 38% and 36%, at two and three years respectively. In 2012, Allergan sold the Lap-Band unit to Apollo Endosurgery, along with the Orbera intragastric balloon.

Figure 39: The Lap Band Device – Apollo Endosurgery



Source: www.apolloendo.com

- **Johnson & Johnson's** REALIZE Band (known outside the US as the Swedish Adjustable Gastric Band) was developed by the Swiss company Obtech Medical AG, which was acquired by Johnson & Johnson in 2002. REALIZE was FDA cleared in September of 2007.

Figure 40: The Realize Band – Johnson and Johnson



Source: www.realize.com

- **Agency for Medical Innovations** (A.M.I.; private) has designed and developed the A.M.I. Soft Gastric Band System. The product is stated to provide a reduced risk of migration, along with being gentler on enclosed tissue. The product has a CE Mark, but the company does not have plans to start a US pivotal trial without a US partner. Additionally, the company offers complementary products that help bariatric surgeons with revisions, such as a gastric band cutter.

Figure 41: Soft Gastric Band System – AMI



Source: www.ami.at

- **Helioscopie** (private) has developed two gastric band options, the HELIOGAST HAGA and the HELIOGAST HAGE. Both bands come with the EV3 adjustment system, the only implantable port in the world with 360° accessibility, which precludes complications related to the rotation of traditional adjustment ports. The HELIOGAST HAGA is the only band of its kind to have an adjustable “double balloon” membrane designed to increase the stability of the band and limit slippage. The bands have received CE Mark certification and are available in more than 30 countries worldwide; however, HelioScopie has no current plans to enter the US market.

Figure 42: Heliogast HAGA



Source: www.helioscopie.fr

Endoluminal gastroplasty

This technique is utilized to decrease the size of the stomach through internally placed sutures. Endoluminal tools gain access to the stomach transorally (without any incisions). Instrumentation is utilized to place sutures in the stomach lining, creating folds that minimize the capacity of the stomach. This procedure has been primarily utilized in revision surgeries for patients who have already undergone gastric bypass or BPD and have experienced stretching of the stomach. Clinical studies show that tissue fundoplication is not particularly effective, as stomach stretching occurs over time, resulting in minimal weight loss.

Below are the products currently being utilized in this application:

- **Apollo Endosurgery** (private) – developed the OVERSTITCH Endoscopic Suture System, which provides physicians the ability to perform several different types of tissue apposition within the gastrointestinal tract and peritoneal cavity. Additionally, the system allows the surgeon to reload the suture without the need for removing the endoscope. It is fully disposable and slides over standard flexible endoscopes. A 510(k) clearance was obtained October 2008 for endoscopic suturing.

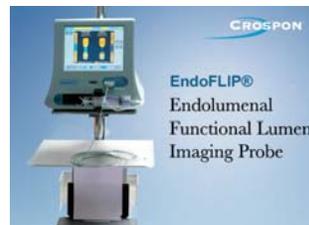
Figure 43: Overstitch Endoscopic Suture System – Apollo Endosurgery



Source: www.apolloendo.com

- Crospan** (private) – developed the EndoFLIP (Endolumenal Functional Lumen Imaging Probe) Imaging System, a minimally invasive device used to measure the dimensions and function of various hollow organs and sphincteric regions throughout the gastrointestinal tract. EndoFLIP has applications in Crospan’s “gastric imbrication” procedure, in which EndoFLIP is used to fold the greater curve of the stomach in on itself and suture the folds in place in order to limit the volume of food patients can consume. EndoFLIP received FDA approval in December 2009. Crospan is also developing applications for EndoFLIP in bariatric revision surgery; however, this use of the product has not been approved by the FDA.

Figure 44: EndoFLIP Imaging System – Crospan



Source: www.crospan.com

- USGI Medical** (private) is currently marketing the Incisionless Operating Platform (IOP). The IOP is differentiated through its use of USGI’s Expandable Tissue Anchors, which the company believes are more durable than traditional stapling or suturing. For the treatment of obesity, USGI has developed the POSE (Primary Obesity Surgery, Endolumenal) procedure. The IOP received 510(k) clearance in 2008 for use in various endolumenal procedures, including the POSE procedure. In October 2013, USGI received conditional approval from the FDA for its IDE application to launch a 350-patient US pivotal trial for the POSE procedure. In July 2014, the company completed enrollment in its ESSENTIAL trial, for which follow-up is expected to be complete in 1 year. Additionally FDA clearance and commercialization is expected in early 2016.

Figure 45: TransPort Endoscopic Access Device – USGI



Source: USGI Medical

Oral volume restriction products

New technology

- **Scientific Intake** (private) has developed a removable oral device to restrict bite size, the SMART Device (Sensor Monitored Alimentary Restriction Therapy). The company suggests that by helping the patient to consume food at a slower rate, they will experience an earlier signaling of satiety and therefore consume less total volume. The product is a removable device that is worn while eating and can track consumption and compliance through a microsensor in order to help alter the patient's eating habits for long-term results. The SMART Device is not yet available for sale in the US. It has been designated by the FDA as a non-significant risk device, but it is investigational at this time. Scientific Intake expects FDA approval for the device in 2015.

Figure 46: SMART Device – Scientific Intake



Source: Scientific Intake

Restrictive implants

New technology

- **GI Windows** (private), an early-stage company spun out of Beacon Technologies is developing Smart Self-Assembling Magnets for Endoscopy (SAMSEN) that mimic a gastric bypass without surgical intervention. The magnets form rings where an anastomosis is formed to bypass parts of the intestine. GI Windows has completed animal and cadaver trials to date and expects first-in-man trials by YE2014.

Figure 47: GI Windows device



 Source: GI Windows

- **BFKW** (private), an early stage company has developed the Full Sense™ Device (FSD) and is currently conducting clinical trials outside the US. The FSD is a temporary and fully reversible bariatric device that induces satiety through “continuous implied satiety.” The device is placed endoscopically in the distal portion of the esophagus and connects to the cardia via struts. Early clinical trials showed %EWL at 42% after 13 weeks.

Figure 48: Full Sense device - BKFV



 Source: BKFV

- **Oncimed** (private) is developing the Gastric Vest System (GVS), a minimally invasive, fully reversible, long-term implant for the treatment of obesity and type 2 diabetes. During a laparoscopic procedure, the GVS is placed and secured around the stomach in order to fold the stomach in on itself and mold it into the shape of a tube or channel leading directly to the small intestine. This procedure is intended to make food pass through the stomach more quickly, thereby triggering satiety signals to the brain earlier, speeding up gastric emptying time, decreasing total food consumption, and reducing absorption of fat and glucose. The GVS is approved for investigational use only.

in the US. Onciomed is currently conducting clinical trials OUS and hopes to begin commercializing the device outside the US in late 2015.

- **ValenTx** (private) has developed a reversible prosthetic implant that is placed endoscopically and is meant to mimic the effects of gastric bypass surgery by combining both restrictive and malabsorptive components. The 120 centimeter-long device reroutes chyme from the stomach to the lower small intestine, bypassing the duodenum. The product is currently undergoing clinical trials outside the United States with results expected in 2015.

Figure 49: ValenTx Implant – ValenTx



Source: ValenTx

Laparoscopic tools

- **TransEnterix's** Spider Surgical System is a laparoscopic platform that is used to perform minimally invasive surgery. The Spider Surgical System received FDA clearance in 2009. The system is comprised of small, flexible instruments that are inserted into right and left channels, allowing the surgeon to perform a variety of surgical techniques including bariatric surgery.

Figure 50: Spider Surgical System – Transenterix



Source: Transenterix

Figure 51: Volume restrictive products – competitive landscape

Company	Product or Brand	%EWL	Differentiation	Stage of Commercialization
A.M.I (Agency for Medical Innovations)	A.M.I. Soft Gastric Band System	N/A	Provides reduced risk of migration; gentler on enclosed tissue	Currently marketed in EU
Apollo Endosurgery	LAP-BAND	38% @ 2 years, 36% @ 3 years (n=299)	First to market, industry standard	Marketed in US since 2001 and EU since 1994.
Apollo Endosurgery	OverStitch Endoscopic Suture System	N/A	Surgeon can reload suture without removal of endoscope, integrates with Olympus scope.	510(k) clearance - October 2008
BFKW	Full Sense™ Device	42% @ 4 months	Device is placed on the distale portion of the esophagus and creates satiety through "continuous implied satiety."	Currently conducting clinical trials in Europe.
Crospon	EndoFLIP Imaging System	N/A	Used to measure dimesions and functions of hollow organs and sphincteric regions; applications in endoluminal gastroplasty	Marketed in US and EU since 2009
GI Windows	SAMSEN Magnets	N/A	SAMSEN Magnets mimic a gastric bypass without surgical intervention	GI Windows recently completed animal and cadaver trials. First-in-man trials to begin by YE2014
Helioscopie	HELIOGAST gastric banding system	68% @ 5 years	Includes EV3 adjustment system, the only implantable port in the world with 360° accessibility	CE Mark certified; available in more than 30 countries; no plans to enter US market
Johnson and Johnson	REALIZE Adjustable Gastric Band	45% @ 2 years, 43% @ 3 years (n=276)	Greater %EWL in US pivotal compared to LAP-BAND	Marketed in US since 2008 and EU since 1996.
Onciomed	Gastric Vest System	N/A	Device molds stomach into a narrow channel to reduce stomach capacity and gastric emptying time	Completed animal trials; currently conducting human trials OUS
Scientific Intake	SMART Device	38.1% @ 4-months (n=174), BMI 27-35	Non-invasive oral device used only while eating to reduce bite size	Completed US pivotal trial; designated by FDA as investigational non-significant risk device
TransEnterix	SPIDER Surgical System	N/A	Laparoscopic platform used to perform minimally invasive surgery	FDA approved and marketed in the US since 2009; marketed in the EU since 2010; marketed in the Middle East since 2012
USGI Medical	Incisionless Operating Platform (IOP)	40% @ 12-months	Durable tissue anchors with incisionless platform	510(k) clearance in 2008; conditional FDA approval for IDE application to launch US pivotal trial; ESSENTIAL trial completed enrollment in July 2014
ValenTx	gastric and intestinal sleeve	40% @ 12-months	Mimics both restrictive and malabsorptive components of gastric bypass	Conducting OUS clinical trials

Source: Company reports

SPACE OCCUPATION/FILLER PRODUCTS AND PROCEDURES

Most bariatric-related devices have focused on the surgical treatment of obesity. The concept of restricting the volume of food that is able to be consumed has centered on creating a small pouch that will become the new stomach. The second generation of products is inhibiting large volume consumption through space occupation, with the placement of a balloon or polymer in the stomach. These products are temporary devices that must be removed after three months, six months, or one year (or, in the case of Tulip Medical's product, must be replaced daily – see below for more information). They fit into the "bridge to surgery" category, but we believe they also fit into the "cosmetic" category for patients who do not require bariatric surgery. The products are much less invasive than surgical options, and many can be done in the physician's office rather than an operating

room. Additionally, they can be completed by gastroenterologists endoscopically rather than requiring a surgeon to place the device, expanding the capable physician population who can offer treatments for obesity.

Approved products

There are currently no products approved in the US with a mechanism of action that occupies space in the stomach to limit the volume of food that can be consumed.

New technology

- **Allurion Technologies** – is a clinical stage company developing an intra-gastric balloon that can be swallowed via a capsule and is eliminated after the treatment period using a timed-release mechanism from within the balloon. After three to four months, the balloon self-deflates passing through GI tract.

Figure 52: Gastric balloon – Allurion Technologies



Source: Allurion Technologies

- **Apollo Endosurgery** (private) is currently marketing the Orbera Managed Weight Loss Program OUS, which is comprised of the six-month Orbera intragastric balloon system, along with a 12-month professional support program. The Orbera balloon is placed endoscopically and filled with saline to partially fill the stomach. The product was acquired by Apollo Endosurgery from Allergan in 2012, along with the Lap-Band. The Orbera balloon has CE Mark certification, is available for commercial sale in 40 countries outside the US, and is the market leading balloon. Apollo submitted a PMA application for Orbera in April 2014.

Figure 53: Orbera balloon – Apollo Endosurgery



Source: www.apolloendo.com

- **Helioscopie** (private) is currently marketing its Heliosphere BAG intragastric balloon. The product is approved in international markets and is indicated for use for up to six months. The balloon is filled with air and weighs less than 30 grams, which, according to the company, limits nausea and vomiting. Helioscopie was bought in 2010 by Santé Actions Group, a French medical device company.

Figure 54: Heliosphere – Helioscopie



Source: www.helioscopie.fr

- **Obalon** (private) has created a proprietary gastric balloon that can be swallowed via a capsule, and therefore does not require sedation of any kind to implant. The capsule (attached to a small tube) dissolves in the stomach, the balloon is inflated with gas (up to three balloons) and the tube is removed. Patients can elect to have multiple balloons in their stomach, as the Obalon balloon is smaller than many other intragastric balloons. After three months, the balloon(s) are either removed endoscopically or defecated out of the patient if deflated. The product is currently sold outside the US and the company expects FDA approval in 2016.

Figure 55: The Obalon balloon – Obalon



Source: Obalon

- **PlenSat** (private) has developed a short-term intragastric digestible balloon system. Patients ingest a small capsule that encases the balloon, which then self-inflates in the acidic environment of the stomach. The balloons are significantly smaller than other balloons in the space. PlenSat expect patients will be able to tolerate four to five balloons at one time if they elect to. The balloons will remain in the stomach for between two and four weeks, after which they will break down mechanically and pass through the intestines, requiring no surgical or endoscopic intervention. PlenSat has conducted animal trials; however the balloons have not yet been tested in humans.

Figure 56: PlenSat digestible balloon – PlenSat



Source: PlenSat

- **ReShape Medical** (private) is designing a multi-chamber space occupation device called the ReShape Duo. The patented design is believed to have addressed migration and safety issues historically associated with balloon devices by using a dual-balloon, rather than a single-balloon. The dual-balloon structure is designed to allow the stomach to tolerate more filler volume than a single-balloon without causing over-distention or discomfort. The ReShape Duo has been available commercially in Europe since 2007. On July 1, 2014, ReShape Medical announced that it had submitted a PMA application to the FDA for the ReShape Duo.

Figure 57: The ReShape Duo – ReShape Medical



Source: ReShape Medical

- **Spatz FGIA** (private) has developed and commercialized a therapeutic intragastric balloon device for pre-operative medical and aesthetic weight reduction. The Spatz technology has a proprietary inflation tube that allows for volume adjustments while the balloon is in place. Additionally, it is approved outside the United States for up to 1 year in a patient and further studies are pointing to longer-term implementation. To date, 5,000 Spatz devices have been implanted worldwide.

Figure 58: Spatz adjustable balloon system – Spatz FGIA



Source: Spatz FGIA

- Tulip Medical** (private) has designed a very-short-term intragastric balloon system. The company's balloons are swallowed daily via a small capsule and remain in the stomach for 5-6 hours, after which they are broken down mechanically by gastric fluids and passed through the intestines and out of the patient. The patient must swallow a new capsule each day during the treatment period. Tulip Medical is currently pre-clinical in the US and has conducted one small human clinical trial in Israel, where the company is based. Tulip Medical is currently pursuing CE Mark.

Figure 59: Filler products – competitive landscape

Company	Product or Brand	%EWL	Differentiation	Stage of Commercialization
Allurion Technologies	intragastric balloon	N/A	Requires no procedure for implantation or explantation; self-passing	Developmental stage
Apollo Endosurgery	Orbera intragastric balloon	33.9% @ 6-months (n=2215), Avg. BMI=44.4	First to market after Garren-Edwards bubble, filled with saline	CE Mark certified; commercially available in more than 40 countries OUS; submitted PMA application to FDA in April 2014
Helioscopie	Heliosphere BAG intragastric balloon	5 international trials w/ >670 patients; measured weight loss: 9-24 kgs	Balloon is filled with air and weighs less than 30 grams, limiting nausea and vomiting	Marketed OUS in more than 30 countries
Obalon	Obalon intragastric balloon	50.2% @ 3 months (n=110)	Balloon swallowed in a capsule; multiple balloons can be implanted due to small size of balloon	Marketed OUS; limited to investigational use in the US
PlenSat	Digestible Balloon	N/A	Balloon swallowed in a capsule and broken down by stomach; multiple balloons can be implanted due to small size of balloon	Conducting animal trials
ReShape Medical	ReShape Duo intragastric balloon	33% @ 6 months	Multi-chamber design to address migration	Marketed in EU since 2007; submitted PMA application to FDA in July 2014 with data from REDUCE Trial
Spatz FGIA	Spatz3 Adjustable Balloon System	48.1% @ 12 months (n=48), 28.8% @ 3 months (n=158)	Only balloon approved for one-year use; only adjustable balloon	Marketed in EU since 2012; marketed in select additional regions; currently preparing application to FDA
Tulip Medical	intragastric balloon	N/A	Balloon is swallowed daily via capsule; digested mechanically by stomach fluids after 5-6 hours and passed naturally through intestines	Conducting human trials in Israel; expects to receive CE Mark in 2015; plans to commercialize in 2016

Source: Company reports

FLOW CONTROL PRODUCTS AND PROCEDURES

A number of companies are developing products designed to manipulate the rate at which food exits the stomach. It is known that the body will experience faster gastric emptying when large quantities are consumed. Causing delayed gastric emptying can have multiple effects, including prolonged digestion, inability to consume food beyond the stomach's capacity, and generation of an earlier sense of satiety. Delayed gastric emptying can provide better regulation for diabetics, reducing sugar spikes post consuming a large meal.

Approved products

There are currently no products approved in the US with a mechanism of action that manages/manipulates the flow of materials out of the stomach.

New technology

- **Bariatric embolization** is a new clinical procedure that is currently being investigated at Johns Hopkins University with sponsorship from multiple companies. The interventional radiology procedure, similar to a cardiac catheterization, involves placing a catheter through the groin and using an obstructive agent to block blood flow to the gastric artery. Early studies have shown encouraging results with patients losing up to 8% EWL and sustaining the loss for up to 1 year.
- **BAROnova** (private) has developed the TransPyloric Shuttle (TPS), which restricts food from entering into the small intestine from the stomach by repeatedly blocking and unblocking the pyloric valve mechanically. Additionally, after food exits the stomach, there is further resistance, which increases contact time with the walls of the small intestine and is believed to induce satiety from smaller amounts of food. The TPS is delivered and retrieved endoscopically under conscious sedation and does not require any fixation to anchor the device. An Australian study showed results of 58.4% EWL at six months for patients in the 30-40 BMI range. BAROnova expects to enter into a US pivotal trial in 2015, focused on patients in the 30-40 BMI range.

Figure 60: TransPyloric Shuttle - BAROnova

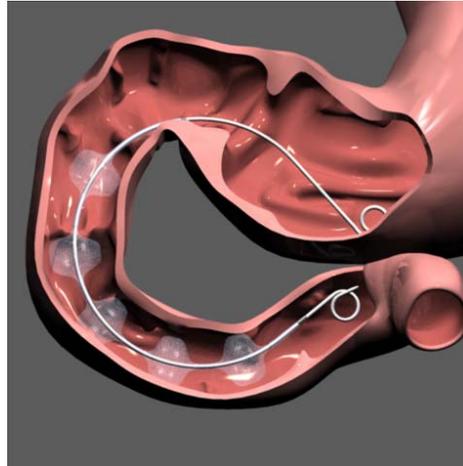


Source: BAROnova

- **EndoSphere** (private) has developed the SatiSphere, a C-shaped intestinal/duodenal implant that restricts flow through the upper GI tract using soft spheres distributed along the backbone of the device. The spheres are designed to delay the passage of chyme through the duodenum and increase contact time between the partially digested food and nerve receptors of the duodenum in order to “trick” the brain into feeling satiated with smaller amounts of food. The implant is approximately 20cm-25cm in length and is placed in the distal stomach (25%) and the duodenum (75%) for a period of three months. The

SatiSphere is commercially available in Europe and EndoSphere expects to begin its US pivotal trial in 2016.

Figure 61: Satisphere - EndoSphere



Source: EndoSphere

Figure 62: Flow control products – competitive landscape

Company	Product or Brand	%EWL	Differentiation	Stage of Commercialization
BAROnova	TransPyloric Shuttle (TPS)	58.4% @ 6 months (BMI 30-40), 50.0% @ 6 months (BMI 30-50)	Anchor placed in stomach and small intestine to restrict food from entering small intestine by repeatedly blocking and unblocking pyloric valve	Currently conducting ENDObesity study; plans to begin US pivotal trial in 2015
EndoSphere	SatiSphere System	12% @ 1-month (n=11)	C-shaped intestinal/duodenal insert; increases contact time of chyme with duodenum, slowing digestion and increasing satiety	Currently conducting post-market study in EU; plans to make device fully commercially available in EU in 2016; plans to begin US pivotal trial in 2016

Source: Company reports

MALABSORPTIVE/INTESTINAL BYPASS PRODUCTS

One key concept that has been discovered through gastric bypass and biliopancreatic procedures is that creating malabsorptive effects can lead to excellent %EWL endpoints. Furthermore, there is an ancillary benefit of remission of type 2 diabetes in a significant number of patients.

Approved products

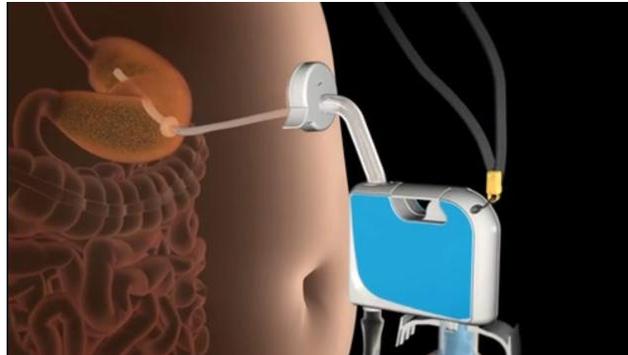
There are currently no products approved with a mechanism of action that inhibits absorption of calories.

New technology

- **Aspire Bariatrics** (private) has developed the AspireAssist, a removable device that allows a patient to empty approximately one third of the food in his or her stomach after consuming a meal before the calories are absorbed. A specially designed tube is

implanted in an outpatient procedure, connecting the stomach to a port on the outside of the abdomen. 20 minutes after finishing a meal, the patient attaches a small, hand-held device to the port, which allows him or her to empty one third of his or her stomach contents in a toilet. The device is currently available on a limited basis in Europe and select additional OUS regions. The company plans to submit a PMA application to the FDA in Q2/15 and hopes to receive FDA clearance by the end of 2015.

Figure 63: AspireAssist – Aspire Bariatrics



Source: Aspire Bariatrics

- **Endobetix** (private) is developing an endoscopic bile diversion device that doesn't restrict food intake but prohibits bile from entering the duodenum and mixing with stomach chyme. The bile is re-routed to the end of the small intestine through a small tube-like system where it reenters and is discharged. It functions similarly to a malabsorptive device but without anchoring. It uses a 6-inch stent placed at the opening of the stomach into the small intestine. Endobetix is currently conducting animal trials on the device and plans to begin human trials in 2015-2016.

Figure 64: Bile diversion device – Endobetix



Source: www.endobetix.com

- **GI Dynamics** has developed the EndoBarrier Liner that is placed in the duodenum and allows food to pass through without being mixed with digestive juices, thereby reducing the amount of food absorbed. Studies from 2010 show a reduction of 46.3% EWL after 12 months with the EndoBarrier. Currently the EndoBarrier has CE mark and is commercially available in Australia, South America, and the Middle East. GI Dynamics is currently undergoing a pivotal clinical trial in the US (the ENDO trial) for patients with type 2 diabetes and obesity.

Figure 65: EndoBarrier – GI Dynamics

Source: GI Dynamics

Figure 66: Malabsorptive products – competitive landscape

Company	Product or Brand	%EWL	Differentiation	Stage of Commercialization
Aspire Bariatrics	AspireAssist	40% EWL @ 6 months	Endoscopically placed tube connects stomach to port on outside of abdomen; patients aspirate 30% of food volume out of port after each meal	CE Mark since 2011; marketed in EU and other regions; conducting EU postmarket studies and US PATHWAY pivotal trial; plans to submit PMA application to FDA in June 2015
Endobetix	Bile Diversion Device (BDD)	N/A	Bile is re-routed to the end of the small intestine through a small tube like system where it reenters and is discharged	Currently conducting animal trials; plans to begin human trials in 2015-2016
GI Dynamics	EndoBarrier	20% @ 12-weeks, 30% @ 6 months, 46.3% @ 12 months	Combination of weight loss & immediate resolution of T2D	CE Mark since 2009; marketed in EU, Australia, Middle East, South America; currently conducting US pivotal trial (ENDO Trial) for obese type 2 diabetics

Source: Company reports

APPETITE SUPPRESSION PRODUCTS AND PROCEDURES

Compared with the historic approaches of volume restriction and flow control, attempting to suppress the appetite in obese patients is not an exact science. The ultimate goal is to interfere with signals between the gastrointestinal tract and the brain in the hope that the obese patient will not feel the need to eat as much. The companies developing these products utilize a variety of mechanisms, such as: gastric stimulation; neuromodulation (stimulation and/or blocking); nerve resection; and endoscopic procedures on the gastrointestinal tract, in the brain, and various points in between. Furthermore, most of the products with other primary mechanisms of action (restriction, filler, etc.) utilize appetite suppression as a way to induce weight loss.

Approved products

There are currently no products approved with a mechanism of action that attempts to suppress the appetite in obese patients.

New technology and procedures

Vagotomy – nerve resection

A minimally invasive endoscopic procedure under development is use of vagotomy. Vagotomy is the resection of the vagus nerve. Open surgical vagotomy was the primary treatment for ulcer disease from 1945 until the mid-1980s. Ten years post truncal vagotomy, patients were found to be 20-25 lbs. under the average weight of the population. The mechanism of action is the combination of decreased acid production and gastric relaxation along with an interrupted ghrelin signal (a hormone produced in the stomach and pancreas that stimulates appetite).

Neuromodulation and gastric stimulation

These implantable pacemaker-like devices are inserted just below the skin where electrode leads are laparoscopically connected to the vagal nerve trunk or stomach lining. The objective of this therapy is to create the feeling of satiety for patients without surgically modifying the gastrointestinal tract. Thus, these procedures affect neither the volume of food that can be consumed nor the absorptive capabilities.

- **Beta-Stim** (private) is developing a minimally invasive implantable pulse generator (IPG) to treat obesity and type 2 diabetes by applying electrical stimulation to the duodenum. When food reaches the stomach, the system detects it and the IPG applies electric stimulation to close the pyloric sphincter, where the contents of the stomach empty into the duodenum. This process delays gastric emptying, leading to early satiety, and enhances duodenal motility, reducing the absorption rate of sugars and fats. The company is currently not divulging its clinical progress.
- **EnteroMedics** currently offers the closest product to commercialization in the neuromodulation product category specifically targeting obesity. The Maestro System is a vagal blocking (VBLOC) therapeutic device that sends high-frequency but low-energy pulses to intermittently block gastrointestinal signals along the vagus nerve between the digestive system and the brain. However, the predefined efficacy thresholds for the company's ReCharge pivotal trial were not met in the Intent-To-Treat and Per-Protocol patient populations at 12-months. In June, 2014, EnteroMedics went before a panel of industry experts and the FDA. The FDA took into consideration the panel's thoughts on the device, which were mixed due to the failure to meet the pre-defined endpoints of its ReCharge trial. The company expects a formal FDA decision by YE2014 for its PMA application.

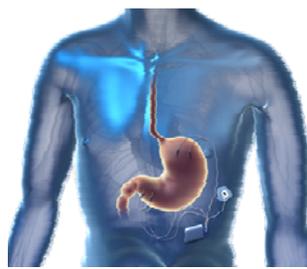
Figure 67: Maestro System - EnteroMedics



Source: www.venturebeat.com

- MetaCure** (private) has developed the DIAMOND System (previously the TANTALUS System), a gastric stimulator used to sense when the patient is eating and automatically apply electrical stimulation (using three leads) during meal times. Data can be non-invasively read by the physician for further tailoring of the treatment parameters. Stimulation during initial stages of meals is designed to provoke an early response of the gut typical of a full meal. The DIAMOND System was granted a CE Mark in 2006 for the treatment of obesity. The product also received a CE Mark in January 2007 for the indication to treat obese type 2 diabetics.

Figure 68: DIAMOND System – MetaCure



Source:www.metacure.com

Figure 69: Appetite suppression products – competitive landscape

Company	Product or Brand	%EWL	Differentiation	Stage of Commercialization
Beta-Stim	Implantable Pulse Generator (IPG)	N/A	IPG applies electrical stimulation to duodenum to delay gastric emptying and enhance duodenal motility	Developmental stage
EnteroMedics	Maestro System - VBLOC Therapy	37.6% @ 18-months (n=9), 28.1% @ 12-months (n=17), 17.9% @ 6-months (n=35)	Uses high frequency, low energy signals to block vagal nerve transmission	Completed Re-Charge pivotal trial; went before FDA and industry panel in June 2014 w/ mixed results; hopes for FDA approval by 2015
MetaCure	DIAMOND System	5% weight loss (5-7 kilograms)	Utilizes an eating detection mechanism, automatically applies electrical stimulation to gastric muscles while eating	CE Mark for treatment of obese patients since 2006, CE Mark for treatment of obese, type 2 diabetic patients since Jan. 2007

Source: Company reports

Figure 70: Scientific advisors in obesity related companies

	Allurion Tech	Apollo	Aspire	BAROnova	Endobetix	EndoSphere	EnteroMedics	GI Windows	MetaCure	Onciomed	PlenSat	Scientific Intake	Spatz	Tulip	USGI	ValenTx
Almino Ramos, MD																
Anir Gupta, MD																
Anthony Kalloo, MD																
Ashutosh Kaul, MD																
Bipand Chand, MD																
Bruce Bode, MD																
Bruce Schirmer, MD																
Christopher Gostout, MD																
Christopher Thompson, MD																
Clifton Baile, PhD																
D. Walter Cohen, MD																
Daniel Jones, MD																
Daniel Smith, MD																
David Cummings, MD																
David Lautz, MD																
David Sarwer, PhD																
Dirk Mueller-Wieland, MD																
Donald Simonson, MD																
Douglas Pleskow, MD																
Efrat Broide, MD																
Ellen Duke																
Evzen Machytka, MD																
Flavia Soto, MD																
Frank Greenway, MD																
George Blackburn, MD, PhD																
George Woodman, MD																
Glen Lehman, MD																
Harold Labovitz, MD																
Harold Solomon, MD																
Henry Buchwald, MD, PhD																
Hideo Makimura, MD, PhD																
Jamie Ponce, MD																
Janice Hogan, JD																
Jeff Peters, MD																
John Dixon, MBBS, PhD																
Jordan Busch, MD																
Kelly Brownell, PhD																
Kenneth Binmoeller, MD																
L Mathus Vliegen, MD																
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Manoel Neto, MD																
Marc Bessler, MD																
Marvin Ryou, MD																
Michael Berelowitz, MB ChB																
Michael Federle, MD																
Michael Gonzales-Campoy, MD																
Mitch Roslin, MD																
Moshe Shike, MD																
Nezam Afdhal, MD																
Ori Segol, MD																
Pankanj Pasricha, MD																
Paul Akerman, MD																
Paul Swain, MD																
Peter Cotton, MD																
Peter Siersema, MD, PhD																
Philip Schauer, MD																
Raman Muthusamy, MD																
Randy Seeley, PhD																
Raul Rosenthal, MD																
Richard Rothstein, MD																
Robert Hawes, MD																
Robin Blackstone, MD																
Ronnie Fass, MD																
Samuel Klein, MD																
Santiago Horgan, MD																
Sayeed Ikramuddin, MD																
Scott Shikora, MD																
Sergey Kantsevov, MD																
Shashank Shah, MD																
Stacy Alan Brethauer, MD																
Stephen Solomon, MD																
Sydney Chung, MD																
Thomas Haak, MD																
Thomas Inge, MD, PhD																
Tom DeMeester, MD																
Tom Lavin, MD																
Tomasz Rogula, MD																
William Snape, MD																
Yehuda Handelsman, MD																
Zamir Halpern, MD																

Source: Company reports and Canaccord Genuity

THANK YOU

We would like to thank the following people for their contributions in preparing this document. We appreciate their efforts and valuable insights. We believe we have captured all those who contributed, and apologized if we have excluded anyone.

The executives of the companies in the obesity space, most of whom spoke with us and provided details regarding their products and strategies. It is their knowledge and insight that provided the foundation of our thesis.

The physicians that we spoke with: Dr. Roman Turro Arau – Hospital Quiron Teknon, Barcelona, Spain; Dr. Frank Greenway – Louisiana State University; Dr. Theo Ngatchu – Royal Free Hospital, London, UK; Dr Lee Swanson – The Oregon Clinic; and Dr. Clifford Weiss – Johns Hopkins Hospital. The insights and experiences with several of the products in US clinical trials and commercially available OUS were invaluable in our analysis of the competitive landscape. We thank them for their time and effort.

The Venture Capital community: Many of our VC friends were very helpful in facilitating introductions to management teams in the space. We are grateful for these connections.

Corey Davis and Lidia Liu: Corey is a Managing Director, Equity Research covering biotech/spec pharma for Canaccord. He is our resident expert on the obesity drug space and along with Lidia, his associate, provided the synopsis of the pharma/biotech landscape for this report.

Ryan Zimmerman: Ryan is the newest member of the Canaccord Med-Tech research team and this was his first major project as an equity research associate.

Samantha Essig: Sam was our summer consultant who worked tirelessly on fact-checking the data that underpin our market assumptions, and constructing the company “tear” sheets in the back of this report.

ALLURION TECHNOLOGIES (PRIVATE)

COMPANY INFORMATION

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Phone: 781-235-7050



Gastric Balloon
Source: Allurion Technologies

General overview

Mechanism of action
Filler

Permanent or temporary
Temporary – multiple months

Regulatory status
Developmental stage

Target population
Overweight and obese patients

Company description

Allurion Technologies was founded in 2009 and is developing a liquid-filled gastric balloon that is swallowed via a capsule and is naturally excreted following treatment. While in place, the device displaces stomach volume and interrupts gastric emptying as a therapy for overweight and obese individuals.

Product description

The device is manufactured using thin-film thermoplastic technology that allows it to expand in the stomach over 200 times its starting volume, taking up room and exerting pressure on the walls of the stomach to induce satiety. The device is swallowed under physician supervision (without surgery or endoscopy) and, following a multi-month course of therapy, empties and exits the body naturally. The balloon was developed to minimize and/or eliminate the procedural requirements and associated costs involved with endoscopic intra-gastric balloons. The patient does not require a return visit to the physician for removal as the balloon is expelled naturally through the digestive track.

Target population

Overweight and obese patients

Restrictions

There are no dietary restrictions associated with the product at this time. Prior bariatric surgery is contra-indicated.

Cost

While a price has not been formally set, the company expects to offer the device at a discount to currently marketed intragastric balloons, which retail for \$6,000-\$8,000 outside of the US market.

Clinical data

The product is currently in clinical trials in Europe. Data has not been published as of October 3, 2014.

Regulatory status & strategy

US

Allurion Technologies is currently conducting clinical trials in Europe. It is seeking OUS regulatory approval prior to US approval.

OUS

Allurion hopes to receive CE mark approval in Europe in 2015 and plans to launch commercially in Europe and several other OUS geographies prior to US commercialization.

Financials

Total funding to date: \$6.8M

\$750,000 (Dec. 2011) – Loan from the Massachusetts Life Sciences Center

\$1.7M (Jul. 2012) – Equity financing from 25 investors

\$2.8M (Aug. 2013) – Equity financing

\$1.6M (Jul. 2014) – Equity financing (first closing)

Management

- Jonathan Wecker – CEO
- Dr. Shantanu Gaur – Co-Founder and Chief Scientific Officer
- Dr. Samuel Levy – Co-Founder and President
- Dr. Ram Chuttani – Senior Medical Advisor
- Matt Lake, P.E. – Director of Engineering and Manufacturing
- Vince Panzano, Ph.D. – Research and Clinical Affairs Coordinator

Medical advisors

- Nezam Afdhal, MD
- George Blackburn, MD, Ph.D.
- Jordan Busch, MD
- Daniel Jones, MD, MS, FACS
- Richard Rothstein, MD
- Bruce Schirmer, MD
- Peter Siersema, MD, Ph.D., FASGE, FACG
- Harold Solomon, MD

A.M.I. (AGENCY FOR MEDICAL INNOVATIONS) (PRIVATE)

COMPANY INFORMATION

A.M.I. GmbH Austria
Im Letten 1
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Austria

www.ami.at
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Phone: +43 5522 90505-0



Soft Gastric Band
Source: www.ami.at

General Overview

Mechanism of Action
Restrictive

Permanent or Temporary
Permanent/Reversible

Regulatory Status
Current: CE Mark in EU

No current plans to enter US market

Target Population
BMI 30-40

Company description

Agency for Medical Innovations (A.M.I.) is an Austrian device maker selling products for the treatment of morbid obesity in the European market.

Product description

Gastric banding

Soft Gastric Band System – The product is developed to be gentler on enclosed tissue and offer lower risk of migration.

Soft Basket Band – The product is designed to prevent dilation of esophageal-gastric function.

B-Band – The product is implanted around the stomach pouch in gastric bypass patients to stabilize the gastroenterostomy (connection of stomach and jejunum) and prevent later dilation of the stoma.

Finger Disposable Instrument – The disposable device is used for blunt dissecting the posterior side of organs or structures and pulling slings or implants through and/or behind these organs.

Gastric Band Cutter – The device is designed to remove eroded gastric bands via gastroscope rather than through open or laparoscopic removal.

Target population

A.M.I.'s gastric banding products and procedures are intended for obese patients who qualify for bariatric surgery, typically in the BMI range of 30 to 40.

Restrictions

After a gastric banding procedure, patients are only able to ingest liquid or pureed foods for two to three weeks following surgery. Vitamin and mineral deficiencies are also common, so patients may need to take dietary supplements.

Cost

The cost is comparable to other gastric banding procedures.

Regulatory status & strategy

US

A.M.I.'s products are not commercially available in the US at this time. The company has no current plans to enter the US market.

OUS

A.M.I.'s gastric banding system has CE Mark approval and is commercially available in the EU.

Financials

Total funding to date: \$30M

Management

- Marc Jablonowski – Managing Director/CEO
- Markus Sonderegger – Managing Director/ Chief Operating Officer
- Martin Hohlrieder – Managing Director/ Chief Technology Officer
- Stefanie Hoellger – Quality Assurance & Regulatory Affairs

APOLLO ENDOSURGERY (PRIVATE)

COMPANY INFORMATION

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www.apolloendo.com

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Orbera
Source: www.apolloendo.com



LAP-BAND
Source: www.apolloendo.com

General Overview

Mechanism of Action

LAP-BAND: Restrictive
OverStitch: Restrictive
Orbera: Filler

Permanent or Temporary

LAP-BAND:
Permanent/Reversible
OverStitch: Temporary
Orbera: Temporary up to 6 months; second procedure to remove.

Regulatory Status

LAP-BAND: FDA approved (2001)
OverStitch: 510(k) clearance (Oct. 2008)
Orbera: PMA submitted (Apr. 2014)

Target Population

LAP-BAND: BMI \geq 40,
BMI \geq 30 with one or more co-morbidities
OverStitch: N/A
Orbera: BMI \geq 27

Company description

Founded in 2006 by the Apollo group, an international think tank of world-renowned gastroenterologists and surgeons from five leading universities, Apollo Endosurgery is a medical device company dedicated to the development of less invasive endoscopic surgery products that help physicians perform a range of bariatric and endoscopic procedures.

History

Apollo acquired the obesity intervention division of Allergan in December 2013 for up to \$110 million (an upfront cash payment of \$75 million, minority equity interest of \$15 million, and up to \$20 million in additional contingent consideration to be paid upon achievement of certain regulatory and sales milestones). The products acquired include the LAP-BAND Adjustable Gastric Band System and the Orbera intragastric balloon system.

Product description

Apollo offers the OverStitch Endoscopic Suturing System, which allows surgeons to place sutures endoscopically in revisional bariatric procedures and GI defect repairs. Additionally, Apollo offers the OverTube Endoscopic Access System and the Tissue Helix., complementary products for endoscopic surgery.

Apollo is currently developing a new product called the SuMO Endoscopic Tissue Access and Resection System, which provides physicians with a means to remove large, flat precancerous gastrointestinal polyps during endoscopic procedures.

Gastric banding

The LAP-BAND system, originally developed by Allergan, is an adjustable gastric banding system. LAP-BAND was the first gastric band on the market and comes in multiple configurations and two different sizes. To date, over 700,000 LAP-BANDS have been implanted worldwide.

Gastric balloon

The Orbera Managed Weight Loss Program, which includes the 6-month Orbera intragastric balloon, was also acquired from Allergan. The Orbera balloon is placed endoscopically in a 20-30 minute outpatient procedure and filled with saline. Approximately 190,000 Orbera procedures have been performed to date outside the US. Orbera is the WW market leading gastric balloon.

Target population

LAP-BAND: Targeted toward patients with BMIs greater than 40 and patients with BMIs greater than 30 with at least one co-morbidity.

Orbera: Targeted toward patients with BMIs of 27 or greater.

Restrictions

LAP-BAND: After a procedure, patients are only able to ingest liquid or pureed foods for two to three weeks after surgery. Vitamin and mineral deficiencies are also common, so patients may need to take dietary supplements.

Cost

LAP-BAND: The approximate cost of LAP-BAND surgery, including the cost of the device, in the US ranges from \$9,000 to \$15,000.

Orbera: The cost of the Orbera Managed Weight Loss procedure, including the device cost of \$500 - \$800, will likely range from \$4,000 to \$7,000 in the US market.

Clinical data

Orbera: Multiple studies have been performed on the balloon. In a 2,515-patient Italian study published in 2005, researchers observed an average EWL of 33.9% at six months. In the same trial, of the patients who initially presented with one or more co-morbidities, 44.3% experienced resolution of their co-morbidities at six months, 44.8% experienced improvement, and 10.9% were unchanged. The overall complication rate was 2.8%.

APOLLO ENDOSURGERY (PRIVATE) (CONTINUED)

COMPANY INFORMATION

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www.apolloendo.com

Email: CustomerService@apolloendo.com

Phone: 512.279.5100



OverStitch System

Source: www.apolloendo.com

LAP-BAND: In Allergan's 299-patient US pivotal trial on the LAP-BAND, which was published in 2000, patients who were able to complete three years of follow-up experienced average EWL of 36% and average TBL of 18% at 36 months.

Regulatory status & strategy

LAP-BAND: LAP-BAND is FDA approved. The first generation device was launched commercially in the US in 2001. The device has been in use in Europe since 1993 and received CE Mark in 1997. Regulatory approval was also gained in multiple other countries in the 1990s, such as Australia, Canada, Israel, and Mexico.

OverStitch: The OverStitch Endoscopic Suturing System was granted 510(k) clearance for marketing in the US in October 2008. OverStitch obtained CE Mark in April 2013.

SuMO: The SuMO system has received 510(k) clearance for marketing in the US.

Orbera: Apollo submitted a PMA application to the FDA for the Orbera balloon in April 2014. Orbera has CE Mark certification and is approved for commercial sale outside the US in more than 60 countries.

Financials

\$11.5M: Venture Financing (2007)

\$47.6M: Venture (February 2012)

\$5M: Venture (July 2013)

\$50M: Debt Financing (December 2013)

\$40M: Private Equity (December 2013)

Management

- Todd Newton – Chief Executive Officer
- Rich Meelia – Chairman of the Board
- Dennis L. McWilliams – Founder, President and Chief Commercial Officer
- Christopher J. Gostout, MD – Chief Medical Officer
- J. Lee Putman – VP of US Sales
- Randy Price – VP of International Sales
- Charlie Dean – R&D Director
- Ted Stephens – VP of Global Marketing

Advisors (Apollo Group)

- Peter Benjamin Cotton, MD
- Christopher J. Gostout, MD
- Robert H. Hawes, MD
- Sergey V. Kantsevov, MD, Ph.D.
- Anthony N. Kalloo, MD
- Pankaj Jay Pasricha, MD
- Sydney Chung, MD

ASPIRE BARIATRICS (PRIVATE)

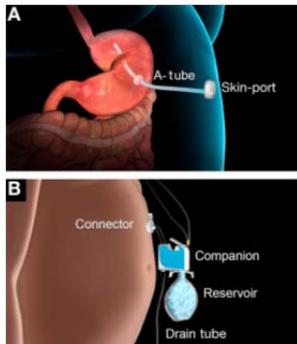
COMPANY INFORMATION

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www.aspirebariatrics.com

Email: info@aspirebariatrics.com

Phone: (610) 590-1577



AspireAssist

Source: Aspire Bariatrics

General Overview

Mechanism of Action

Malabsorptive (portion control at level of stomach)

Permanent or Temporary

Permanent/reversible

Regulatory Status

Current: CE Mark in EU

US pivotal trial underway.
PMA - 2015

Target Population

BMI 35-55+, focused on higher BMI patients.

Company description

Aspire Bariatrics was founded in 2005 by three physicians who specialize in gastroenterology and obesity, and provides aspiration therapy products for the treatment of obesity.

Product description

AspireAssist

The AspireAssist works by reducing the proportion of calories consumed that are ultimately absorbed by the body. After eating, food travels to the stomach, where it is temporarily stored and the digestion process begins. The AspireAssist allows patients to remove about 30% of contents from their stomach before the calories are absorbed.

A specially designed tube called the A-Tube is placed in the stomach during a 20-minute outpatient procedure and connects the inside of the stomach directly to a Skin-Port on the outside of the abdomen. The patient can open the port and “aspirate” 30% of the stomach contents into the toilet after each meal using a small, hand-held device that he or she connects to the Skin-Port. The 5- to 10-minute aspiration process is performed 20 minutes after the patient finishes eating a meal.

The A-Tube can be removed at any time through a 15-minute outpatient procedure, and the stoma typically closes and heals on its own after device removal.

The company believes that the AspireAssist reinforces good dietary habits by requiring patients to chew their food thoroughly and drink significant amounts of water to ensure that food in their stomachs is small enough to be aspirated and by discouraging snacking, as only meals, not snacks, are aspirated.

Target population

The AspireAssist is intended for obese patients with BMIs between 35 and 55. Aspire is currently testing the device in patients with higher BMIs (up to 80 kg/m²) in the EU.

Restrictions

There are no dietary restrictions associated with the device.

Cost

The approximate cost of the device in the European market ranges from €5,000 to €10,000.

Clinical data

According to Aspire, patients who aspirate regularly experience approximately 40% EWL at six months. Aspire Bariatrics has completed a US pivotal clinical trial on the AspireAssist, in which patients lost an average of 46 pounds after one year and an average of 50 pounds after two years.

Regulatory status & strategy

US

The AspireAssist is currently an investigational device in the US and is not available commercially at this time. The US PATHWAY pivotal trial for the AspireAssist completed enrollment in June 2014 with 175 patients at 10 clinical sites with BMIs between 35.8 and 54.3.

Aspire Bariatrics plans to submit a PMA application to the FDA in Q2/15 and expects to receive FDA approval by 2015 at the latest. The company has five US patents issued and eight patent applications pending.

OUS

The AspireAssist received CE Mark approval for sale in Europe in December 2011 and is now available on a limited basis in Europe and select additional regions. The company is beginning postmarketing studies in Italy, the UK, Austria, and Germany as well as continuing postmarket testing in Sweden, the Czech Republic, and Spain.

ASPIRE BARIATRICS (PRIVATE) (CONTINUED)

COMPANY INFORMATION

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Email: info@aspirebariatrics.com

Phone: (610) 590-1577

Financials

Total funding to date: \$30M

Management

- Katherine D. Crothall, Ph.D. – CEO, President and Chairman of the Board
- Audrey Finkelstein – Executive VP of Sales, Marketing, and Clinical Support
- Monica Ferrante – VP of Regulatory & Quality
- Heidi Goldsmith – Clinical
- Sean O'Connor – Research & Development
- Ed Schieferstein – Operations

Advisors

- Dr. Samuel Klein – Co-Founder
- Dr. Moshe Shike – Co-Founder
- Dr. Stephen Solomon – Co-Founder

BARONOVA (PRIVATE)

COMPANY INFORMATION

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Phone: 805-681-7000



TransPyloric Shuttle
Source: BAROnova



TransPyloric Shuttle in the transpyloric position
Source: BAROnova

General overview

Mechanism of action

Flow Control (Slowed
Gastric Emptying)

Permanent or temporary

Temporary – 6 months, 2nd
procedure to remove

Regulatory status

Current: OUS clinical trial
underway

US pivotal trial in 2015

Target population

BMI 30-40

Company description

BAROnova, Inc., founded in 2006 and based in Goleta, CA, is a clinical-stage medical-device company focused on developing non-surgical, non-pharmacologic devices to induce weight loss.

Product description

TransPyloric Shuttle

The TransPyloric Shuttle is an innovative medical device which restricts food from entering into the small intestine from the stomach by repeatedly blocking and unblocking the pyloric valve mechanically. Additionally, after food exits the stomach, there is further resistance, which increases contact time with the walls of the small intestine and is intended to induce satiety from smaller amounts of food.

The TPS is delivered and retrieved endoscopically under sedation and does not require any fixation to anchor the device. BAROnova uses medical grade silicone to construct the device, which is 100 cubic centimeters in volume.

Target population

The device has been successfully tested in patients with BMIs between 30 and 50; however, the company is initially targeting patients with BMIs in the range of 30 to 40.

Restrictions

There are no dietary restrictions associated with the TPS, nor are patients required to take dietary supplements.

Cost

US patients can expect the total cost of the implantation procedure, including the cost of the device, to be approximately \$6,000 to \$7,000.

Clinical data

BAROnova recently completed its ENDObesity I study, a six-month clinical trial on the TransPyloric Shuttle in Australia with 20 patients in the 30-50 BMI range. In the ENDObesity I study, the TransPyloric Shuttle remained in the patients' stomachs for between three and six months.

There were no procedure-related safety issues or extended hospital stay complications prior to discharge associated with the trial. After six months, the average EWL was 50.0% for the entire trial population and 58.4% for the subset of patients in the 30-40 BMI range.

Regulatory status & strategy

US

The company plans to begin its pivotal trial in the US within the next 12 months using patients in the 30-40 BMI range.

OUS

No regulatory clearances OUS.

Financials

Total funding to date: \$50M

Series A: \$6.5M – Highland Capital Partners, ONSET Ventures, Arboretum Ventures

Series B: \$7.5M – ONSET Ventures, Allergan, Highland Capital Partners, Arboretum Ventures

Series C: \$27.3M (February 2013) – Boston Scientific, Sante Ventures, Arboretum Ventures, Highland Capital Partners, ONSET Ventures, Lumira Capital

Management

- Hugh Narciso – Founder, CEO and President
- Lian Cunningham, MD, Ph.D. – VP of Clinical Affairs
- Kobi Iki – VP of Research & Development

Strategic medical advisors

- Richard Rothstein, MD
- Frank Greenway, MD
- Raman Muthusamy, MD
- David Sarwer, Ph.D.

BETA-STIM (PRIVATE)

COMPANY INFORMATION

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North Industrial Park
Caesarea, 38900
Israel

www.betastim.com

General overview

Mechanism of action

Appetite Suppression

Permanent or temporary

Permanent/Reversible

Regulatory status

Current: Developmental stage

Target population

Unknown

Company description

Beta-Stim LTD is a medical device company developing a minimally invasive implantable pulse generator (IPG) that seeks to treat obesity and type 2 diabetes by applying electrical stimulation to the duodenum in the small intestine. Although the company is primarily targeting type 2 diabetics with the IPG, the device also has applications in the treatment of obesity.

Product description

Gastric stimulation

Beta-Stim's Implantable Pulse Generator (IPG) is a "balance system," designed to control blood sugar levels in type 2 diabetics through intestinal electric stimulation. When food reaches the stomach, the balance system detects it and the treatment procedure is activated. Intestinal electric stimulation closes the pyloric sphincter, where the contents of the stomach empty into the duodenum, and enhances duodenal motility.

Closing the pyloric sphincter delays gastric emptying, leading to early satiety, and allows only small portions of food to pass from the stomach to the duodenum. By enhancing duodenal motility, the IPG causes the small food portions to travel through the duodenum quickly, leaving less time for fats and sugars to be absorbed. Thus, the body handles less fat and sugar at any single moment and absorbs less fat and sugar overall.

The system consists of two parts: an internal part, with an implantable pulse generator and two electrodes, and an external part, which includes a wand programmer and dedicated medical computer. Wireless communication between all system components allows physicians to easily adjust therapy parameters.

Target population

The company has not disclosed this information.

Restrictions

Beta-Stim claims that the IPG is able to keep blood sugar balanced with no need for additional medications, treatment, and (or) no side effects.

Cost

The company has not disclosed this information.

Regulatory status & strategy

The IPG is a developmental stage product. It is not available for commercial sale anywhere in the world.

Financials

The company does not disclose this information.

Management

The company does not disclose this information.

BKFW (PRIVATE)

Company description

BKFW, a clinical stage company, has developed the Full Sense Device (FSD). The device is a temporary implant that induces continuous satiety leading to significant weight loss and resolution of comorbidities.

Product description

The Full Sense Device is a temporary and fully reversible bariatric procedure, deployed and removed via endoscopy. The implanted device induces satiety in patients and does not require a modified diet or dependency on food intake as part of the mechanism of action. It incorporates an esophageal component and a gastric disk connected by struts that allow for complete functioning of the GE junction. FSD is comprised of braided nitinol with a silicone coating. FSD is unique as it is designed to induce satiety and fullness in the absence of food by placing pressure on the distal esophagus and cardiac region of the stomach. Further the FSD does not interfere with other body functions, such as the normal reflux mechanism, bile ducts, absorption of nutrients or medications, and the like. Unlike gastric banding and gastric bypass, which require the presence of food in the stomach to cause satiety (resulting in intermittent or transient satiety), this novel invention utilizes a new principle of “continuous implied satiety” to achieve significant EWL in the absence of food being present in the stomach and without the need for major surgery.

Clinical data

BKFW continues to gain clinical experience and has implanted over 85 Full Sense Devices in humans. In one study, a three-month randomized blind trial of the device, patients had an average BMI of 41. In an eighteen patient study, for the three-month period, the average EWL was 42% vs. the control group EWL of 15.3%. Statistical significance was achieved in week 2 with a final p value of 0.0016. A cross-over study was performed on control patients from the randomized study which also showed a statistical significant EWL difference. As with this and other studies, there were zero non-respondents and patients recorded increased satiety. In longer duration studies, with implant durations of up to six months, EWL of 74% was observed.

Target population

Obese patients with BMI 30 or higher

Restrictions

Patients will be required to be on a liquid diet post implantation for up to two weeks.

Cost

The estimated cost of the procedure will be less than \$10,000 with all follow-up care included.

Regulatory status & strategy

US

Full Sense does not have regulatory approval

OUS

The next milestone is to obtain design freeze using the first-in-man (FIM) devices from the well-established German based supply chain to be evaluated in Mexico. The goal is to attain CE Mark by Q1 2015. The company would like to commercialize in Europe, Latin America, and EMEA once CE Mark is achieved.

Financials

The company has raised money internally from private investors.

Management

- Fred Walburn
- Barry Smith

Advisors

The company utilizes several advisory groups to support its objective of device commercialization.

COMPANY INFORMATION

BKFW
6223 Cascade Pointe Dr. SE
Grand Rapids, MI 49546



Full Sense™ Device
Source: BKFW

General overview

Mechanism of action
Appetite Suppression

Permanent or temporary
Temporary – 6 months;
second procedure to
remove

Regulatory status
Current: Conducting OUS
clinical trials

Target population
Obese patients with BMI
>35

CROSPON (PRIVATE)

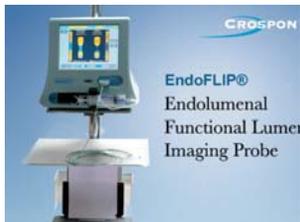
COMPANY INFORMATION

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Phone: 1-855-CROSPON



EndoFLIP Imaging System

Source: www.crospn.com

General overview

Mechanism of action

Restrictive

Permanent or Temporary

N/A

Regulatory status

FDA approved (2009)

Target population

BMI \geq 30

Company description

Crospn was founded in 2006 and is developing minimally invasive medical devices for imaging and aiding in surgery in the esophagus and stomach.

Product description

EndoFLIP

The EndoFLIP (Endolumenal Functional Lumen Imaging Probe) Imaging System is the first of a range of products that Crospn plans to bring to market. EndoFLIP is a technology used to measure the dimensions and function of various hollow organs and sphincteric regions throughout the gastrointestinal tract. EndoFLIP has applications in gastric band surgery, gastric imbrication/plication, and bariatric revision surgery.

Gastric banding: In gastric band surgery, the EndoFLIP allows a surgeon to set a consistent band stoma diameter at surgery for every patient, which minimizes the risk of the band being too tight at the completion of surgery and allows the surgeon to assess if sufficient peri-gastric fat has been removed to create an adequate stoma size.

Gastric imbrication/plication: Gastric imbrication is an experimental procedure that allows surgeons more control over how much stomach restriction is accomplished during surgery and offers patients a reversible bariatric surgery option. Like sleeve gastrectomy, gastric imbrication restricts the amount of food a patient can consume; however, gastric imbrication does not require the removal of any part of the stomach. Crospn's EndoFLIP is used to fold the greater curve of the stomach in on itself and suture the folds in place. The first EndoFLIP gastric imbrication procedure was performed in May 2010.

Revision surgery: In bariatric revision surgery, the EndoFLIP catheter can be deployed into a stoma to measure its diameter in order to assess whether stoma repair is required and/or whether adequate repair has been achieved. However, the use of the EndoFLIP in bariatric revision surgery is not currently a cleared Indication of Use by the FDA for the product in the US.

Target population

EndoFLIP bariatric procedures are targeted toward patients with BMIs greater than or equal 30.

Regulatory status & strategy

US

Crospn received 510(k) FDA clearance for EndoFLIP in December 2009. Crospn also received further approval for various additions to the EndoFlip system, such as catheters and gastric tubes, in subsequent years in both the EU and the US.

OUS

The company received CE Mark certification for EndoFLIP in January 2009.

Financials

The company does not disclose this information.

Management

- John O'Dea – CEO and Chairman of the Board
- Caroline Sherlock – Director of Operations
- Adrian McHugh – Director of Engineering

ENDOBTIX (PRIVATE)

COMPANY INFORMATION

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Israel

www.endobetix.com

Email: chen@endobetix.com

Phone: +972.72.260.7000



Bile Diversion Device
Source: www.endobetix.com

General overview

Mechanism of action
Malabsorptive

Permanent or temporary
Permanent/reversible

Regulatory status
Current: Developmental
stage - animal trials
underway

Target population
Obese type 2 diabetics,
BMI 30-35

Company description

Endobetix is an early-stage medical device company founded in 2012 and developing a minimally invasive treatment for type 2 diabetes and obesity that attempts to mimic the hormonal balance changes achieved by bariatric surgery.

Product description

Endobetix Bile Diversion Device (BDD)

The BDD is implanted endoscopically in the small intestine and employs a small tube, which is approximately 60 centimeters in length, to bypass the duodenum and prevent bile fluids from mixing with partially digested stomach chyme. The tube then deposits the bile fluids into the lower part of the smaller intestine.

This diversion and separation of bile from food alters the body's hormonal balance and induces the release of important hormones, such as GLP-1, which improves glucose tolerance in type 2 diabetics and reduces fat absorption, encouraging weight loss and diabetes resolution.

The device takes 15 to 20 minutes to implant.

Target population

The BDD is intended for obese type 2 diabetics with lower BMIs within the obesity classification (approximately 30 to 35).

Restrictions

According to the company, the BDD has fewer dietary constraints than other devices and surgery options.

Cost

The company does not disclose this information.

Regulatory status & strategy

OUS

Endobetix is currently conducting animal trials and plans to begin human trials in 2015-2016. The company hopes to be awarded CE Mark in the next three years.

US

Endobetix does not plan to pursue US approval until after the BDD has achieved CE Mark.

Financials

Total funding to date: Approximately \$1M

Management

- Chen Porat, MBA – CEO and Co-Founder
- Pierre Sharvit, DVM – Chief Technology Officer and Co-Founder
- Shlomo Lewkowicz, D.Sc. – VP of Clinical & Regulatory Affairs and Co-Founder
- Jean-Paul Rasschaert – VP of Business Development (USA)

Advisors

- Ori Segol, MD
- Peter D. Siersema, MD, Ph.D.
- Stacy Alan Brethauer, MD
- Douglas Pleskow, MD, AGAF, FASGE
- Randy J. Seeley, Ph.D.

ENDOGASTRIC SOLUTIONS (PRIVATE)

COMPANY INFORMATION

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Phone: 650-578-5100

www.endogastricsolutions.com

Email:
info@endogastricsolutions.com



EsophyX
Source:
www.endogastricsolutions.com

General overview

Mechanism of action
Restrictive

Permanent or temporary
N/A

Regulatory status
FDA Approved

Target population
N/A

Company description

EndoGastric Solutions is a medical device company that develops natural orifice surgical products and procedures to advance the treatment of gastrointestinal diseases.

Product description

Transoral Incisionless Fundoplication

The EsophyX device transorally allows a surgeon to create a 270°, 2-3cm esophagogastric fundoplication for the treatment of GERD by using proprietary tissue manipulating elements and polypropylene fasteners. The device is used in conjunction with an endoscope. The EsophyX can also be used for endoluminal bariatric procedures.

Financials

Series A: \$5M (May 2003): Advanced Technology Ventures.

Series B: \$12M (Aug. 2004): MPM Capital, Foundation Medical Partners, and Advanced Technology Ventures.

Series C: \$32M (Feb. 2006): Chicago Growth Partners, and included participation by existing investors MPM Capital, Advanced Technology Ventures, Foundation Medical Partners.

Series D: \$30M (Aug. 2007)

Series E: \$21.5M (November 2009): Led by previous investors.

Series F: \$13M (August 2010): Led by Canaan Partners and Radius Ventures, and included participation by existing investors Advanced Technology Ventures, MPM Capital, Foundation Medical Partners, Chicago Growth Partners, and De Novo Ventures.

Extension of 2010 Series F funding: \$13M (June 2012): Advanced Technology Ventures, Canaan Partners, Chicago Growth Partners, De Novo Ventures, Foundation Medical Partners, Oakwood Medical Investors, and Radius Ventures.

Series G: \$30M (May 2014): Advanced Technology Ventures, Canaan Partners, Chicago Growth Partners, De Novo Ventures, Foundation Medical Partners, Oakwood Medical Investors, and Radius Ventures.

Management

- Skip Baldino – CEO and President
- Darren Crow – General Manager, Redmond Operations
- Josh DeFonzo – VP of Marketing
- Adrian Lobontiu, MD, FACS – Medical Director

Advisors

- Reginald Bell, MD
- John Hunter, MD
- Blair Jobe, MD

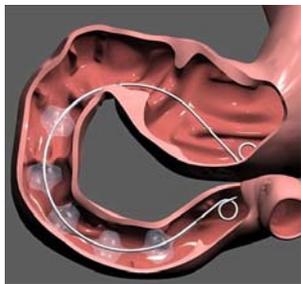
ENDOSPHERE (PRIVATE)

COMPANY INFORMATION

4449 Easton Way, 2nd Floor
Columbus, OH 43219

www.endosphereinc.com

Email: info@endosphereinc.com



SatiSphere
Source: EndoSphere

General overview

Mechanism of action

Flow Control

Permanent or temporary

Temporary – 3 months, 2nd procedure to reverse.

Regulatory status

Current: CE Mark in EU

US pivotal trial – 2016

Target population

BMI 30-40

Company description

EndoSphere is developing an endoscopically implantable duodenal insert that assists patients in losing weight and controlling type 2 diabetes by slowing the passage of chyme through the duodenum, the upper portion of the small intestine, thereby amplifying neurohormonal satiety signals.

Product description

SatiSphere

The SatiSphere System is an intestinal/duodenal artificial fullness device. The C-shaped insert is roughly 25 cm long and is placed in the duodenum and antrum. The implant restricts flow through upper GI tract using polymer spheres distributed along the length of the nitinol backbone, delaying the passage of chyme through the duodenum and increasing the contact time between the partially digested food and the nerve receptors of the duodenum.

This process is thought to induce satiety from a smaller volume of food and help regulate glucose production. In addition, the slowing of the digestion process prevents patients from consuming large volumes of food by “tricking” the brain into believing that adequate amounts have been consumed. The SatiSphere takes 5 to 15 minutes to implant in an outpatient endoscopy suite and is removed three months later in a procedure of the same duration.

Target population

The SatiSphere is intended for obese patients with BMIs ranging from 30 to 40, with or without comorbidities.

Restrictions

The company does not disclose this information.

Cost

The company does not disclose this information.

Regulatory status & strategy

US

SatiSphere has not been approved by the FDA and is not commercially available in the US at this time, but hopes to have IDE approval and begin its US pivotal study in 2016.

OUS

The SatiSphere System has CE Mark and is now conducting a post-market study on the product. EndoSphere hopes to have SatiSphere commercially available in Europe in 2016.

Financials

Total funding to date: Approximately \$8M

Investors include Broadline Capital and Ohio TechAngels Fund.

Management

- Patrick O'Donnell - CEO and President
- Chris Thorne - Executive Chairman of the Board
- Kenneth Binmoeller, MD - Founder and Medical Director
- Fiona M. Sander - VP of Research & Development
- Vladimir Scerbin – VP of Clinical Affairs

Advisors

- Kenneth Binmoeller, MD
- David Cummings, MD
- Michael Federle, MD
- Hideo Makimura, MD, Ph.D.
- Tomasz Rogula, MD
- Scott Shikora, MD
- William Snape, MD
- Lee M. Kaplan, MD, Ph.D.

ENTEROMEDICS (ETRM : NASDAQ : \$1.03 |BUY)

COMPANY INFORMATION

2800 Patton Rd.
St Paul, MN 55113
www.enteromedics.com
Phone: 651-634-3003



VBLOC Maestro System
Source: EnteroMedics

General overview

Mechanism of action
Appetite Suppression

Permanent or temporary
Permanent/reversible

Regulatory status
Current: Completed US pivotal trial; went before an FDA Advisory Committee Panel in June 2014 resulting in a favorable benefit-risk and safety vote as well as a mixed efficacy vote
Expected FDA Approval - 2015

Target population
Obese patients

Company description

EnteroMedics has developed VBLOC vagal blocking therapy, a novel neuroscience-based approach to treating obesity and its related co-morbidities.

Product description

The Maestro System, which delivers VBLOC therapy, implantable components are comprised of a subcutaneously implanted rechargeable neuroregulator and two electrodes that are laparoscopically implanted in a short, outpatient procedure. The electrodes send signals that intermittently block vagal nerve function to create the effect of satiety.

Target population

The Maestro system is intended for obese patients.

Cost

The company does not disclose this information.

Clinical data

Multiple trials have been conducted, and over 600 patients have been implanted with the Maestro System to date. Overall, VBLOC Therapy has demonstrated a positive safety profile including cardiovascular safety. Minimal side effects, mainly transient discomfort at the neuroregulator implantation site and sensations of therapy-like heartburn, have been reported. Efficacy across all trials has resulted in ~25% EWL at 12 months and sustained durable weight loss out to 36 months+ in trials.

EnteroMedics completed the first 12 months of its ReCharge US pivotal Study in which 233 patients were implanted in a double-blind, sham-controlled study. In this study, the safety endpoint was met with a 3.7% implant/revision procedure, device, or therapy-related SAE rate at 12 months, which was substantially below the <15% performance. In the Intent-To-Treat patient populations at 12 months, EWL was 24.4% for the treatment (Tx) group as compared to 15.9% for the control group. The margin missed the predefined threshold set by the FDA; however, VBLOC therapy did demonstrate superiority over the sham. >20% EWL was experienced by 52.5% of the Tx patients and 38.3% of the Tx patients experienced >25% EWL, both missing their predefined responder rates of 55% and 45%, respectively.

Regulatory status & strategy

US

A PMA filing for the Maestro system was submitted in June 2013. In June, 2014 EnteroMedics went before an FDA Advisory Committee, a panel of medical experts, for their opinion on the benefit-risk, safety and efficacy of VBLOC therapy. The panel voted favorably on the benefit-risk profile and safety of VBLOC therapy, and a mixed efficacy vote. The next steps will be to continue dialogue with the FDA and gain clinical approval by 2015.

EnteroMedics is also pursuing reimbursement for VBLOC therapy. The company has already obtained six Category III CPT codes and plans to start conversion to CPT I codes upon FDA approval.

OUS

The Maestro System obtained CE Mark in March 2011 and has been listed on the Australian Register of Therapeutics Goods for supply in Australia.

The company is pursuing reimbursement in both Australia and select CE Mark accepted geographies.

Financials

As of June 30, 2014, EnteroMedics has \$21.7 million in cash.

Management

- Mark B. Knudson, Ph.D. - Chairman, CEO and President
- Gregory S. Lea – Sr. VP, Chief Operating Officer and Chief Financial Officer and Sr. VP
- Daniel L. Cohen – Sr. VP of Government Relations & Health Policy
- Adrianus Donders - Sr. VP of Research & Advanced Development
- Scott Shikora, MD, FACS – Consulting Chief Medical Officer
- Katherine Tweden, Ph.D. – VP of Clinical & Regulatory

GI DYANMICS (GID : ASX : A\$0.28 | NOT RATED)**COMPANY INFORMATION**

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25 Hartwell Ave.
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Phone: 781-357-3300

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4 Columbia Court
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Australia
Phone: + 61 2 9325 9046

www.gidynamics.com
Email: info@gidynamics.com



EndoBarrier
Source: GI Dynamics

General overview

Mechanism of action
Malabsorptive

Permanent or temporary
Temporary – 6 months – 1 year; 2nd procedure for removal.

Regulatory status
Current: CE Mark in EU for diabetes and/or obesity

Pivotal trial underway in US

Target population
Obese type 2 diabetics

Company description

GI Dynamics, founded in 2003 and headquartered in Lexington, MA, develops medical devices to address the epidemic of metabolic diseases such as type 2 diabetes and obesity.

Product description*Endoscopically-delivered device therapy*

EndoBarrier Therapy uses an endoscopically-delivered liner that creates a physical barrier between ingested food and the intestinal wall, preventing the interaction of food with hormones and enzymes in the proximal intestine. In effect, food bypasses the duodenum as in R-Y gastric bypass, but without surgery. EndoBarrier is approved for up to 12 months and is then removed during a brief endoscopic procedure.

Clinical data suggest that treatment with EndoBarrier Therapy affects key gastrointestinal hormones involved in insulin sensitivity, glucose metabolism, satiety and food intake. Studies have shown that EndoBarrier Therapy:

- Has an immediate effect on lowering blood glucose levels
- Results in an average 17% total body weight loss in one year
- Potentially improves cardiometabolic risks, including blood pressure, total cholesterol, LDL and triglycerides

Regulatory status & strategyUS

GI Dynamics is currently conducting a pivotal clinical trial to evaluate the efficacy and safety of EndoBarrier in the treatment of people with uncontrolled type 2 diabetes and obesity (the ENDO Trial). The primary endpoint is improvement in diabetes control as measured by HbA1c levels with secondary endpoints including weight loss, reduction in blood pressure and reductions in LDL and triglycerides. As of June 30, 2014, 22 of a possible 25 clinical sites across the U.S. have initiated patient recruitment in the ENDO Trial. Also as of June 30, 2014, 168 patients have been enrolled in the study out of a total of 500 patients required. Completion of enrollment is targeted for mid-2015.

EndoBarrier is not approved for sale in the U.S. and is limited by federal law to investigational use only in the United States.

OUS

EndoBarrier currently has the CE Mark permitting sale within the European Union, as well as approvals from various countries around the world. EndoBarrier is currently being commercially sold in Germany, the Netherlands, the United Kingdom, Austria, Switzerland, Israel, Chile and Australia. As of June 30, 2014, EndoBarrier Therapy is being offered at 60 centers worldwide.

Financials

Total funding to date: \$238M

IPO on Australian Stock Exchange: A\$80M (September 2011).

Post-IPO Equity: A\$59.9M (July 2013)

Post-IPO Equity: \$34.3M (May 2014)

Investors include M&G and affiliates, Capital Group, Medtronic, Inc., Advanced Technology Ventures, Johnson & Johnson, Greenlight Capital, Hunter Hall.

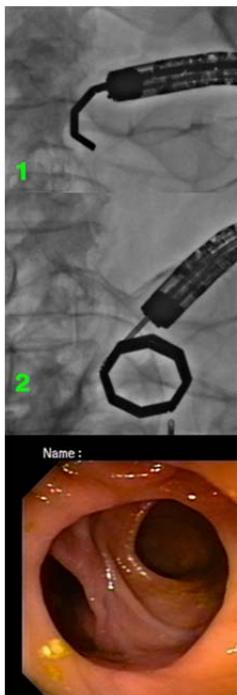
Management

- Michael Dale – President and Chief Executive Officer
- Robert Crane – Chief Financial Officer
- David Maggs, MD – Chief Medical Officer
- Karl Blohm, Ph.D. – Vice President, International

GI WINDOWS (PRIVATE)

COMPANY INFORMATION

GI Windows
375 West Street
West Bridgewater, MA 02379



Source: GI Windows

General overview

Mechanism of action
Malabsorption

Permanent or temporary
Permanent/reversible

Regulatory status
Current: Pre-clinical studies

Target population
Obese patients with BMI of 35-50 with or without type 2 diabetes.

Company description

GI Windows is a pre-clinical stage company formed in 2012 and based on intellectual property obtained from Beacon Endoscopic (recently acquired by Covidien). The company is developing endo-luminal procedures to treat type 2 diabetes and obesity by creating anastomoses that bypass portions of the GI tract.

Product Description

GI Windows devices can be delivered through a catheter or standard endoscope channel. As they are deployed, the devices change from a linear, flexible shape and self-assemble to form larger octagonal geometries. These octagons serve as the structure to create a large-diameter, compression anastomosis. The anastomosis fully forms in 7-10 days and the devices pass naturally through the GI tract. No foreign body is left behind. With this technology, portions of the GI tract, such as the stomach or small bowel, can be bypassed, as commonly done in metabolic surgical procedures. Yet the devices that create the bypass are delivered without incisions. The anastomosis creating the bypass can remain in place permanently. Pre-clinical studies have shown that minimal scarring and an absence of adhesions characterize these anastomoses. The company has demonstrated that the procedures can be easily reversed if desired.

Regulatory status & strategy

GI Windows has completed animal and cadaver trials and plans to begin first-in-man trials by YE2014. The trial design will focus primarily on safety and procedure reproducibility, but weight loss and other metabolic syndrome endpoints will also be measured.

Target population

The GI Windows endo-luminal anastomosis procedures are intended for obese patients with BMI 35-50 with or without type 2 diabetes.

Cost

The company does not disclose this information.

Financials

The company has raised \$2.3M to date through debt financing.

Management

- James Wright – President and CEO
- Peter Lukin – SVP, Development and Operations

Advisors

- Chris Thompson, MD, MSc., Director, Bariatric and Developmental Endoscopy, Brigham and Women's Hospital
- Laurent Biertho, MD, Clinical Professor, Department of Surgery, Laval University
- Donald Simonson, M.D., M.P.H., Sc.D. Division of Endocrinology, Diabetes and Hypertension, Brigham and Women's Hospital
- Paul Akerman, MD, Assistant Clinical Professor, Brown Medical School
- David Lautz, MD, FACS, Massachusetts General Hospital
- Marvin Ryou, MD, Interventional Gastroenterology, Brigham and Women's Hospital, Instructor Harvard Medical School

HELIOSCOPIE (PRIVATE)

COMPANY INFORMATION

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38200 Vienne – France

www.helioscopie.fr

Phone: +33(0)4 74 16 18 18



Heliosphere BAG

Source: www.helioscopie.fr

General overview

Mechanism of action

Gastric bands: restrictive

Heliosphere BAG: Filler

Permanent or temporary

Gastric bands:
Permanent/reversible

Heliosphere BAG:
Temporary

Regulatory status

Current: CE Mark in EU for all products

No current plans to enter US market

Target population

Gastric bands: BMI \geq 40,
BMI \geq 30 with one or more co-morbidities

Heliosphere BAG:
BMI 30-40

Company description

HelioScopie is a French medical device company developing both surgical and non-surgical products for the treatment of obesity.

History

HelioScopie was acquired by Santé Actions in October 2010. Dr. Sauveur Ferrara, the president and founder of the Santé Actions group (a French healthcare company), became the new president of HelioScopie at the time of the merger.

Product description

Intragastric balloon

HelioScopie's Heliosphere BAG is a six-month intragastric balloon. The balloon has a volume of 550 cubic centimeters. The balloon is filled with air and weighs less than 30 grams, limiting patient nausea and vomiting. The balloon is intended for patients with BMIs in the range of 30 to 40.

Adjustable gastric band

Gastric band implantations currently make up 75% of bariatric procedures performed in France.

HelioScopie has developed two types of bands, the HELIOGAST HAGA and the HELIOGAST HAGE.

HelioScopie has marketed more than 60,000 Heliogast gastric bands in the world to date. Both bands come with the EV3 adjustment system, the only implantable port in the world with 360° accessibility, which precludes all complications related to the rotation of traditional adjustment ports.

The HELIOGAST HAGA is the only band of its kind to have an adjustable “double balloon” membrane designed to increase the stability of the band and limit slippage.

Restrictions

HELIOGAST gastric bands: After a gastric banding procedure, patients are only able to eat liquid or pureed foods for two to three weeks after surgery. Vitamin and mineral deficiencies are also common, so patients may need to take dietary supplements. Patients may not drink carbonated beverages.

Clinical data

HelioSphere BAG: HelioSphere has conducted five international trials on a total of more 670 patients. These trials have resulted in measured weight loss between 9 kilograms (19.8 pounds) and 24 kilograms (52.9 pounds).

HELIOGAST gastric bands: The company reports 68% EWL after five years of treatment with Heliogast gastric bands.

Regulatory status & strategy

US

HelioScopie has no current plans to enter the US market.

OUS

HelioScopie has secured CE Mark for all of its products. The company's products are marketed in more than 30 countries.

Financials

The company does not disclose this information

Management

- Sauveur Ferrara – President

JOHNSON AND JOHNSON (JNJ : NYSE : \$99.20 | NOT RATED)

COMPANY INFORMATION

One Johnson & Johnson Plaza
New Brunswick, NJ 08933

www.jnj.com

www.ethicon.com

www.realize.com

Phone: 1-855-273-2549



REALIZE Adjustable Gastric Band
Source: REALIZE

General overview

Mechanism of action

Restrictive

Permanent or temporary

Permanent/reversible

Regulatory status

FDA approved (Sep. 2007)

Target population

BMI \geq 40, BMI \geq 35 with
one or more comorbidities

Company description

Johnson & Johnson (Ethicon Endo-Surgery) develops and markets medical devices for minimally invasive and open surgical procedures treating morbid obesity, as well as multiple other sectors such as orthopedics, diabetes, and cardiovascular. Ethicon Endo-Surgery has products on the market serving both gastric bypass and adjustable banding surgical procedures.

History

The company was founded in 1885 and is based in New Brunswick, New Jersey. Ethicon was formed as a separate company in 1992. Ethicon acquired Obtech Medical AG (a Swiss company), developer of the Swedish Adjustable Gastric Band (SAGB), in 2002.

Product description

Laparoscopic gastric banding

The REALIZE Adjustable Gastric Band is one of only two gastric bands approved for commercial use in the US.

Target population

The REALIZE Band is targeted toward patients with BMIs greater than 40 and patients with BMIs greater than 35 with at least one comorbidity.

Restrictions

After a gastric banding procedure, patients are only able to eat liquid or pureed foods for two to three weeks after surgery. Vitamin and mineral deficiencies are also common, so patients may need to take dietary supplements.

Cost

Generally, the cost of the REALIZE Band procedure is equivalent to that of the LAP-BAND procedure. The total cost typically ranges from \$10,000 to \$20,000.

Clinical data

The pivotal trial for the REALIZE Band showed an average of 42.8% EWL at three years (n=276), with 3.3% experiencing serious adverse events (nausea, vomiting, constipation and GERD).

Regulatory status & strategy

US

The REALIZE Band gained FDA approval in September 2007 and launched in Q1 2008.

OUS

The REALIZE Band has been available outside the US since 1996 and is marketed under the name Swedish Adjustable Gastric Band (SAGB).

Management

- Alex Gorsky - Chairman, CEO, Chairman of Executive Committee and Chairman of Finance Committee
- Dominic J. Caruso - Chief Financial Officer, Corporate Vice President of Finance and Member of Executive Committee
- Gary Pruden - Worldwide Chairman - Global Surgery Group

METACURE LIMITED (PRIVATE)

COMPANY INFORMATION

Israel Office:

7 Atir Yeda (P.O.B 509)
Kfar-Saba, 44104

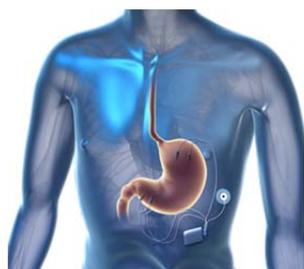
US Office:

30 Ramland Rd., Suite 101
Orangeburg, NY 10962

www.metacure.com

Phone: +49 7112 204 560

Email: info@metacure.com



DIAMOND System

Source: www.metacure.com

General Overview

Mechanism of Action
Appetite Suppression

Permanent or Temporary
Permanent/Reversible
(intended for long-term type 2 diabetes treatment; battery designed to last at least 5 years)

Regulatory Status
Current: CE Mark in EU

No current plans to enter US market

Target Population
Obese type 2 diabetics, BMI 30-45

Company description

MetaCure has developed a gastric stimulation device for the treatment of type 2 diabetes and obesity. The system is targeted toward type 2 diabetics who are also obese and is designed to improve blood glucose levels as well as induce weight loss, reduction in waist circumference, and improvement in blood pressure, cholesterol, and triglyceride levels.

Product description

Gastric stimulation

The DIAMOND System (Diabetes Improvement and Metabolic Normalization Device, formerly the TANTALUS System) is a minimally invasive implantable electric stimulator used to apply gastric stimulation. The system is designed to sense when the patient is eating and automatically apply electrical stimulation during meal times. This stimulation enhances the activity of gastric muscles while eating, which modifies hormone secretion, favorably affecting glucose and fat metabolism. The stimulation also causes patients to feel satiated earlier, reducing food consumption.

The DIAMOND System consists of the DIAMOND Implantable Pulse Generator (IPG), which is implanted (along with electrodes) in a minimally invasive laparoscopic surgical procedure. The charger system is placed over the patient's abdomen for 45 minutes, once a week to recharge the IPG, and a programmer system, which allows the physician to adjust the DIAMOND System's signal parameters according to patient needs.

Over 200 patients have been implanted with the DIAMOND System to date. Many patients keep the system in place for over two years, and some keep it for over four years. The rechargeable battery is designed to last for at least five years. Patients who are implanted with the DIAMOND System are typically able to start eating a few hours after surgery and remain in the hospital for one to two days post-surgery.

Target population

The DIAMOND System is intended for obese type 2 diabetics with BMIs between 30 and 45.

Restrictions

The company does not report any dietary restrictions. Contact sports or other activities that could damage the system are not recommended.

Cost

The company does not disclose this information.

Clinical data

Average weight loss of 4.2 kilograms was observed across MetaCure's multiple clinical studies, with a maximum weight loss of 28 kilograms recorded. Significant reductions of HbA1c levels were also observed (the average decrease in individual trials was as high as 1%, with individual patient HbA1c level reductions as high as 3%).

Regulatory status & strategy

US

The DIAMOND System is not commercially available in the US. MetaCure has no current plans to enter the US market.

OUS

The DIAMOND System was granted a CE Mark in 2006 for the treatment of obesity. The product also received a CE Mark in January 2007 for the indication to treat patients with type 2 diabetics with obesity. The system is currently available in select European and Asian locations.

Financials

Series B: \$20M (May 2009); Morningside Group

Management

- Mateusz Zelewski, MD, Ph.D. – General Manager
- Amir Cohen, MA – Chief Financial Officer

Advisors

- Prof. Harold Lebovitz, MD, FACE
- Prof. Thomas Haak, MD
- Prof. Dirk Muller-Wieland, MD
- Prof. Henry Buchwald, MD
- Dr. Yehuda Handelsman, MD, FACP, FACE, FNLA
- Prof. Philip R. Schauer, MD
- Prof. Michael Berelowitz, MB ChB, FCP(SA), FACP

OBALON (PRIVATE)

COMPANY INFORMATION

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Carlsbad, CA 92008

www.obalon.com

Phone: +1.760.607.5151



Obalon balloon capsule (left) and inflated Obalon balloon (right)
Source: Obalon

General overview

Mechanism of action

Filler

Permanent or temporary

Temporary – 3 months, 2nd procedure to remove

Regulatory status

Current: CE Mark in EU,
Cofepris in Mexico,
Approvals in Middle East

Investigational in US,
FDA approval expected in
2016

Target population

BMI 27-40

Company description

Obalon has developed a swallowable, gas-filled intragastric balloon system for weight loss, in which up to three balloons can be placed over the course of a three-month therapy period.

Product description

Intragastric balloon

Obalon balloons are unique in that patients swallow the balloons in a small capsule attached to a thin tube, rather than having them implanted endoscopically. After the patient swallows the capsule, it opens up and releases the balloon in the stomach. The physician confirms the placement of the balloon using an x-ray and then uses a device to fill the balloon with nitrogen through the tube. The physician then detaches the tube from the balloon and pulls the tube out through the patient's mouth. The procedure can be performed without sedation or anesthesia, differentiating it from other gastric balloons on the market.

Obalon offers patients the opportunity to increase the number of balloons they have in their stomach for continued weight loss over the entire therapy period. Their initial balloon volume is smaller, offering patients flexibility and preventing most of the discomfort that often results from the implantation of the larger balloons currently on the market. Due to their small size and the fact that they can be placed without a procedure, up to three balloons can be inserted over the course of the 12-week treatment period. Approximately one third of patients eventually receive all three balloons, with the other two thirds stopping after one or two balloons. All of the balloons are removed three months after the implantation of the first balloon during a short endoscopic procedure.

Target population

The Obalon balloon is approved and commercially available in select international markets for patients with BMIs of 27 and above. The primary target is for patients with BMIs between 27 and 40.

Restrictions

Patients must drink only clear liquids the day of placement and eat only soft foods the day after the procedure, but may return to solid foods by the third day.

Clinical data

Obalon has conducted seven clinical trials. The most recent was a 110-patient study spread over 11 different sites with an average starting BMI of 33.1. The study resulted in 50.2% average EWL.

Regulatory status & strategy

US

The balloon is limited to investigational use only in the US. Obalon expects FDA approval for the use of the balloon in the US in 2016. The company also hopes to develop a self-deflating and self-passing balloon, eliminating the need for the endoscopic removal procedure that is used currently. Obalon has 6 US patents, 12 patents outside the US, and more than 20 patents pending.

OUS

The Obalon balloon has CE Mark approval and is currently available commercially in Europe, the Middle East, and Mexico.

Financials

Total funding to date: \$35M

Management

- Andy Rasdal – CEO
- Mark Brister – VP of Research & Development
- Adlai Howe – VP of Sales
- Nooshin Hussainy – VP of Finance
- Steve Johnson – VP of Operations
- Mark Mahmood – VP of Marketing
- Alan Marcovecchio – VP of Clinical Affairs
- Amy VandenBerg – VP of Regulatory Affairs

ONCIOMED (PRIVATE)

COMPANY INFORMATION

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Phone: 714-658-3039

General overview

Mechanism of action

Restrictive

Permanent or temporary

Permanent/removable

Regulatory status

Current: Human trials OUS
underway

Target population

BMI 30–50

Company description

Onciomed is a clinical stage medical device company developing a minimally invasive, fully reversible, long-term implant for the treatment of obesity and type 2 diabetes.

Product description

Restrictive implant

The Gastric Vest System (GVS) restricts the intake of food and provides the feeling of fullness without cutting or permanently removing or bypassing any portions of the gastrointestinal (GI) tract. During a laparoscopic procedure, the stomach is folded onto itself to form a banana shape, and the GVS is placed and secured around it, markedly limiting the stomach's reservoir. This is fully reversible yet imitates the anatomical and physiological state of gastric surgery while leaving the GI tract fully intact.

Different from other competitive products, this procedure not only restricts food intake but also makes food pass through the stomach more quickly, thereby triggering satiety signals from the small intestine to the brain much earlier than with a normally shaped stomach with normal emptying. In this manner, total food consumption throughout the day is markedly decreased to allow for rapid and durable weight loss. The safety and efficacy of the GVS are currently being evaluated.

Target population

The GVS is intended for a wide range of obese patients with BMIs between 30 and 50. The technology is designed to address the needs of progressive bariatric surgeons.

Restrictions

Restrictions are similar to all other bariatric procedures, where patients are asked not to eat large pieces of food that may cause obstruction.

Cost

The company has stated that the cost of the procedure is similar to other procedures of its type.

Clinical data

Onciomed has conducted extensive pre-clinical animal trials for the GVS. At three months, the pigs with the GVS lost an average of 21% of their total body weight, while the control pigs gained an average of 36% of their total body weight. At nine months, the weight loss improved to 31%. A successful first in man implantability and reversibility trial has been performed, but no details are available.

Regulatory status & strategy

OUS - The device is not commercially available anywhere in the world at this time. Onciomed is preparing to launch clinical trials in four Latin American countries (Mexico, Argentina, Brazil, and Chile). After completing these, the company will continue trials in Europe to obtain a CE Mark by 2016.

US - Onciomed received two issued US patents in 2013, and two international patents issued in 2014, with over 20 patents pending.

Commercialization - Upon receiving the CE Mark, Onciomed will initiate a marketing and sales campaign in Europe, Latin America, and Asia Pacific. Onciomed is also developing next generation laparoscopic products that are expected to be cleared via 510(k)

Financials

\$1M was raised in a seed round in 2009.

Series A: \$5.5M Onciomed is raising the capital to conduct its clinical trials outside the US.

Management

- Raj Nihalani, MD – Founder and CEO
- Glenn Morimoto – VP of Business Development
- Paul Stein – Director of Research
- Lila Cheng – Director of Finance & Human Resources

Advisors

- Jamie Ponce, MD
- Shashank Shah, MD
- Almino Cardoso Ramos, MD
- Manoel Galvao Neto, MD
- Ashutosh Kaul, MD
- Flavia Soto, MD
- Anir Gupta, MD

PLENSAT (PRIVATE)

COMPANY INFORMATION

46 Paseo Verde
San Clemente, CA 92673

www.plensat.com

Email: info@plensat.com



Digestible Balloon capsule
Source: PlenSat



Inflated Digestible Balloon
Source: PlenSat

General overview

Mechanism of action

Filler

Permanent or temporary

Temporary – Up to 28 days

Regulatory status

Current: Developmental stage, animal trials underway

Target population

Unknown

Company description

Incorporated in 2009, PlenSat is developing a short-term intragastric balloon system to treat obesity, using four to five small balloons inserted over a period of several days rather than one large one to improve tolerability and patient comfort.

Product description

Intragastric balloon

PlenSat's Digestible Balloon is an ingestible "pill" or capsule that self-inflates in the acidic environment of the stomach and remains in the stomach for 14 to 28 days, serving to restrict the volume of food patients can consume, thereby inducing weight loss. After the 14- to 28-day period, the balloon is designed to break down mechanically in the stomach and pass through the intestines, requiring no endoscopic or surgical intervention.

Each Digestible Balloon has a volume of 30 cubic centimeters, which is significantly smaller than most intragastric balloons currently on the market. The balloons are designed so that patients can ingest four to five capsules over the course of several days, in order to minimize discomfort.

Target population

The Digestible Balloon is intended for overweight and obese patients.

Regulatory status & strategy

US

PlenSat has conducted a preclinical pilot study on the Digestible Balloon in canines. The balloons have not yet been tested in humans. The company has two issued US patents.

OUS

Timeline not currently available

PlenSat plans to move forward initially with regulatory and clinical activities outside the US in order to obtain the most rapid market entry.

Financials

PlenSat has raised approximately \$350,000 through individual investors, a grant issued under a federal stimulus program, and convertible debt financing.

Management

- Fred Voss, Ph.D. – Co-Founder, CEO and President
- Bernhard Sterling, Ph.D. – Co-Founder and Chief Technical Officer

Advisors

- Frank Greenway, MD
- Clifton A. Baile, Ph.D.

RESHAPE MEDICAL (PRIVATE)

COMPANY INFORMATION

100 Calle Iglesia
San Clemente, CA 92672

www.reshapemedical.com

Phone: (949) 429-6680



ReShape Duo
Source: ReShape Medical

General overview

Mechanism of action

Filler and slows gastric emptying

Permanent or temporary

Temporary – 6 months, 2nd procedure to remove

Regulatory status

Completed US pivotal trial; submitted PMA in July 2014; currently marketed in EU

Target population

BMI 30 – 40

Company description

ReShape Medical is developing the first and only dual-intragastric balloon for the treatment of obesity.

Product description

ReShape Integrated Dual Balloon System

ReShape Medical's dual-intragastric balloon, ReShape Duo, uses a patented multi-chamber design. It is filled with 900 cubic centimeters of saline, occupying more volume in the stomach than the 400-700 cubic centimeters of typical single gastric balloons. The dual-balloon structure is designed to allow the stomach to tolerate more volume without causing over-distention or excessive patient discomfort. The dual design also addresses migration and safety issues traditionally associated with single balloon devices.

The ReShape Dual Balloon is implanted in the stomach during a 15- to 30-minute endoscopic outpatient procedure using conscious sedation. It occupies existing space in the stomach for six months, serving as built-in portion control so patients feel full and satisfied with less food. While the balloons are in place, patients are counseled by healthcare professionals on nutrition, exercise, and behavior modification to help them develop a healthier lifestyle. The program continues for an additional six months after the balloon is removed during a second, endoscopic outpatient procedure, to encourage new habits and lasting results.

Target population

The ReShape Integrated Dual Balloon System is intended for patients with BMIs of 30 to 40.

Restrictions

There are no dietary restrictions associated with the ReShape Integrated Dual Balloon System. Patients often report nausea and vomiting during the first three days after the implantation procedure.

Cost

The total cost of the procedure in the European market, including 12 months of counseling, is estimated at €5,500.

Clinical data

Recent studies demonstrate 33% average EWL after six months. ReShape will release the data from its 326-patient REDUCE US pivotal trial in November 2014 at Obesity Week where it has been selected as a Top Ten paper. The company reports that subjects from this trial lost more than twice as much weight as the sham-control subjects who received only diet and exercise therapy.

Regulatory status & strategy

US

The ReShape Dual Balloon is limited to investigational use only in the US at this time. On July 1, 2014, the company announced that it had submitted a PMA application for the ReShape Integrated Dual Balloon System to the FDA. The PMA submission includes data from the company's REDUCE trial, which included 326 patients at eight clinical sites in the US.

OUS

The device received CE Mark certification in 2007 and has been available commercially in the EU since December 2011.

Financials

Total funding to date: \$46M

Series A: \$3M (August 2007): SV Life Sciences

Series B: \$20M (February 2008): US Venture Partners, New Leaf Venture Partners, and SV Life Sciences.

Venture Round: \$1.5M

Series C: \$18M (October 2012): US Venture Partners, New Leaf Venture Partners, SV Life Sciences and Venture Investors

Debt Financing: \$4M (June 2014)

Management

- Richard Thompson – CEO and President
- John Lehmann, MD, MPH – Chief Medical Officer
- Mary Lou Mooney – VP of Clinical, Regulatory & Quality
- Janel Birk – VP of Research, Development & Operations
- Amy Scott – VP of Marketing & Sales

SCIENTIFIC INTAKE (PRIVATE)

COMPANY INFORMATION

2859 Paces Ferry Rd.
Suite 1710
Atlanta, GA 30339

www.scientificintake.com

Email: info@scientificintake.com

Phone: (404) 307-2076



SMART Device
Source: Scientific Intake

General overview

Mechanism of action

Restrictive

Permanent or temporary

Temporary – At meal time.

Regulatory status

Completed US pivotal trial; designated by FDA as investigational non-significant risk device

Target population

BMI 27-35, but can be used by anyone

Company description

Scientific Intake was founded in 2004 and has developed the Scientific Intake SMART Device (Sensor Monitored Alimentary Restriction Therapy), the only medical device intended for weight loss that is classified by the FDA as a non-significant risk device and as a Class I device by EU, Health Canada, Brazilian, and Australian regulatory bodies.

Product description

Removable restrictive device

This non-invasive bariatric device is placed into the mouth only while eating. The device physically increases savoring, reduces bolus size, slows and restricts the rate of ingestion, and allows the body's built-in obesity defense mechanism, the satiety response, to self-trigger.

It is custom-made and contains an uploadable microsensor that captures medical informatics every five minutes for up to 14 months. Healthcare providers will then be able to remotely monitor their patients' compliance, progress, and behavior dynamics.

Target population

Due to its non-invasiveness, Scientific Intake has the advantage of targeting the lower BMI population. While it can be prescribed to treat morbid obesity (either alone or in combination therapy), this device is primarily targeted toward people in the BMI 27-33 range.

Cost

The total cost of the device to the patient, including procedural fees, will likely be around \$800 in the US market. Patient and provider acceptance testing has validated high purchase intent for the device.

Clinical data

Management has stated that clinical data has shown 38.1% EWL with compliant patients at four months (with only 2.5% EWL seen in the control group). In a study published in *Obesity Research* in November 2004, the SMART device reduced food intake by 23%, and patients consumed an average of 533 fewer calories per day.

A multi-site field study revealed similar results, with an average of 805 fewer calories consumed per day, an average of 5.9 pounds lost after 30 days, and 79% patient compliance. A subsequent study similar to the US pivotal trial conducted by John Dixon et al. at Monash University, Baker IDI in Melbourne, AU showed results consistent with all other studies on the device with TBL of 6.4% at 16 weeks (*Obesity Research*, January 2012).

Regulatory status & strategy

US

The SMART Device has been designated by the FDA as a non-significant risk device, but it is investigational at this time. The company's 173-patient US pivotal trial has been completed and data has been submitted to regulatory bodies. Scientific Intake met with the FDA for a pre-IDE meeting in October 2012 and was instructed to submit a Direct De Novo petition with revised analysis of clinical data.

The company submitted a Direct De Novo petition on January 15, 2013, as the first safe and effective non-invasive, non-endoscopic obesity device. The FDA has required Scientific Intake to conduct a small confirmatory study before they will grant approval for the device. The study was fully enrolled as of July 30, 2014, and completion is expected in December 2014. Scientific Intake will submit the updated Direct De Novo petition to the FDA in early 2015.

OUS

Scientific Intake is currently focused on FDA market clearance in the US. The SMART device has received CE Mark and has also been approved for commercial use in Canada, Australia, and Brazil. Several broad international patents have been obtained surrounding restriction of diet at the oral cavity. The company also has several patents pending in relation to its microsensor, reader, and software intellectual property.

SCIENTIFIC INTAKE (PRIVATE) (CONTINUED)

COMPANY INFORMATION

2859 Paces Ferry Rd.
Suite 1710
Atlanta, GA 30339

www.scientificintake.com

Email: info@scientificintake.com

Phone: (404) 307-2076

Financials

Total funding to date: \$17.9M (raised through individual investors)

Management

- William Longley – CEO
- Richard Schneider – Chief Operating Officer
- Donna H. Ryan, MD – Chief Medical Officer
- Joe Popowicz – Clinical and Regulatory
- Scott Huge – Manufacturing

Advisors

- Bruce Bode, MD, FACE
- John Dixon, MBBS, Ph.D.
- Ellen Duke
- Kelly Brownell, Ph.D.
- D. Walter Cohen, MD

SPATZ FGIA (PRIVATE)

COMPANY INFORMATION

15 Cuttermill Road # 147
Great Neck, NY 11021

www.spatzmedical.com

Phone: +1 516 303 0613



Spatz3 Adjustable Balloon
Source: Spatz FGIA

General overview

Mechanism of action

Filler

Permanent or temporary

Temporary – 1 year; 2nd
procedure to remove

Regulatory status

Preparing PMA application;
currently marketed OUS

Target population

BMI ≥ 30

Company description

Spatz FGIA was founded in 2005 and has developed the first adjustable, one-year intragastric balloon for the treatment of obesity.

Product description

Intragastric balloon

The Spatz3 Adjustable Balloon is the only adjustable balloon currently on the market and therefore can be inflated periodically to maximize %EWL or deflated if the patient is experiencing discomfort. It is also implanted for one year rather than the typical six-month period in order to encourage maximum efficacy and improve the likelihood of weight loss maintenance over time.

The balloon's design is gastroenterologist-friendly, offering easy delivery and removal. Since June 2010, more than 5,000 Spatz intragastric balloons have been implanted.

Target population

The balloon is targeted toward obese patients with BMIs of 30 and greater.

Cost

The total cost of the procedure in the European market is estimated to range from €4,000 to €6,000.

Clinical data

In Spatz's clinical trials with the Spatz3 balloon, 76% of patients maintained at least 10% weight loss two years after the removal of the device, compared with 25% of six-month balloon patients. Published studies in peer reviewed journals have reported weight losses of 46-54 pounds at one year, compared to 26-32 pounds with six-month balloons. In a 158-patient Canadian study, all 158 patients kept the device in for at least three months. At three months, average EWL was 28.8%. In the same study, 48 of the 158 patients reached 12 months with the device at the time of publication, with an average EWL of 48.1% at 12 months.

Regulatory status & strategy

US

The Spatz3 Adjustable Balloon System has not been approved by the FDA and is not commercially available in the US. Spatz is currently preparing its application to the FDA and hopes to receive approval in the US by 2017-2018.

OUS

The product was granted CE Mark approval for one-year use in 2012 and has also received approval in Canada, the Middle East, India, Turkey, Australia, Korea, Malaysia, Colombia, Argentina, Peru, and Paraguay. The product is currently available in many countries in Europe, the Middle East, South America, and Asia. Spatz expects regulatory approval in Mexico in Q3 2014 and in Brazil in Q2 2015.

Financials

Total funding to date: \$5M

Management

- Jeffrey Brooks, MD – Founder, Inventor, and CEO
- David Hofstadter – Director of Business Development & Marketing
- Sharon Dinar – Director of Engineering, Manufacturing & Quality Assurance
- Uri Koch – Director of Logistics & Regulatory Affairs

Advisors

- Prof. Christopher J. Gostout, MD
- Prof. Scott A. Shikora, MD
- Prof. L. Mathus-Vliegen, MD
- Evzen Machytka, MD, Ph.D.

TRANSENERIX (TRXC : NYSE : \$4.05 | NOT RATED)**COMPANY INFORMATION**

635 Davis Dr.
Suite 300
Durham, NC 27713

www.transenterix.com

Investor Inquiries:
Joseph Slattery
Phone: 919-765-8443
Email: investors@transenterix.com



SurgiBot
Source: TransEnterix

General overview

Mechanism of action
Restrictive

Permanent or temporary
N/A

Regulatory status
FDA approved (2009)

Target population
N/A

Company description

TransEnterix is a medical device company that is pioneering the use of robotics and flexible instruments to improve minimally invasive surgery. The company is focused on the development and commercialization of the SurgiBot, a minimally invasive surgical robotic system that allows the surgeon to be patient-side within the sterile field.

History

TransEnterix was founded in 2006. TransEnterix merged with SafeStitch, which was developing an intraluminal gastroplasty device for the treatment of obesity, on September 3, 2013. The merged company now goes by the name TransEnterix and is traded on the NYSE under the ticker symbol TRXC.

Product descriptionRobotic and laparoscopic platforms

The company is developing the SurgiBot System, a single-port robotic surgery platform designed to utilize flexible instruments through articulating channels controlled directly by the surgeon, while the surgeon remains patient-side within the sterile field. The SurgiBot is designed to provide many of the benefits of robotic assistance to surgeons while minimizing the cost and complexity of implementing a robotic surgery program. The system features 3DHD steerable vision, robotic precision and strength, enhanced ergonomics and reduces the number of incisions to one in many surgeries.

The company also markets the SPIDER Surgical System, a laparoscopic platform that is 510(k) cleared with over 3,500 procedures performed to date. The system has found greatest acceptance in obesity surgery (sleeve gastrectomy), but also has the ability to be used in wide range of abdominal surgeries.

The company also has developed a full range of flexible laparoscopic instruments to be used with the SPIDER Surgical System and the SurgiBot. The company launched an advanced energy tissue sealing device in April 2014.

Regulatory status & strategyUS

The SPIDER Surgical System was approved by the FDA in 2009 and is commercially available in the US. SurgiBot expected filing in Q4 2014.

OUS

SPIDER received CE Mark and became commercially available in the EU in 2010. Surgeons in the Middle East began using SPIDER in 2012. SurgiBot expected filing in Q4 2014.

Financials

2008: Secured \$21M in first round of institutional financing

2009: Secured \$55M in second round of institutional financing

2013: Secured \$30M round of financing after SafeStitch-TransEnterix merger

2014: Secured net financing of \$52M through public stock offering

Management

- Todd M. Pope – CEO and President
- Paul Laviolette – Chairman of the Board
- Joseph P. Slattery – Chief Financial Officer and Executive VP
- Richard M. Mueller – Chief Operating Officer
- Joshua Weingard – Chief Legal Officer
- Nicole Bell – VP of Research & Development
- Tammy Carrea – VP of Quality & Regulatory Affairs
- Larry Pope – VP of Manufacturing
- Mohan Nathan – VP of Global Marketing

TULIP MEDICAL (PRIVATE)

COMPANY INFORMATION

16 Galgalei Haplada
Herzliya 4672216
Israel

www.tulipmed.com

Email: info@tulipmed.com

General overview

Mechanism of action

Filler

Permanent or temporary

Temporary - Daily

Regulatory status

Current: Second phase, after successful completion of pilot study in Israel.

CE Mark expected in 2015

FDA approval expected in 2016

Target population

BMI 27-40

Company description

Founded in 2006 and based in Herzliya, Israel, Tulip Medical is a medical device company developing a very short-term intragastric balloon for the treatment of the overweight and obese that is ingested daily, via a capsule.

Product description

Tulip Medical is developing a biodegradable (digestible), self-deploying intragastric balloon that is swallowed daily by the patient via a capsule. Once swallowed, the implant self-expands in the acidic environment of the stomach within approximately 15 minutes and applies pressure against the stomach wall to provide a feeling of satiety. After five to six hours, the implant breaks down mechanically and dissolves with the assistance of natural gastric fluids. The degraded balloon then passes out of the stomach and through the intestines, to be defecated by the patient.

Patients take a capsule daily for as long as the treatment period lasts. The product is made from commercially available and FDA approved polymers currently utilized in the US pharmaceutical and food industries.

Target population

Tulip Medical is primarily targeting patients in the BMI range of 27-40.

Restrictions

There are no dietary restrictions associated with the balloons, and patients are not required to take nutritional supplements.

Cost

The company reports that the balloons will likely cost around \$1 per day.

Clinical data

The company performed a 30-day, 13-patient pilot human clinical trial on the product in Israel, which was preceded by pre-clinical animal trials. In this human trial, total weight loss of up to 4% was recorded at one month. A three-month, Phase II trial is currently being conducted.

Regulatory status & strategy

US

Tulip Medical plans to pursue FDA approval after having achieved approval in the EU.

OUS

The company expects to receive CE Mark certification in 2015 and plans to begin commercialization of the device in 2016, assuming CE Mark is obtained.

Financials

Total funding to date: Approximately \$10M (raised through VCs and private investors)

Investors include Dr. Shimon Eckhouse, Agrate Medical Investments, 7Main VC, and Carisbrook Investments Group.

Management

- Nir Betser – CEO
- Shimon Eckhouse, Ph.D. – Chairman of the Board and Co-Founder
- Tair Lapidot, Ph.D. – Director of Product Development

Advisors

- Zamir Halpern, MD
- Efrat Broide, MD
- Ronnie Fass, MD

USGI MEDICAL (PRIVATE)

COMPANY INFORMATION

1140 Calle Cordillera
San Clemente CA 92673

www.usgimedical.com
Email: info@usgimedical.com
Phone: (949) 369-3890



Incisionless Operating Platform™
Source: USGI Medical

General overview

Mechanism of action

Reduces hunger, prolongs satiety, reduces portion size.

Permanent or temporary

N/A

Regulatory status

Current: 510(k) clearance enrollment in US pivotal trial complete, commercialized in EU with CE Mark.

Target population

BMI 30-40

Company description

USGI Medical is a medical device manufacturer addressing a significant unmet need in the growing, multibillion-dollar obesity/weight loss market with an incisionless, safe and cost-effective procedure that has led to significant weight loss and improvement in obesity's co-morbid conditions in both investigational and commercial settings.

Product description

USGI's Incisionless Operating Platform (IOP) is designed to provide an incisionless and durable method to remodel the stomach with the company's novel tissue anchors in an optimal, individualized manner so patients feel full faster and longer so they eat less and lose a significant amount of weight. The company believes that the tissue anchors are more durable than other approaches to transoral gastric remodeling.

The IOP has been used for a variety of applications, with a research focus on primary (de novo) obesity. This primary weight loss procedure, known as POSE (Primary Obesity Surgery, Endolumenal) offers patients a bridge between diet, exercise and drugs, which are not effective long term, and invasive surgery, which many people fear due to the time invasiveness, long recovery and high risk of complications.

Target population

The POSE procedure is intended for patients with BMIs between 30 and 40.

Cost

The company does not disclose this information.

Clinical data

Data from European studies of POSE demonstrated 62% average EWL (which equates to between 40 to 45 pounds lost, on average, or close to 20% of the patients' total weight) at 12 months with an excellent safety record. These studies included data from 137 consecutive procedures performed between February 2011 and July 2013. The average BMI of the subjects was 36.9 and the average age was 42.8 years. 74% of the subjects were female.

Regulatory status & strategy

US

USGI's IOP products all received 510(k) clearance in 2007 for use in general/therapeutic endoscopic procedures. In October 2013, USGI received conditional approval from the FDA for its IDE application to launch a 300+ subject pivotal study of POSE, known as the ESSENTIAL Trial.

The company completed enrollment of this trial in June 2014. A total of 332 patients at 11 clinical sites in the US were enrolled. Assuming the trial's end points are met, USGI expects FDA approval for a weight loss indication by Q1 2016. The company has 66 issued US patents and 24 US patents pending.

OUS

All components of the IOP received CE Mark in March 2010. In Europe, the procedure is typically performed in an outpatient setting. The company has three issued patents in Japan and seven patents pending internationally. In 2010, USGI initiated a single-country test market of the POSE procedure, leading to rapid adoption and growth. Details are not disclosed by the company.

Financials

Series 1: \$16.8M (May 2012)

Series 2: \$12.5M (June 2014)

Participants included Alta Partners, Johnson & Johnson Development Corporation and InterWest Partners.

Management

- Scott Moonly – CEO and President
- Guy Nohra – Chairman of the Board
- John Cox – Chief Commercial Officer
- Tracy Maahs – Chief Technical Officer

Advisors

- Lee M. Kaplan, MD, PhD (SAB Chair)
- Louis J. Aronne, MD
- Sayeed Ikramuddin, MD
- Tom Lavin, MD
- Christopher Thompson, MD, MHES
- George Woodman, MD

VALENTX (PRIVATE)

COMPANY INFORMATION

6901 E. Fish Lake Rd.
Suite 118
Maple Grove, MN 55369

www.valentx.com
Email: info@valentx.com
Phone: 763-222-1560



ValenTx implant
Source: ValenTx

General overview

Mechanism of Action

Restrictive and malabsorptive

Permanent or temporary

Temporary – up to 1 year;
2nd procedure to remove.

Regulatory status

Current: Pursuing US IDE
Pivotal and CE Mark
approval

US pivotal trial expected in
2015

Target population

Obese patients and obese
type 2 diabetics

Company description

Founded in 2003, ValenTx has developed an endoluminal bypass device that mimics both the restrictive and malabsorptive effects of gastric bypass surgery while still remaining completely reversible.

Product description

Restrictive and malabsorptive implant

The ValenTx endoluminal bypass procedure seeks to achieve all three major elements of gastric bypass surgery (control of food intake, early satiation, and control of nutrient absorption) without surgical intervention and offering reversibility if patients choose. The device is implanted at the gastroesophageal junction (GEJ, the junction between the distal esophagus and the proximal stomach) and has a total length of approximately 120 centimeters. The device reroutes food from the GEJ to the distal small intestine, bypassing the proximal small intestine and the duodenum.

Additionally, the way in which the device is implanted at the gastroesophageal junction allows the patient to absorb nutrients that are lost with gastric bypass surgery. This method eliminates the need for the dietary supplements that gastric bypass requires. The device is implanted and removed endoscopically.

Target population

The endoluminal bypass procedure is intended for obese patients and obese type 2 diabetics.

Cost

The total cost of the procedure, including the cost of the device itself, will likely range from \$10,000 to \$15,000 in the US market.

Clinical data

ValenTx published ASMBS data in July 2011, which combined data from two prospective studies, both at a single center but of different durations. Twelve patients were implanted with the ValenTx endoluminal bypass device for three months, while another 12 patients were implanted with the device for 12 months. The 24 total subjects had a mean pre-operative BMI of 42.2. Average EWL was 38.9% at three months for the three-month group and 41.9% at nine months for the 12-month group.

All patients with type 2 diabetes in both groups experienced improvement in fasting glucose and HbA1c levels. The study also revealed a 73% hypertension resolution rate for the 11 patients with pre-operative hypertension. In subsequent studies that have not yet been published, ValenTx reports EWL in excess of 50% at 12 months, a near 90% reduction in Type II diabetes, and 75% reduction in hypertension.

Regulatory status & strategy

US

The ValenTx endoluminal bypass therapy is not FDA approved. The company plans to begin its pivotal trial in the US in 2015-2016, after obtaining CE Mark. ValenTx has 13 issued US patents and 22 pending patent applications.

OUS

The company is currently pursuing CE Mark.

VALENTX (PRIVATE) (CONTINUED)**COMPANY INFORMATION**

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Suite 118
Maple Grove, MN 55369

www.valentx.com
Email: info@valentx.com
Phone: 763-222-1560

Financials

Total funding to date: Approximately \$29M

Up to and including Series A: \$7M (May 2006):

Participants included EDF Ventures, Sapient Capital, Affinity Capital Partners, Kaiser-Permanente Ventures and T-Gap Ventures.

Series B: \$22M (2009): Participants included the aforementioned, along with SV Life Science, Covidien, and Niagara Gorge Venture Partners.

Management

- Hans Neisz – CEO
- David Krenn – Chief Financial Officer
- Jon St. Germain – Chief Operating Officer
- C. Daniel Smith, MD – Chief Medical Officer
- Allen Putnam – VP of Clinical, Regulatory & Quality

Advisors

- C. Daniel Smith, MD
- Santiago Horgan, MD
- Mitch Roslin, MD
- Chris Thompson, MD
- Marc Bessler, MD
- Michael Gonzales-Campoy, MD
- Paul Swain, MD
- Bipan Chand, MD

INVESTMENT RISKS

We note typical medical technology risks. These risks include product pipeline delays, the potential for product recalls, patent infringement or product liability lawsuits, and anti-trust litigation.

APPENDIX: IMPORTANT DISCLOSURES

Analyst Certification:

Each authoring analyst of Canaccord Genuity whose name appears on the front page of this research hereby certifies that (i) the recommendations and opinions expressed in this research accurately reflect the authoring analyst's personal, independent and objective views about any and all of the designated investments or relevant issuers discussed herein that are within such authoring analyst's coverage universe and (ii) no part of the authoring analyst's compensation was, is, or will be, directly or indirectly, related to the specific recommendations or views expressed by the authoring analyst in the research.

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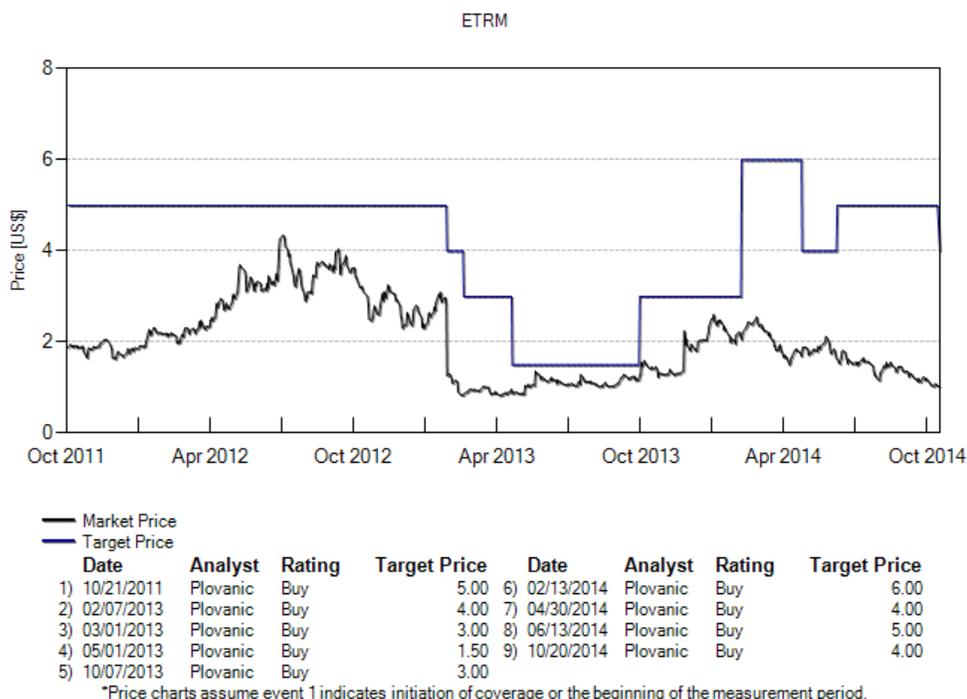
Compendium Report:

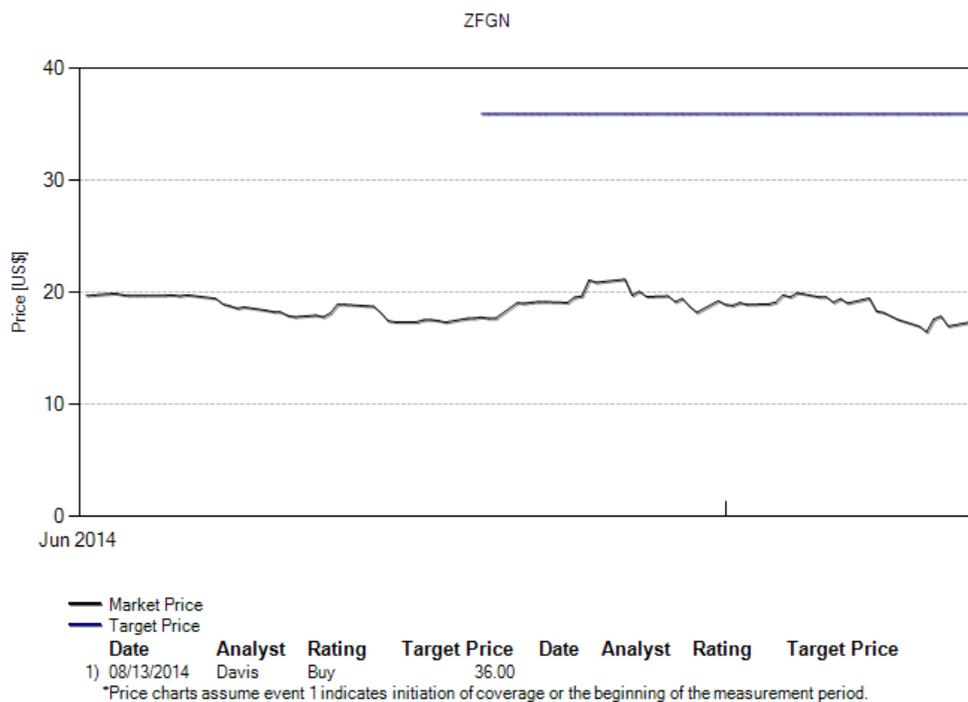
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Site Visit:

An analyst has visited EnteroMedics' material operations in St. Paul, Minnesota. No payment or reimbursement was received from the issuer for the related travel costs. An analyst has not visited Zafgen's material operations.

Price Chart:*





Distribution of Ratings:
Global Stock Ratings
(as of 1 October 2014)

Rating	Coverage Universe		IB Clients	
	#	%	#	%
Buy	627	60.2%	36.7%	
Speculative Buy	53	5.1%	54.7%	
Hold	317	30.5%	13.9%	
Sell	43	4.1%	2.3%	
	1041	100.0%		

*Total includes stocks that are Under Review

Canaccord Genuity Ratings System:

BUY: The stock is expected to generate risk-adjusted returns of over 10% during the next 12 months.

HOLD: The stock is expected to generate risk-adjusted returns of 0-10% during the next 12 months.

SELL: The stock is expected to generate negative risk-adjusted returns during the next 12 months.

NOT RATED: Canaccord Genuity does not provide research coverage of the relevant issuer.

“Risk-adjusted return” refers to the expected return in relation to the amount of risk associated with the designated investment or the relevant issuer.

Risk Qualifier:

SPECULATIVE: Stocks bear significantly higher risk that typically cannot be valued by normal fundamental criteria. Investments in the stock may result in material loss.

Canaccord Genuity Research Disclosures as of 21 October 2014

Company	Disclosure
EnteroMedics, Inc.	1A, 2, 3, 5, 7
Zafgen	1A, 2, 3, 5, 7

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