Primer

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The Skinny on Obesity

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2012: important year for the future of obesity treatments

While obesity as a medically-treated disease is a controversial topic, the condition is faced by more than 100mn people in the US and 500mn worldwide, creating a significant market opportunity for new weight loss drugs. In this obesity primer, we provide an overview of obesity, its impact on co-morbidities and healthcare costs, previous failed weight loss drugs, current treatment options and limitations, and payor and physician perspectives.

FDA aversion toward new weight loss drugs could be waning

In response to CMS' estimate that obesity and related co-morbidities account for 10% of US healthcare costs (~$150bn/yr), the Senate Appropriations Committee mandated that the FDA develop a strategy to approve new weight loss drugs and report back to Congress by late-March 2012. The FDA has historically had little risk tolerance for weight loss drugs, but recently has shown increased support for the development of new weight loss drugs. The multiple advisory panels and approval decisions in coming months could lead to more transparency about the path to approval for obesity drugs.

Vivus' Qnexa: next up with the FDA

Vivus' Qnexa has demonstrated >10% average weight loss in users sustained for 2 years, but has a fetal malformation risk. The drug has demonstrated meaningful cardio-protective benefits which could attract government and private payor interest. An FDA advisory committee will review Qnexa for the second time on February 22nd with an FDA decision by April 17th. FDA's CRL highlighted issues including the company's proposed REMS program to reduce birth defect risk, CV issues and questions on potential fetal malformations from use of Qnexa.

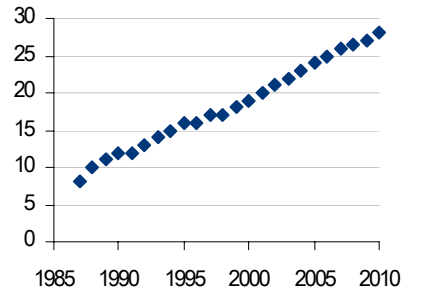
Arena's Lorqess: focus is on tumor risk

In January 2012, ARNA provided results from its 3-month rat mammary tumor studies that were generally supportive of a prolactin-mediated mechanism, which is generally considered to not be relevant to humans. Lorqess has an upcoming ad com in Q2 2012 where FDA's interpretation of newly submitted data on cancer risk will be discussed. Lorqess has a June 27th PDUFA.

Orexigen's Contrave: CV outcomes trial underway

An interim read of the cardiovascular outcomes trial (CVOT) for Orexigen's drug Contrave is expected by the end of 2013, now that the FDA has approved the study protocol. If the interim results meet specific relative risk criteria, conditional approval of Contrave could be granted. This pre-approval CVOT study was required even though the ad com voted in favor of a post-approval study. The FDA did, however, accept Orexigen's study protocol designed to generate actionable data within 2 years.

Chart 1: Obesity in the US on the rise



Source: Data obtained from CDC/NCHS

Refer to important disclosures on page 25 to 27. Link to Definitions on page 24.

The obesity epidemic: facts

WHO estimates that almost 500 million adults worldwide are obese

According to the World Health Organization (WHO), obesity is the fifth leading global risk for death, accounting for at least 2.8mn adult deaths each year. The Organization for Economic Co-operation and Development (OECD) cites 50% or more of its member country populations as being overweight or obese. The US and Mexico have two of the highest obesity rates, while Japan and Korea have two of the lowest.

Body Mass Index, or BMI is calculated as [weight ÷ height^2] x 703

Trends indicate a rapid rise in obesity even in countries with low current rates. The Centers for Disease Control (CDC) categorizes individuals as overweight if one has a body mass index (BMI) between 25 and 30, obese for BMIs ≥ 30 and morbidly obese for BMIs ≥ 40. BMI can be misleading, however, depending on ethnicity and muscle mass; as a result, waist circumference and body fat percentage are alternate obesity metrics. Researchers estimate that in the year 2030, there will be 65mn more obese adults in the US and 11mn more in the UK (Wang et al, Lancet).

Vivus estimates that 95% of obese patients are already being treated in the primary care setting for hypertension, hyperlipidemia, or diabetes.

Obesity results in significant co-morbidities

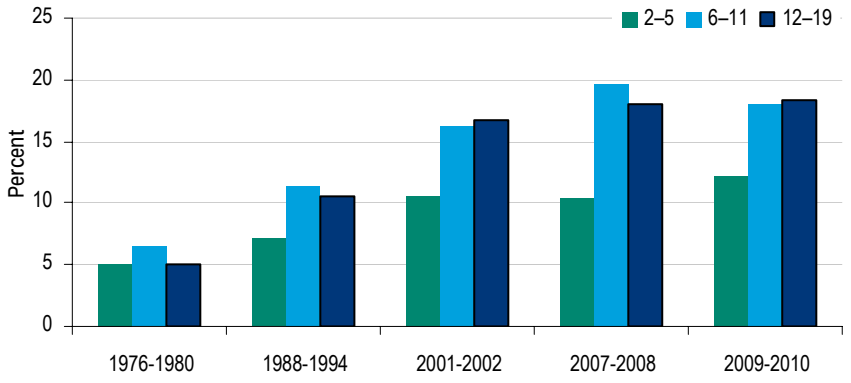
WHO estimates that the diagnoses of 44% of diabetes, 23% of ischemic heart disease and between 7-41% of certain cancers are attributable to patients being overweight and obese. Additional co-morbidities include high cholesterol, hypertension, respiratory problems, arthritis, and other CV diseases. Furthermore, obesity has psychological impacts, and doctors in the US have estimated that 63% of their obese patients are depressed or show signs of untreated depression.

The International Association for the Study of Obesity estimates that 20% of children aged 5-17 are overweight

Obese children more likely to become obese adults

A significant number of children are becoming obese, which can lead to longer-term problems that include shortened life, various disabilities, breathing difficulties, cardiovascular diseases, insulin resistance, as well as psychological factors such as social problems and mental health issues. In many developing countries, lower cost diets with poor nutritional value are more greatly consumed by children and thus contribute to the growth in obesity rates. OECD studies show that even if this excess weight is lost, adults who were obese children are more likely to suffer from cardiovascular (CV) problems. Furthermore, this population is at a greater risk of regaining weight after loss. Obesity rates in children are rapidly rising; reaching double digits in most OECD countries.

Chart 2: Prevalence of Childhood obesity in the U.S.



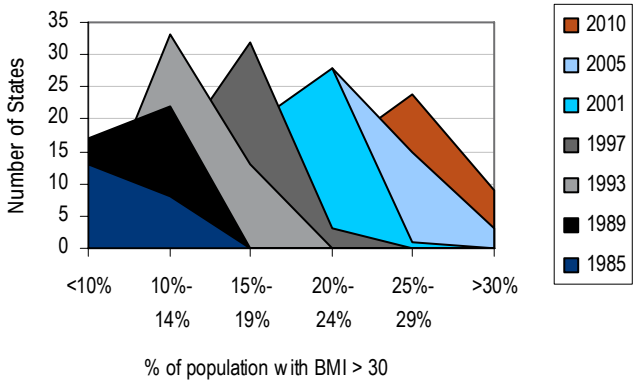
Source: data obtained from CDC/NCHS

In the United States, children and adolescents ages 12-19 had an 18.4% prevalence of obesity in 2009-2010 (see Chart 2). The prevalence of obesity among children within the ages of 6-11 and 2-5 was 18% and 12.1%, respectively. Total obesity prevalence for all three age cohorts was 16.9%, flat compared to 2007-2008, but 10% higher than when compared to 2001-2002.

The United States obesity epidemic

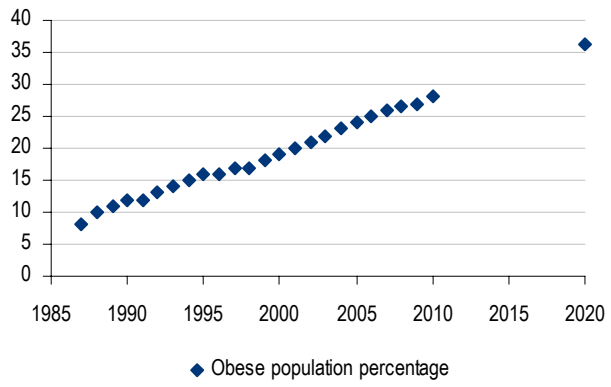
The prevalence of obesity in the US has increased dramatically over the past several decades (see Charts 3 and 4), and according to recent CDC studies, almost 70% of Americans are overweight and nearly one third are obese. Studies estimate that 50% of the US population will be obese by 2030 (Wang et al, Lancet).

Chart 3: Obesity in the US has increased ...



Source: Data obtained from CDC/NCHS

Chart 4: ... at a roughly linear pace

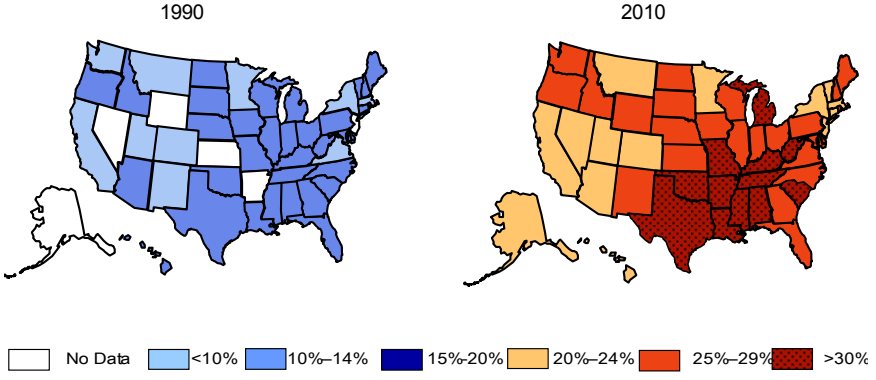


Source: Data obtained from CDC/NCHS

All states now have at least a 20% prevalence of obesity

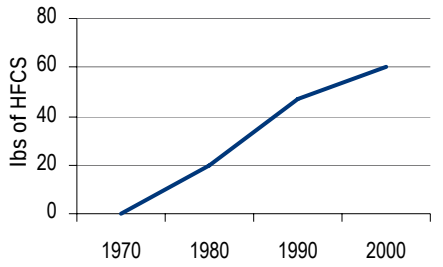
In 1990, 10 states that participated in the CDC's Behavioral Risk Factor Surveillance System (BRFSS) had an obesity prevalence of less than 10% and no state had prevalence equal to or greater than 15% (see Chart 5). By 2010, no state had a prevalence of obesity less than 20% and twelve states (up from 9 in 2009) had an obesity prevalence equal to or greater than 30%. The highest prevalence of obesity in the US is in the South. Mississippi, the most obese state (34%) for the sixth consecutive year, is also one of the poorest and plagued by low insurance coverage, weak education systems and high unemployment.

Chart 5: Comparison of obesity trends (in percent) in the United States in 1990 and 2010



Source: Data obtained from CDC

Chart 6: High fructose corn syrup intake
(per capita, annually)



Source: data obtained from USDA

Fast Food Nation

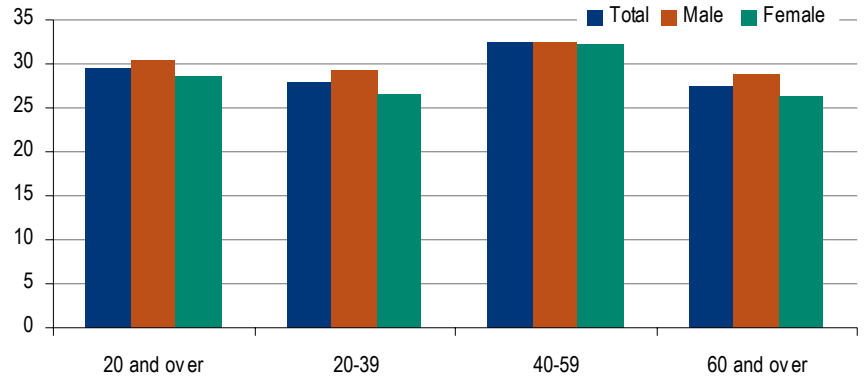
Obesity specialists suggest that a gradual shift to high calorie fast food diets combined with a lack of physical activity is a major driver of the obesity trend. A key component in soft drinks is high fructose corn syrup, which has increased significantly in the last four decades (see Chart 6). Looking at portion sizes, this becomes evident; for example, in 1990 a Hershey bar was 2 oz. and 297 calories versus 7 oz. and triple the calories by 2011. Fast food sales increased 54% from ~$107bn in 2000 to ~$165bn in 2010. Annual consumption of cheese, a food that can be very high in fat, increased 287% from the 1950s, while milk consumption decreased 38%.

- Rats fed fructose developed leptin resistance whereas starch-fed rats did not even with no weight gain difference. Then when these rats were fed high fat diets, the leptin resistant rats gained much more weight than the starch fed rats, representing a strong similarity with a Western high-sugar, high fat diet (Shapiro et al., 2008).
- High fructose diets in humans have led to increased plasma triglycerides levels within four weeks (Reiser et al., 1989).
- Fructose stimulates triglyceride synthesis and fat deposition in the liver (Stanhope and Havel, 2008).

Obesity affects all age groups

When comparing adults aged 20 and over by age group and sex, preliminary 2011 data shows that obesity is slightly more prevalent in the 40-59 year-old age cohort: 32.4% Total, 32.6% Male, 32.2% Female (see Chart 7).

Chart 7: Obesity fairly consistent among age groups



Source: CDC/NCHS, National Health Interview Survey, January-March 2011, Sample Adult Core Component

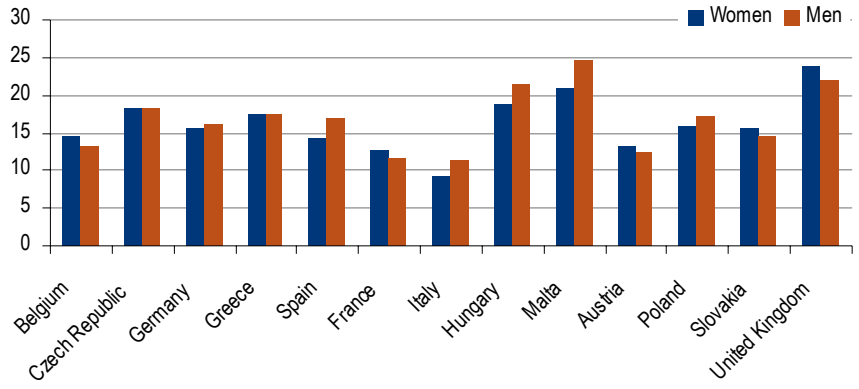
Obesity is not just a US problem

While many highlight the United States as the epicenter of obesity, this disease is on the rise throughout the world.

- According to a survey in 2007-2008, more than 1 in 4 Canadian children and youth are considered to be overweight or obese. In 2010, in Canada, the percentage of obese women was 16.5%, while the percentage of obese men was 19.8% (compared to 14.5% and 16.0%, respectively, in 2003).

- In Mexico, 4.5 million children between 5 and 11 are already overweight; and according to an OECD study, 7 out of 10 people in Mexico are overweight, and 3 out of 10 obese.
- South America, a region that was largely affected by an underweight population, has been moving towards one that is overweight. A recent article in the Telegraph explained that around 1 in 7 Brazilians are obese, and nearly half are overweight.
- In Hong Kong, obesity rates in children were 22.2% in 2009-2010 (up from 16.7% in 1996-1997).
- Studies suggest that, at least in South Asians, the BMI at which one is technically obese should be lowered. In India, for example, a person is considered overweight if he or she has a BMI of 23 (elsewhere up to 25 is considered normal).
- Throughout Europe, obesity is responsible for 2-8% of health costs and 10-13% of deaths (WHO). The proportion of obese people in Europe, for the available countries surveyed, varied between 8.0% and 23.9% for women and between 7.6% and 24.7% for men (see Chart 8). For women, obesity numbers increased with age.

Chart 8: In 2008-2009, UK and Malta highest prevalence of obesity in Europe



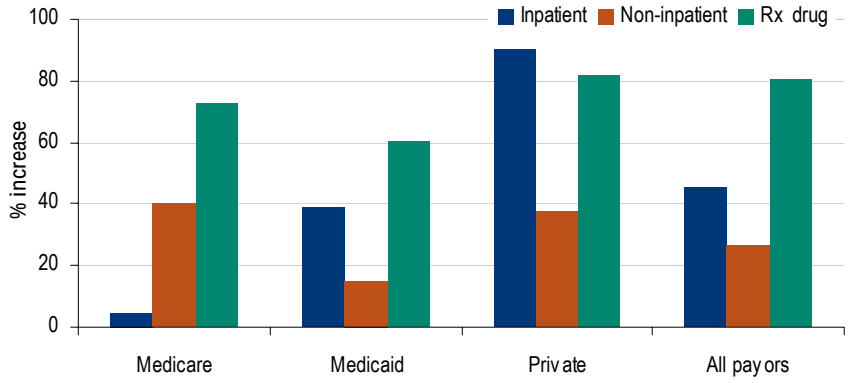
Source: Eurostat, European Health Interview Survey (EHIS)

Obesity leads to higher healthcare costs

Obesity-related healthcare costs in the US could increase from $147bn to approximately $344bn per year by 2018

Because of the growing epidemic and lack of effective treatment options, total healthcare costs from obesity-related diseases in 2010 were estimated to be $147bn in the US and $158bn in the EU. Total healthcare costs are more than 40% higher for obese patients than normal weight patients (see Chart 9, Finkelstein et al., *Health Affairs*) and work-comp claims are 7-fold higher (Ostbye et al., *Arch Intern Med*).

Chart 9: Increase in costs due to obesity affects all payors



Source: Finkelstein, Eric et al, *Health Affairs* 28, no. 5 (2009): w822-w831, Medical Expenditure Panel Survey

While obesity has been on the rise, so has healthcare spending. Of the $147bn estimated yearly cost of obesity on healthcare, 23% ($32.8bn) is paid by Medicare and 19% ($27.17bn) by Medicaid (Trogdon et al, *Obesity*). It is estimated that 30% of Medicare's coverage population is obese, and the costs for obese people on Medicare, for prescription drugs alone, are 72% greater.

Expenses of an average normal weight person on Medicare: $3400/year. Expenses of an obese person on Medicare: $4870/year.

Co-morbidities increase healthcare spending

A recent Lancet article estimates global adult diabetes prevalence at nearly 10%, up steadily in the last 3 decades (Danaei et al., *Lancet*), in line with obesity trends (CDC). According to another study, every BMI unit increase above 25 was associated with a 12% increased risk of diabetes and 4% increase in total healthcare costs (Wang et al. *Lancet*). A major risk factor for diabetes, an estimated $180bn/year condition, is being overweight or obese. The Diabetes Prevention Program (DPP) showed that modest weight loss and dietary changes can delay or even prevent onset of diabetes.

In 20 years CDC estimates one out of every three Americans will be diabetic by 2050 (half a trillion dollars of spending).

Failed weight loss drugs

The FDA has not approved a weight loss drug in more than 10 years (Orlistat in 1999), and in October 2010 the FDA removed the weight loss drug Meridia from the market. In the last decade several new drugs have been in clinical development. We look for the FDA to maintain low tolerance for safety issues due to a tainted history of oral obesity therapies that developed serious concerns post commercialization, as discussed below.

Fen-phen (fenfluramine, phentermine, Wyeth):

Fen-phen (fenfluramine and phentermine), showed impressive efficacy with 12%-15% average weight loss from baseline. Fenfluramine, a 5HT2c receptor agonist, worked by increasing serotonin and norepinephrine levels to stimulate satiety. However, this drug was removed from the US market in 1997 after reports surfaced that 24 women developed valvular heart disease after an average of 12 months of therapy, with one patient having only taken fen-phen for one month. Fenfluramine was also associated with increased risk of primary pulmonary hypertension (narrowing of pulmonary blood vessels).

An estimated 6 million Americans took fen-phen while it was on the market

Studies later suggested that fenfluramine did not exhibit selectivity between 5HT2c receptors in the brain versus other areas in the body including 5HT2b receptors in the heart and lungs, resulting in the serious side effects. Prior to approval, the FDA didn't fully evaluate the fen-phen combination and only had short term studies.

Zimulti (rimonabant, Sanofi):

rimonabant was associated with an average of 10% weight loss from baseline

Rimonabant worked by blocking the brain's cannabinoid receptors, which control hunger levels. Clinical trials showed impressive efficacy (up to 10% of weight loss from baseline after one year of use) but concerns surrounding psychiatric events prompted the FDA to ask the company to do further studies. Subsequently, in June 2007 an FDA advisory committee voted 14-0 against approving rimonabant for obesity after analyzing a number of studies that showed the drug nearly doubled suicidal thinking and doubled the incidence of anxiety, depression, and other mood disorders. See the discussion on the next page for a summary of psychiatric effects from weight loss drugs.

Meridia (sibutramine, Abbott)

Meridia was associated with 3%-4% average weight loss from baseline

The FDA approved Meridia in 1997 for obesity management after an advisory committee had voted against approval in a 5 to 3 vote. The negative vote was due to concerns surrounding increased blood pressure and heart rate seen in patients during clinical trials. However, the agency approved the product as the prevailing view at the time was that the benefits offset the risks.

As part of a post-approval commitment between the European Medicines Agency (EMA) and Abbott, the company conducted a 10,000 patient post approval study known as the SCOUT trial with the goal of showing that weight loss with sibutramine and standard of care was more effective in reducing CV events versus weight loss from placebo and standard of care.

An FDA advisory committee met on September 15 to discuss the findings of the SCOUT trial, followed by the removal of the drug from the US market.

However, the topline analysis reported in the New England Journal of Medicine showed that CV events were reported in 11.4% of patients using sibutramine compared to 10% of patients using placebo (see Table 1). The observed difference was higher than expected and statistically significant (p = .02), driven by both strokes and myocardial infarctions. Similar results were observed for high risk patients with pre-existing cardiovascular disease and diabetes, indicating an exacerbation of risks rather than mitigation (see bottom half of Table 1).

Table 1: SCOUT results for cardiovascular events

Subgroup	Sibutramine % events	Placebo % events	Hazard Ratio (95% CI)	P Value
Overall Population				
Nonfatal myocardial infarc.	4.1%	3.2%	1.28 (1.04-1.57)	0.02
Nonfatal stroke	2.6%	1.9%	1.36 (1.04-1.77)	0.03
Cardiovascular death	4.5%	4.7%	0.99 (0.82-1.19)	0.90
Total	11.4%	10.0%	1.16 (1.03-1.31)	0.02
CV and DM patients				
Nonfatal myocardial infarc.	4.9%	4.1%	1.23 (0.97-1.57)	0.09
Nonfatal stroke	3.1%	2.2%	1.45 (1.05-2.00)	0.02
Cardiovascular death	5.5%	5.5%	1.03 (0.82-1.28)	0.83
Total	13.9%	11.9%	1.18 (1.02-1.37)	0.02

Source: James et al., 2010. NEJM 363(10): 905-917

Meridia removal due to CV risks

After the SCOUT data were published, Meridia was removed from the European marketplace. Additionally, the FDA had an ad com and subsequently released a Safety Communication in which it recommended against the continued use of Meridia, requesting that Abbott remove its drug from the market. Weight loss was insufficient (mean % change of ~2.5%), in the view of the FDA, to outweigh the risks.

Summary of psychiatric issues with weight loss drugs

Psychiatric adverse events are commonly associated with weight loss drugs. While hunger and satiety signals are the primary targets, the modulation of serotonergic, dopaminergic, cannabinoid, and opioid neurotransmitter systems frequently results in non-target effects. The most serious psychiatric effects were observed with rimonabant, a cannabinoid receptor antagonist, which resulted in increased anxiety, depression, and suicidal ideation. Merck had been developing taranabant for obesity, which also modulated cannabinoid receptors, but development was terminated in 2008 due to increased depression. Conversely, other weight loss drugs like bupropion that target dopamine and noradrenaline neurotransmitters have shown to significantly reduce depression. Insomnia and nervousness are common with many of these drugs.

Table 2: Summary of psychiatric effects from weight loss drugs

Drug	Mechanism of action	Psychiatric effects
fenfluramine	serotonin reuptake inhibitor	Reduced anxiety and depression
sibutramine	serotonin and noradrenaline reuptake inhibitor	Reduced depression
lorcaserin	serotonin agonist	Modest increase in depression adverse events
bupropion	dopamine and noradrenaline reuptake inhibitor	Insomnia, nervousness, with reduced depression
naltrexone	opioid receptor antagonist	Minor effects
rimonabant	cannabinoid receptor antagonist	Increased anxiety, depression, and suicidal ideation
topiramate	antiepileptic	Cognitive impairment and increased anxiety and depression
phentermine	amphetamine	Increased insomnia and nervousness

Source: Nathan et al. 2010. CNS Neuroscience & Therapeutics. 1-16

Weight Loss Industry

The current weight loss industry consists of three prescription drugs, an FDA approved OTC drug, weight loss and lifestyle counseling, dietary supplements and meal replacement products. Many physicians see the first line of defense as diet and exercise, followed by prescription drugs, and ultimately bariatric surgery.

Limitations & concerns of current obesity treatments

Current oral treatment options for obesity are limited and show only modest efficacy with a variety of adverse effects, as listed below:

FDA requires that *one* of the following two outcomes is reached during clinical trials for drugs seeking approval for weight loss: 1) at least 5% placebo-subtracted reduction in body weight compared to baseline at one year; 2) at least 35% of patients on active drug lose ≥ 5% of body weight and this proportion is approximately twice that of placebo and statistically significant.

- **Phentermine** An adrenergic reuptake inhibitor known as an anorectic that works on the sympathetic nervous system to increase resting metabolism and decrease appetite. It is approved for short-term use (12 weeks) to aid in weight reduction. *Positive*: as a generic drug, it has a low price. *Negative:* side effects include hypertension and tachycardia.

- **Topiramate** (generic from of Topamax, Johnson & Johnson). An anticonvulsant drug for treating epilepsy and as an antipsychotic drug for treating bipolar disorder. One-third of scripts are estimated to be used off label to control binge eating. *Positive:* approved for several years to treat epilepsy and side effect profile is well known; the generic drug has a low price. *Negative:* side effects include cognitive impairment and peripheral neuropathy.

- **Orlistat** (trade name Xenical, Roche and over the counter Alli, GlaxoSmithKline). *Positive:* available in over the counter strength. *Negative:* associated with significant GI related side effects from fat retention in stools.

Table 3: Summary of Currently Available Obesity Therapies

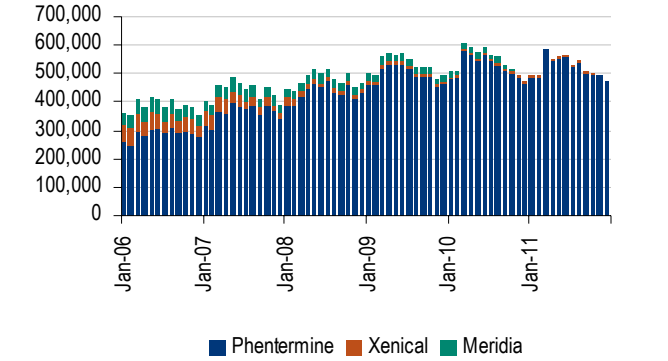
Drug	Drug Class	Label Recommended Time of Use	Common Adverse Events
Phentermine	adrenergic reuptake inhibitor	3 months	elevated blood pressure, increased heart rate
Xenical (Orlistat)	lipase inhibitor	up to one year	GI side effects
Topiramate	carbonic anhydrase inhibitor	used off label in obesity	cognitive impairment

Source: BofAML Global Research

Script trends

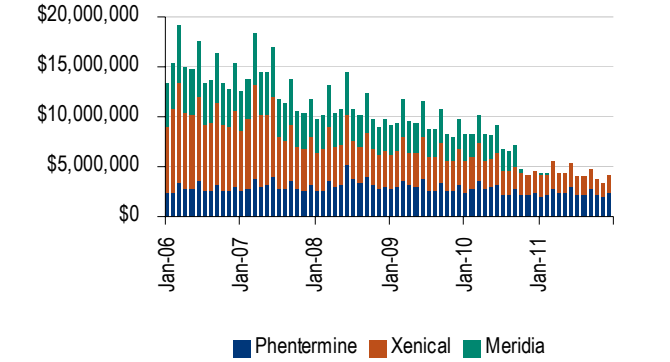
While only approved for short-term weight loss, phentermine has been the standard of care in this indication, with roughly 500,000 scripts per month, generating $2-3mn in sales (see Charts 10 and 11). Xenical generated $5-10mn in US monthly sales a few years ago, but this market has shifted to OTC Alli. Roche reported 2011 global Xenical sales of ~$260mn, down from ~$370mn in 2010. Meridia was a $5mn per month drug but was removed from the market in 2010.

Chart 10: Script trends for weight loss drugs
(TRx per month)



Source: IMS

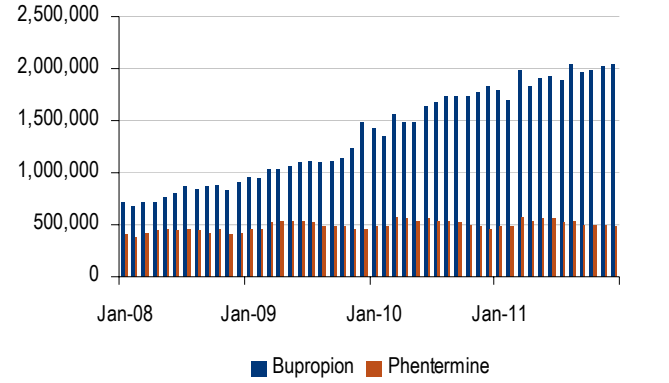
Chart 11: Sales of weight loss drugs have declined
(sales per month)



Source: IMS

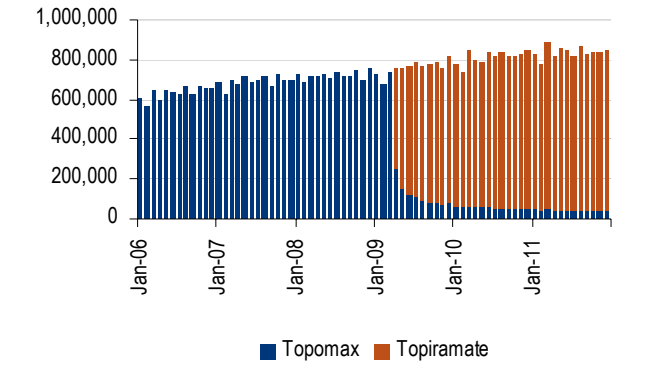
We do not view phentermine scripts as the sole indicator of the market potential for purchases of weight loss drugs. For example, bupropion is one of the two active ingredients in Orexigen's Contrave, and more than 2 million scripts of buproprion are written each month, primarily for depression. We believe Contrave, if approved, could capture a large portion of bupropion scripts, as weight loss has been demonstrated to reduce depressive symptoms. Similarly, topiramate is one of two ingredients in Vivus' Qnexa, and more than 800,000 scripts of topiramate are written per month, largely for migraine prophylaxis.

Chart 12: Bupropion script trends
(TRx per month)



Source: IMS

Chart 13: Topiramate script trends
(TRx per month)



Source: IMS

Over-the-Counter weight loss industry substantial

Alli (Orlistat), purchased over the counter, is an FDA approved weight loss drug. There are several other products, weight loss supplements or weight management products (not FDA approved), that can be ordered online, from TV, vitamin shops, drug stores, and other retailers. Many of these products are advertised with slogans such as “lose up to 2 pounds per day,” like HCG (human chronic gonadotropin).

According to the Nutrition Business Journal, Americans spent about $1.7bn for weight loss pills in 2007

Products containing bitter orange, an ingredient similar to Ephedra (an adrenaline-like stimulant removed from the market in 2004, known to have CV effects and increased BP), had estimated sales of $20mn in 2009. There are many other weight loss supplements that can be purchased, but these can also contain certain risks. Many have contained traces of bumetanide and sibutramine.

According to the CDC, In the United States, 15% of adults reported use of weight-loss supplements in 2007

Americans spent an estimated $28.1bn on dietary supplements in 2010 (including non-weight loss products). Furthermore, Americans spend around $40bn/year on weight loss programs and products; people are spending money to lose weight and most likely trying several options. According to IASO, sales of weight-loss OTC products in Western Europe reached $1.4bn in 2009. While weight loss drugs are most often not covered by payors (with few exceptions), people are willing to pay out of pocket for weight loss.

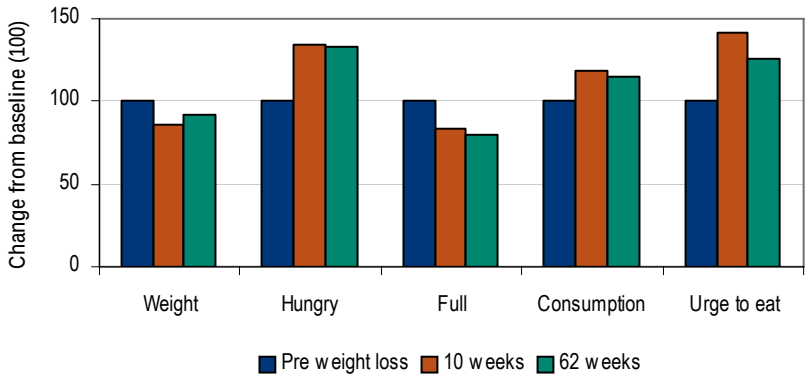
Non-drug Weight Loss Programs

A recently published NEJM study demonstrated that several peripheral hormones that encourage weight gain are altered significantly in response to aggressive weight loss and do not revert to pre-weight loss levels after more than one year (see Charts 14 and 15). These compensatory mechanisms likely encourage weight regain, which is widely observed in weight loss patients. The authors conclude that effectively countering this hormonal response may require a combination of weight loss drugs.

Hormones resist weight change

Sumithran et al. monitored hormone levels in obese patients (ave. BMI of 34.7) that completed an aggressive 10-week weight loss program (average weight loss of 14%). Roughly half the lost weight was regained in the first year, an outcome typical of many weight loss programs. Coincident with the initial weight loss and the gradual weight regain, patient hunger levels, sensation of fullness, prospective food consumption and the urge to eat all remained significantly different from baseline levels after one year (see Chart 14).

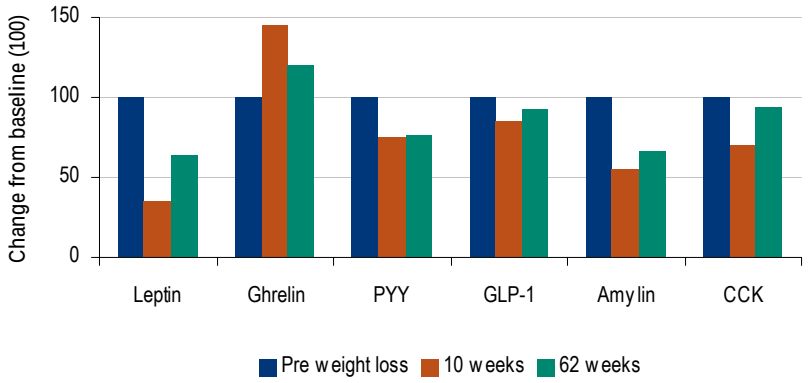
Chart 14: Hunger and urge to eat rise after weight loss
(values normalized to 100)



Source: Data obtained from N Engl J Med 2011: 365: 1597-604

The key hormones that were also associated with the weight change included the adipocyte hormone leptin, and the gastrointestinal hormones peptide YY, GLP-1, amylin, and cholecystokinin, which all act by decreasing appetite, and all remained well below baseline levels after one year of weight loss (see Chart 15). On the contrary, the gastrointestinal hormone ghrelin acts by stimulating hunger, and remained significantly above baseline levels after one year, which likely also contributed to weight regain.

Chart 15: Hormone changes after weight loss
(values normalized to 100)



Source: Data obtained from N Engl J Med 2011: 365: 1597-604

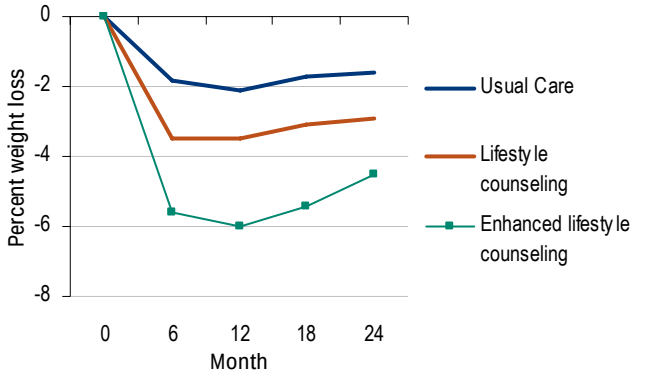
Coaching studies have limited effectiveness

Two NEJM articles published recently discussed several methods of behavioral weight loss intervention, which had limited effectiveness. Wadden et al examined three weight loss methods for obese patients (avg. BMI of 38.5); usual care, brief lifestyle counseling, and enhanced brief lifestyle counseling. Patients in the enhanced study received Sibutramine, Orlistat, or meal replacements to increase weight loss. Weight loss in this latter group was significantly improved from the control treatment, but peaked near 5% weight loss (see Chart 16).

Appel et al examined the effects of remote vs. in-person support, as well as a self-directed control group for obese patients (avg. BMI of 36.6) with at least one CV risk factor. The two types of support mechanisms were roughly equivalent in

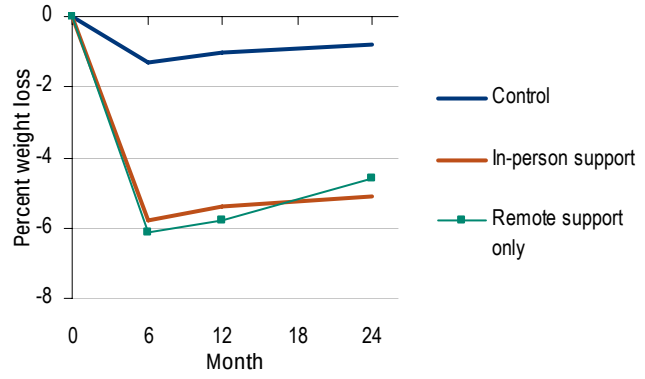
weight loss, peaking near 5% (see Chart 17). Neither study observed significant changes in cardiovascular parameters.

Chart 16: Medication or meal replacement enhances results



Source: Data obtained from NEJM 10.1056/NEJMoa1109220)

Chart 17: Minimal difference in weight loss by support type



Source: Data obtained from NEJM (10.1056/NEJMoa1108660)

Bariatric surgery

Achieving significant weight loss (greater than 15%) in morbidly obese patients using non-surgical methods (e.g. diet, exercise, drugs) is challenging. For these patients, surgery is the only treatment demonstrated to achieve and maintain significant weight loss. There are three basic types of surgical procedures used for the treatment of morbid obesity: (1) restrictive procedures reduce the size of the stomach, leading to a feeling a fullness after eating small amounts of food, (2) malabsorptive procedures bypass areas of the gastrointestinal tract, leading to lower absorption of digested food, and (3) combination procedures involve both restrictive and malabsorptive elements.

The most common bariatric procedure in the US is gastric banding, which involves laparoscopically placing an adjustable silicone band around the upper part of the stomach, reducing the pathway for food (restrictive). Following gastric banding, patients generally lose less excess weight (40-50%) over a longer period of time (2 years) relative to gastric bypass, but the procedure is simpler than gastric bypass, reversible, and has a lower rate of mortality and complications. Two companies currently market gastric bands in the US, Allergan (Lap-Band) and J&J (Realize band).

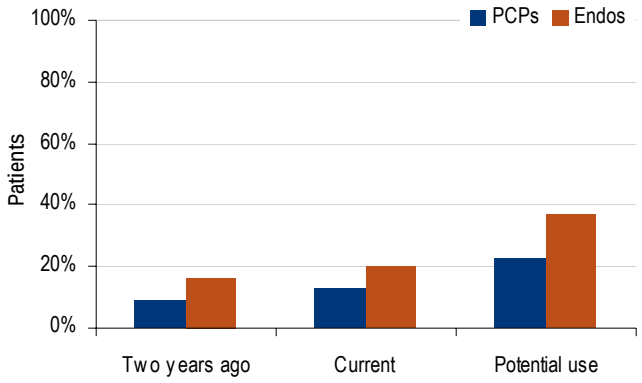
Previously the most common bariatric procedure (before banding gained in popularity), gastric bypass involves reducing the size of the stomach (restrictive) and re-routing the small intestine to reduce digestion (malabsorptive). Gastric bypass can lead to a significant amount of excess weight loss (60-70%) in a relatively short period of time (1-2 years), which can be sustainable for many years. However, given the invasive nature of the procedure and generally poor health status of patients, there are high rates of morbidity and mortality. Another procedure that has been gaining popularity in the US is sleeve gastrectomy, which involves significantly reducing the size of the stomach (restrictive) while leaving the small intestine intact. While sleeve gastrectomy can lead to less excess weight loss relative to gastric bypass, the procedure helps patients avoid complications associated with re-routing the small intestine.

Physicians eager for new therapies

Our survey screening criteria included a requirement that at least 10% of physician patients had to be treated for weight loss (likely well above the national average).

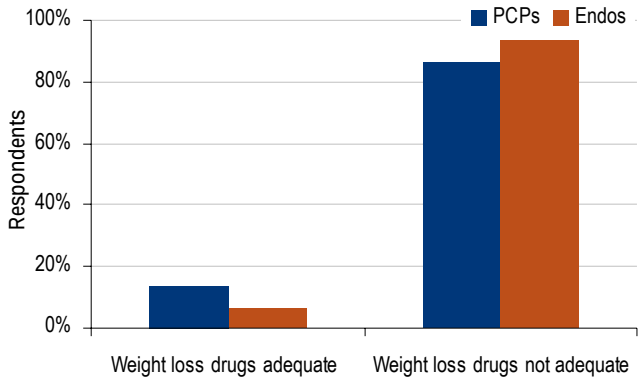
Our survey of 75 physicians conducted in October 2011 indicated that 23% of PCPs and 37% of Endos believed that their patients not currently on weight loss drugs would benefit from weight loss therapy (Chart 18). Compared to a year earlier, doctors have increased the number of weight loss scripts, and see an even greater potential in the future, while also expressing the need for new drug treatment options (Chart 19).

Chart 18: Physicians plan to increase number of weight loss scripts...



Source: BofAML Global Research

Chart 19: ...but are looking for a better drug

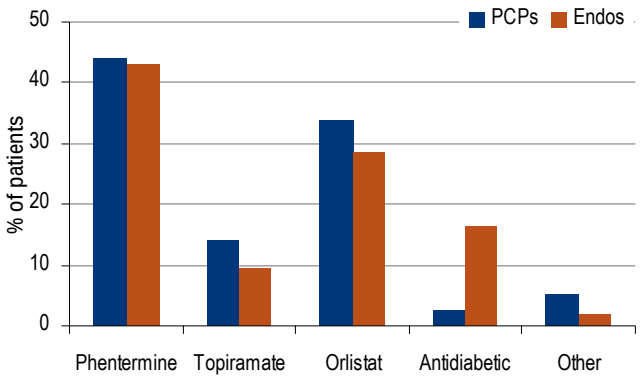


Source: BofAML Global Research

Limited options, short time period

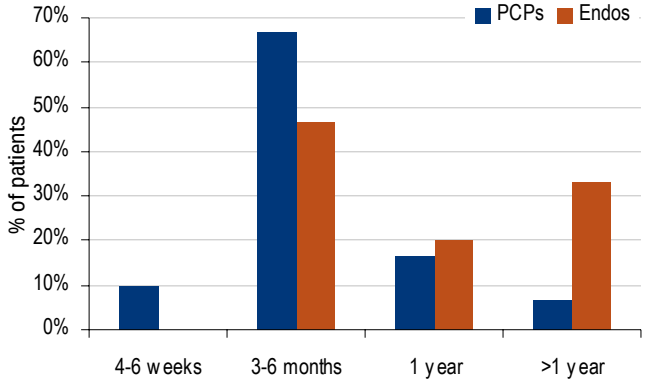
The highest percentage of both PCPs (44%) and Endos(43%) prescribed phentermine as their weight loss therapy of choice, followed by 34% of PCPs and 29% of Endos prescribing Orlistat (see Chart 20). Most patients stayed on these medications for 3-6 months (see Chart 21).

Chart 20: Current weight loss scripts



Source: BofAML Global Research

Chart 21: Current time period on drugs



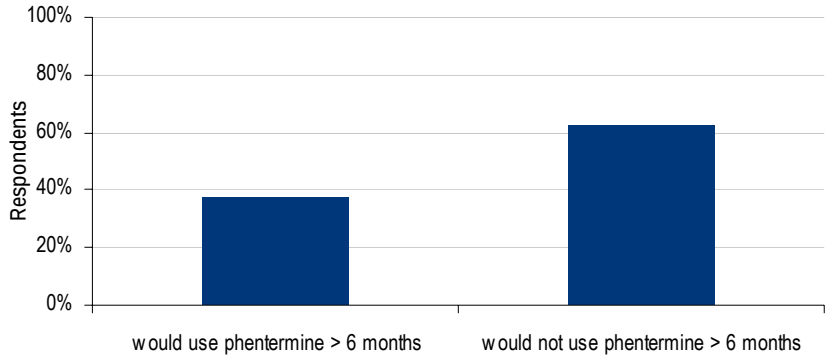
Source: BofAML Global Research

There is need for medications that can be used long-term

According to our survey, 61% of patients pay for obesity therapy out of pocket

While doctors plan to continue prescribing phentermine, they would be less inclined to prescribe this drug for longer than a 6-month period (Chart 22). The average length of time that patients were prescribed phentermine was 18 weeks.

Chart 22: 63% of doctors surveyed would not prescribe phentermine long term



Source: BofAML Global Research

Payor Perspectives

Lack of insurance coverage

According to a recent NEJM editorial, less than 50% of PCPs report providing diet and weight-control advice to overweight and obese patients and less than 25% report following up with patients on weight management or referring them for outside help. On July 15, 2004, the Center for Medicare and Medicaid services (CMS) removed the restriction that stated obesity was not a disease. This was subsequently followed by adding coverage of bariatric surgery, but did not affect weight loss drugs. According to National Coverage Determinations (NCD) 40.4 on the treatment of obesity, surgery is only covered if a patient has a co-morbid condition: “Treatments for obesity alone remain non-covered.” Most insurance policies have focused on bariatric surgery, while weight loss drug coverage remains more uncertain.

Medicare

In 2005 Medicare began coverage of weight loss surgery for patients with a BMI ≥ 35, a co-morbidity, documented evidence of repeated failure to lose weight, the fact that the patient had ruled out of all other medical treatments, and a psych evaluation. As of 2011, Medicare implemented coverage of up to three hours of weight loss counseling in the first year and two hours each year after that. Coverage after one year is contingent upon weight loss of at least 6.6 lb weight in 6 months. Yet, according to a STOP Obesity Alliance survey, 72% of PCPs do not have training in weight management. In terms of weight loss medications, Part D plan sponsors can include weight loss drugs as part of supplemental benefits.

Medicaid

In 2008, 10 states covered weight-loss drugs under Medicaid (only 2 without restrictions or pre-authorization)

Medicaid weight loss surgery and other obesity coverage vary state by state (see Tables 4 and 5). According to the data, 10 states covered drug therapy, 8 stated they did not and 33 were not explicit on the subject. In terms of covering bariatric surgery, 45 states mentioned coverage, 3 stated they did not, while 3 did not mention the topic.

Regarding childhood obesity, 4 states discuss treatment standards, 9 provide details on how to screen for childhood obesity, and 10 provide for reimbursement of nutritional behavioral counseling.

Table 4: Legend

Y = strong evidence for coverage
N = specifically excluded
UN = undetermined
* = restrictions
** = preauthorization required

Table 5: Medicaid coverage: adult obesity

2008 Medicaid data

State	Nutritional Consultation	Drug Therapy	Bariatric Surgery
Alabama	N	N	Y*
Alaska	Y*	N	Y**
Arizona	Y	UN	Y
Arkansas	UN	UN	Y**
California	N	UN	Y**
Colorado	N	Y**	Y*
Connecticut	N	UN	Y
Delaware	Y**	Y**	Y**
District of Columbia	UN	UN	Y**
Florida	N	UN	Y**
Georgia	Y	N	Y**
Hawaii	N	UN	Y**
Idaho	Y*	UN	Y*
Illinois	N	UN	Y**
Indiana	Y	Y	Y
Iowa	Y	Y**	Y**
Kansas	N	N	UN
Kentucky	Y	UN	N
Louisiana	Y	Y	Y
Maine	Y	UN	Y**
Maryland	UN	UN	Y**
Massachusetts	UN	UN	Y*
Michigan	Y*	UN	Y*
Minnesota	Y	Y**	Y**
Mississippi	Y	Y**	N
Missouri	Y*	UN	Y*
Montana	N	UN	UN
Nebraska	N	UN	Y*
Nevada	Y	UN	Y*
New Hampshire	N	UN	Y*
New Jersey	N	UN	UN
New Mexico	N	UN	Y**
New York	UN	UN	Y*
North Carolina	Y	UN	Y*/**
North Dakota	Y*	UN	Y**
Ohio	N	N	Y**
Oklahoma	Y	N	Y*
Oregon	Y*	UN	Y**
Pennsylvania	Y	UN	Y**
Rhode Island	Y	UN	Y**
South Carolina	Y*	Y**	Y*
South Dakota	N	UN	Y*
Tennessee	N	UN	Y
Texas	N	UN	N
Utah	N	UN	Y**
Vermont	Y	UN	Y**
Virginia	Y*	Y**	Y**
Washington	Y*	N	Y
West Virginia	N	UN	Y*/**
Wisconsin	Y*	Y**	Y**
Wyoming	N	N	Y**

Source: Leee et al. Public Health Reports. (based on online Medicaid data 2008).

According to a 2008 Conference board report, employers investing in wellness and health programs can generate an ROI of 500%.

Private Payors

Private Payors can offer coverage for weight loss drugs if the employer chooses to do so. The drugs would fall under the 3rd tier (non-preferred brand-name drugs; most expensive) and would require prior approval (PA). According to a recent Vivus presentation, Boeing, Pitney Bowes, and the United Auto Workers all offer coverage options.

In a state-wide private insurance survey conducted by George Washington University's Department of Health Policy, less than half of the states mentioned any coverage of obesity-related treatments. Of the 21 that mention obesity related coverage, 2 (Utah and Illinois) mention that they allow plans to *not* cover obesity-related procedures (Illinois does allow plans to provide discounts for wellness programs to small groups. Of the 19 remaining states that offer coverage, most state that the plans *may* provide coverage, in most cases this coverage entails financial incentives for participation in health promotion programs. Only 5 states require any sort of obesity coverage (all 5 in both Small Group and Individual):

Table 6: States that require coverage of obesity related treatment

State	Coverage
Indiana	Requires surgical treatment of morbid obesity (if persisted for at least 5 years & unresponsive to other treatment)
Maryland	Must cover surgical treatments of morbid obesity, may provide up to 20% cost of coverage health incentives for wellness programs
New Hampshire	Requires coverage of obesity treatment (incl. surgery) and treatments of diseases caused by obesity
New Jersey	Requires coverage of health wellness exams and counseling
Virginia	Requires availability of coverage for treatment of morbid obesity through gastric bypass surgery and other methods

Source: data obtained from GWU Department of Health Policy

None of the states mentioned drugs, yet New Hampshire covers obesity treatment, which could potentially include drug therapy.

Regulatory Perspectives

In 1994, the Institute of Medicine released a study stating that obesity is a chronic condition, and should be treated the same way doctors treat other diseases; with medication and/or surgery. The United Nations met in September to discuss NCD's and ideas on controlling disease, with a focus on obesity and diabetes and plans to enact new policies (taxes, price measures, marketing of fatty foods, promotion of healthy diet etc). Chris Viehbacker, the CEO of Sanofi and Chairman of PhRMA, recently spoke out about the lack of guidelines towards development of obesity drugs. The group pointed out that there needs to be more clarity on drug approval for obesity drugs, so companies can determine if it would be a suitable investment.

Recent US actions

We view Medicare's adoption of obesity counseling onto coverage as a significant step in recognizing obesity as a legitimate health concern. There have also been proposals on how the government can aid in the fight against obesity including levying taxes on unhealthy food and drink, educational programs and incentives to maintain a healthy weight. Because of the difficulty of adults losing weight once obese, preventative measures have been vastly aimed at children, including Michelle Obama's LetsMove! campaign, Georgia's Strong4Life campaign, and infants, including recommendations to breast feed.

Proposed legislation at the state level

- MI: Obesity registry track BMI for children under age 18
- AZ: $50 annual fee on obese Medicaid beneficiaries (who are not trying to improve health)
- 12 states: proposed 20 bills on taxation of food and/or beverages; 7 failed, 13 pending
- 13 states: 26 bills on sugary beverages; 19 failed, 7 pending

FDA

The Senate Appropriations committee stated in their September 2011 report that the "lack of obesity medications is a significant unmet medical need," and therefore by March 30, 2012 the FDA must report back with "the steps it will take to support the development of new treatments for obesity, including the use of its Risk Evaluation and Mitigation Strategy and other post-marketing authorities, to mitigate risk and ensure rigorous post-market scrutiny while increasing access to novel medications."

Senate Appropriations Committee: "the lack of obesity medications is a significant unmet medical need"

EU Outlook

The EMA removed Meridia just prior to FDA's actions and we believe a similar level of caution will be shown to obesity drug applications in the European Union. The EMA is currently reviewing liver toxicity cases in Orlistat, and is also expected to respond to VVUS' MAA in Q1 2012.

Round two for FDA obesity ad coms

ARNA's Lorqess

Lorcaserin is well tolerated, but modestly efficacious

Lorcaserin (trade name Lorqess) is a specific agonist for 5HT2c receptors in the brain, which control hunger levels. By acting as an agonist at this receptor, lorcaserin increases the sensation of satiety. Fenfluramine, 5HT2c receptor agonist with less binding specificity than lorcaserin, was one of two components in the diet drug fen-phen (marketed by Wyeth) that showed impressive 15%+ weight loss but was withdrawn from the market in 1997. Fenfluramine was found to bind 5HT2b receptors in the heart, which led to increased risk of carcinoid-like cardiac valvular disease (over 20 cases had been reported by 1997).

The key phase 3 trials for lorcaserin were the BLOOM (Behavior Modification and Lorcaserin for Overweight and Obesity Management) and BLOSSOM (Behavior Modification and Lorcaserin Second Study for Obesity Management) studies. The BLOOM-DM trial which examined the drug's impact on obese patients with diabetes showed weight loss greater than placebo, improved glycemic control and minor adverse events (mostly headache).

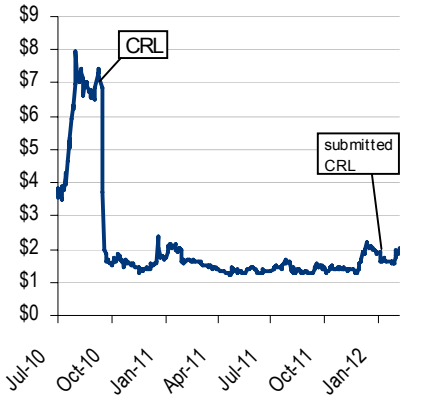
Both the BLOOM and BLOSSOM studies achieved the second requirement of 35% of patients losing equal to or greater than 5% of their body weight. Adverse events from lorcaserin were mild. Discontinuation rates in Year 1 of the BLOOM trial for the lorcaserin and PBO arms were 7.1% and 6.7%, respectively, and were 3.0% for both arms in Year 2. There was no increased incidence of valvulopathy in the two-year BLOOM trial (lorcaserin treated patients actually had slightly fewer cases valvulopathy than placebo treated patients).

Table 7: Pending obesity drug FDA action dates

Company	Drug	Ad Com date	PDUFA date
Arena	Lorqess	2Q 2012	6/27/12
Vivus	Qnexa	2/22/12	4/17/12
Orexigen	Contrave	TBD	est. 2H 2014

Source: company reports

Chart 23: ARNA Price chart



Source: Bloomberg, company reports

Table 8: Summary of BLOOM and BLOSSOM weight loss results

	BLOOM		BLOSSOM		
	10mg BID	PBO	10mg BID	10 mg QD	PBO
Mean weight loss (per protocol)	8.20%	3.40%	7.90%	6.50%	3.90%
Mean weight loss (ITT-LOCF)	5.80%	2.20%	5.90%	4.80%	2.80%
≥5% weight loss (per protocol)	66.40%	32.10%	63.20%	53.10%	34.90%
≥5% weight loss (ITT-LOCF)	47.50%	20.30%	47.20%	40.20%	25.00%
≥10% weight loss (per protocol)	36.20%	13.60%	35.10%	26.30%	16.10%
≥10% weight loss (ITT-LOCF)	22.60%	7.70%	22.60%	17.40%	9.70%

Source: company reports (ITT-LOCF is Intent to treat with last observation carried forward)

BLOOM-DM Results

In November 2010 Arena provided positive topline results from its BLOOM-DM trial (604 obese diabetics). At week 52, 37.5% of lorcaserin (10mg 2x/day) treated patients achieved 5% weight loss, vs. 16.1% of those on placebo (PBO).

While the relatively small BLOOM-DM trial (~250 in each of the PBO and 2x/day drug arms) was not powered to assess risk of valvulopathy and previous larger trials have not shown a valvulopathy signal, there were 6 reported cases of FDA defined valvulopathy in the lorcaserin-treated patients (1 in the PBO arm).

FDA requested several data points in Lorqess' CRL

In October 2010 Arena received a complete response letter (CRL) from FDA for Lorqess (lorcaserin), in the treatment of obesity. The FDA requested Arena's results from its BLOOM-DM trial in diabetic patients, highlighting the 'marginal efficacy' seen in non-diabetic patients.

Arena presented various data in 2011 to address key questions highlighted in the CRL. We summarize their findings below:

Valvulopathy: Arena assessed lorcaserin's serotonin 2B receptor activity relative to reference compounds known to cause valvulopathy. While not yet complete, these analyses are generally supportive of a minor valvulopathy signal.

Brain astrocytomas: Partitioning data for lorcaserin between blood serum and cerebrospinal fluid, relative to comparable results for rats, represents a 70-fold margin of safety between lorcaserin doses that did not cause astrocytomas in rats and the proposed human dose.

Mammary tumors: The readjudication of the rat mammary tumors justified the inclusion of only the malignant types, which provided a 24-fold margin of safety for the proposed human dose (no margin of safety previously). Arena also conducted time to death from adenocarcinomas in rats, which was generally consistent with this margin of safety conclusion. Arena provided results from 3-month rat mammary tumor studies to evaluate whether its weight loss drug lorcaserin causes mammary tumors through a prolactin-mediated mechanism, which is generally viewed as being not relevant to humans.

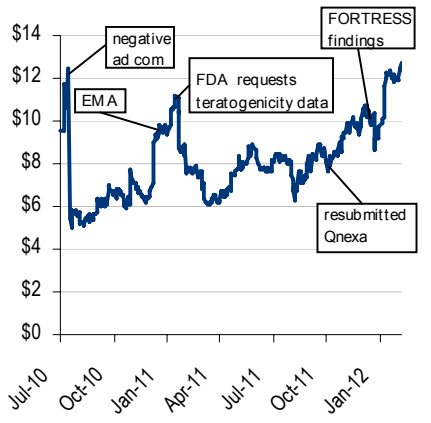
Arena submitted a response to the FDA's CRL on December 27, 2011 and was assigned a PDUFA date of June 27, 2012, with an ad com scheduled for 2Q 2012. The company plans to file an MAA in Europe 1H 2012, and is looking to secure a partner outside of U.S.

Table 9: Key issues for upcoming ad com

Impact on plasma prolactin was short term, raising doubts about L/T impacts
Illogical inverse relationship between lorcaserin dose and PCNA staining
Inconsistency between 3-month and 2-yr studies in pituitary prolactin impacts
Inconclusive results when compared to positive control (perphenazine)
Male rat tumor study not supportive of prolactin hypothesis

Source: BofAML Global Research

Chart 24: VVUS price chart



Source: Bloomberg, company reports

VVUS' Qnexa

Qnexa shows greater than 10% efficacy

Qnexa is the combination of two drugs, topiramate and phentermine, both of which have been approved for several years and have individually been shown to cause weight loss. Topiramate (branded as JNJ's Topamax) is an anticonvulsant that is approved to treat epilepsy and migraine headaches, while phentermine is an amphetamine that is indicated for short-term use for weight loss through appetite suppression. When the components are taken individually, both can induce weight loss but with significant side effects. The combination of the two drugs in the key phase 3 trials (CONQUER and EQUIP) resulted in more pronounced weight loss with fewer side effects than when taken individually.

The CONQUER study included 2,487 overweight and obese patients (1,737 females and 750 males) with high blood pressure, high cholesterol or type 2 diabetes. The study was a randomized, double-blind, placebo-controlled, 3-arm prospective trial with patients randomized to receive once-a-day treatment with mid-dose Qnexa, full-dose Qnexa or placebo. The average baseline BMI of the study population was 36.6 kg/ m2 and baseline weight was 227 pounds. Patients had a 4-week dose titration period followed by 52 weeks of treatment. At the end of the 56-week study, average weight loss for the intent to treat patients (ITT-LOCF) was 8.4% and 10.4% for the mid-dose and full-dose, respectively. Patients that received all treatments (completers) had even higher weight loss percentages. Completion rates were 57%, 69% and 64% for patients taking placebo, mid-dose and full-dose, respectively.

Table 10: CONQUER trial results

	ITT LOCF			Completers		
	PBO (n=979)	Mid (n=488)	Full (n=981)	PBO (n=564)	Mid (n=344)	Full (n=634)
Mean Wgt loss	1.80%	8.4%*	10.4%*	2.4%*	10.5%*	13.2%*
≥5% weight loss	21%	62%*	70%*	26%	75%*	85%*

Source: Company reports; * p<0.001

Table 11: CV risk factors in high risk patients (upper 25%ile of a co-morbidity)

	Drug	PBO
Systolic BP*	-20 mmHg	-14 mmHg
TG*	-98mg/dL	-42mg/dL
HbA1C	-0.6%	-0.10%

Source: Company reports

The EQUIP study evaluated 1,267 morbidly obese patients (1,050 females and 217 males) with low-dose Qnexa (3.75/23), full-dose Qnexa (15/92) or placebo. About 26% of patients enrolled in the study had previously reported some history of psychiatric disorder that consisted primarily of depression. The average BMI of the study population was 42.1 kg/m^2 and baseline weight was 256 pounds. Patients had a four-week dose titration period followed by 52 weeks of treatment. average weight loss for the intent to treat patients (ITT-LOCF) was 5.1% and 11% for the low-dose and full-dose, respectively. Nearly 60% of the full dose Qnexa patients who completed the study lost at least 10% of their baseline weight, and 43% of the patients who completed the study lost at least 15% of their baseline weight. The completion rates for patients were 47%, 57% and 59%, respectively, for patients taking placebo, low dose and full-dose Qnexa.

Table 12: EQUIP Study results

	ITT LOCF			Completers		
	PBO (n=498)	Low (n=234)	Full (n=498)	PBO (n=241)	Low (n=138)	Full (n=301)
Mean Wgt loss	1.60%	5.1%*	11%*	2.50%	7%*	14.7%*
≥5% weight loss	17%	45%*	67%*	26%	59%*	84%*

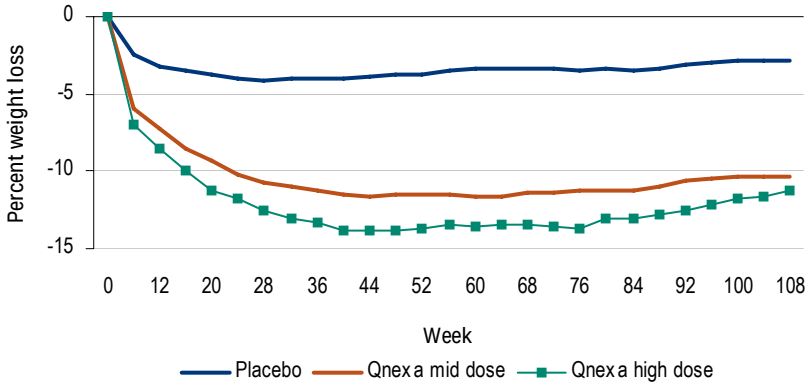
Source: Company reports; *P<0.0001 vs. PBO

Paresthesias were reported by 20% of high dose Qnexa patients in the two trials, and 17% of high dose Qnexa patients discontinued due to AEs (adverse events), which was twice the placebo rate. In 2007 Johnson & Johnson terminated its

development program for topiramate (Topamax) in obesity due to CNS effects that included paresthesias. Topamax has been associated with side effects that include cognitive impairment and mood changes. Other adverse events that demonstrated a significant treatment effect included gastrointestinal disorders (dry mouth and constipation) and psychiatric disorders (insomnia and disorder). However, based on the Patient Health Questionnaire 9 (PHQ-9) depression scale, there was no significant treatment effect on worsening depression scores. The label for Topamax in migraine prevention notes a 3% discontinuation rate due to disturbance in attention.

The SEQUEL study demonstrated significantly increased weight loss in both the mid and high doses of Qnexa versus the control treatment (see Chart 25). Patients in this study experienced reduced progression to diabetes, higher resolution of metabolic syndrome, and reduced cardiovascular risk factors, including reductions in systolic and diastolic blood pressure in all groups and reduced need for antihypertensive medications.

Chart 25: SEQUEL results



Source: Data obtained from data presented at 2011 ACC conference

FDA highlighted safety in its Qnexa CRL

The 10-6 negative vote by an FDA advisory committee in July 2010 was based primarily on panel members' concerns surrounding safety. The specific concerns revolved around teratogenicity, CV risk, cognitive and neuropsychiatric adverse events. The committee suggested drug labeling and post approval risk mitigation would be the best path to follow with regard to the teratogenicity concern.

FORTRESS Study of fetal malformations

The FORTRESS study reviewed medical claims databases to assess cleft palate presence in two topiramate and two control cohorts (Table 13). Cohort #1 (topiramate combo therapy) is additive to cohort #2 (topiramate monotherapy) by including patients treated with topiramate along with other antiepileptic drugs. Note the additional 205 patients had 2 oral clefts, representing a prevalence rate of 1% vs. 0.29% for the monotherapy cohort. Cohort #3 (prior topiramate use) was similar to #2, only patients in the control group were not receiving topiramate during the pregnancy. Cohort #4 (similar medical profile) was represented by similar disease diagnoses (ICD-9 codes) as #1, but had no requirement for previous topiramate use, and thus disease severity could have been less.

Table 13: Oral cleft prevalence in four cohorts

	#1: Topiramate combo therapy	#2: Topiramate monotherapy	#3: Prior topiramate use	#4: Similar medical profile
# of oral clefts	7	5	21	9
# of dyads	1945	1740	13512	13614
Prevalence rate	0.36%	0.29%	0.16%	0.07%

Source: Vivus

Cohort comparisons

The prevalence ratios and respective 95% confidence intervals for the four pair-wise comparisons are presented in Table 14. Note that 2 of the 4 comparisons are not statistically significant (95% confidence interval includes 1.0). Due to the confounding bias from combo treatments in cohort #1, the first two pairs of comparisons are biased estimators of topiramate risk.

Table 14: Prevalence ratios for four cohort comparisons

Cohort comparison	Prevalence ratio	95% confidence interval
#1 vs #3	0.36/0.16 = 2.32	0.99 – 5.47
#1 vs #4	0.36/0.07 = 5.46	2.03 – 14.68
#2 vs #3	0.29/0.16 = 1.85	0.7 – 4.92
#2 vs #4	0.29/0.07 = 4.35	1.46 – 13.0

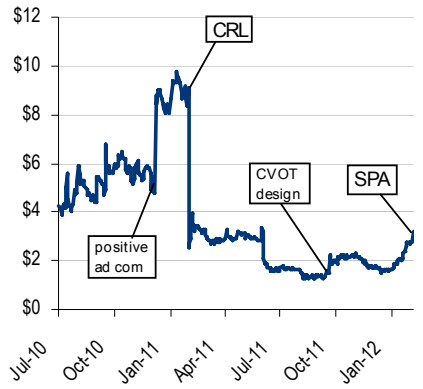
Source: Vivus

OREX' Contrave

Contrave weight loss: in between Lorcaserin and Qnexa

Contrave is a twice daily oral formulation of naltrexone (a generic opioid receptor antagonist used for substance abuse treatment) and bupropion (brand name Wellbutrin, used to treat depression), both of which have long been approved in their respective therapeutic categories. The key clinical trials for Contrave were the COR studies (COR-I, COR-II, COR-BMOD, COR-Diabetes). The primary endpoints for each trial were proportion of patients achieving at least 5% weight loss and percent change in body weight compared to placebo. Results from Orexigen's COR-I and COR-II trials indicated approximately 25-33% of patients on Contrave lost 10% or more of body weight and 12-16% lost at least 15%.

Chart 26: OREX price chart



Source: Bloomberg, company reports

Table 15: Results from COR-I and COR-II trials

	COR-1		COR-II	
	PBO (N=511)	Contrave32 (N=471)	PBO (N=456)	Contrave32 (N=702)
Mean Weight Loss (%)	1.3%	6.1%*	1.2%	6.4%*
≥5% weight loss	16.4%	48.0%*	17.1%	56.3%*
≥10% weight loss	7.4%	24.6%	5.7%	32.9%
≥15% weight loss	2.0%	11.9%	2.4%	15.7%
waist circumference (cm)	-2.5	-6.2	-2.1	-6.7
Fasting TGs (mg/dL)	-3.5	-18.1	-0.5	-11.8
Fasting HDL (mg/dL)	-0.1	+3.4	-0.9	+3.6
Fasting LDL (mg/dL)	-3.3	-4.4	-2.1	-6.2
hsCRP (mg/L)	-0.4	-1.1	+0.2	-0.8
High risk patients				
waist circumference (cm)	-2.8	-7.1	-2.2	-7.3
Fasting TGs (mg/dL)	-32	-66.3	-13.9	-51.2
Fasting HDL (mg/dL)	+1.3	+5.0	+1.3	+6.2
Fasting LDL (mg/dL)	-22.5	-12.8	-8	-27.3
hsCRP (mg/L)	-0.7	-2.9	-1.1	-1.6

Source: company reports

Patients on Contrave had significant improvements in markers of cardiometabolic risk, including waist circumference, HDL and triglycerides, particularly with high risk patients.

Orexigen's COR-DM trial for diabetics indicated that patients on Contrave experienced an average reduction in HbA1c (marker used to assess blood glucose control) levels of 0.6%, versus 0.1% for placebo. Over 44% of patients achieved the ADA treatment target of less than 7% A1c, compared to 26% of patients taking placebo. Patients that had starting A1c levels greater than 8% experienced an average improvement of -1.1% compared to -0.5% in patients on placebo (p<0.01), indicating the drug has applicability in patients with poor glycemic control. Improvements in other key measures of CV and metabolic risks were also observed (see Table 16).

CV risks highlighted at ad com

Key discussions at the December 2010 ad com surrounded cardiovascular risks associated with the drug, ending with the panel requesting a post-approval CV trial. However, in January 2011, the FDA issued Contrave a CRL citing unresolved questions on the drug's impact on CV function.

After much discussion, OREX and the FDA have reached a final agreement on a cardiovascular outcomes trial (CVOT) planned to begin in Q2 2012. In the study, patients who do not achieve weight loss by week 16 as well as those with significant increases in blood pressure will be discontinued. We calculate that the CVOT will achieve the targeted goal of excluding an upper confidence interval for the hazard ratio of 2.0 if there are as many as 49 MACE events in the Contrave arm vs. 38 in the placebo arm.

OREX recently announced (Feb. 6) that its CVOT will be conducted under a Special Protocol Assessment (SPA), a contract with the FDA regarding clinical trial design and analysis.

Table 16: Key end points in COR-DM trial

	Contrave32	Placebo
waist circum. (cm)	-5.0**	-2.9
Triglycerides, %	-11.2%**	-0.80%
HDL cholesterol, mg/dL	+3.0***	-0.3
LDL cholesterol, ml/dL	-1.4	0.0
Glucose, mg/dL	-11.9	-4.0
Insulin, %	-13.5%	-10.4%
HOMA-IR, %	-20.6%	-14.7%
hs-CRP %	-20.9%	-13.3%

**p<0.01 vs. PBO; ***p<0.001 vs. PBO; source: company reports

New approaches towards obesity

The limited treatment options available as well as the few currently in development are either aimed at suppressing appetite or speeding up metabolism, and thus can have CV or psychological risks. There are several early-stage development companies taking novel approaches towards tackling obesity. We highlight three obesity-centric private companies below:

Table 17: Obesity related catalysts

Feb. 22, 2012	Qnexa ad com
Mar. 28-29, 2012	Weight loss drugs CV ad com
March 2012	FDA response to senate
April 17, 2012	Qnexa PDUFA
Q2 2012	Lorcaserin ad com
Q2 2012	Planned start of Contrave CVOT
June 27, 2012	Lorcaserin PDUFA
H2 2014	Potential Contrave PDUFA

Source: Company reports

- **Ablaris Therapeutics**, through work at M.D. Anderson (cancer center), is developing an obesity drug, adipotide, that targets blood vessels that feed white fat tissue. In a 28-day trial in obese monkeys, the monkeys lost on average 11% of their body weight. The experimental drug is not yet being tested in humans, but researchers hope to begin trials in 2012, with the first in obese prostate cancer patients.
- **Zafgen Inc**., a private venture backed company founded in 2005, is in phase 1b development with a drug, ZGN-433, designed to directly target and shrink fat cells in extremely obese patients. ZGN-433 is a Novel Methionine Aminopeptidase 2 (MetAP-2) Inhibitor, and because of the nature of the drug, appears to have lower cardiac or CNS risks than typical anti-obesity drugs. Data from a phase 1b study showed changes in fat metabolism as well as in leptin and adiponectin, hormones that affect energy and metabolism. The study showed an increased ratio of adiponectin/leptin by 241 percent, a decline in hunger and changes in lipid parameters. Zafgen plans to initiate phase 2 trials in the coming year.

White fat stores energy, brown fat burns off caloric energy.

- **Ember Therapeutics, Inc.** was launched by Third Rock Ventures in December 2011, with a focus on brown fat biology and metabolic diseases. Adults lose most of brown fat stores, so this drug, the hormone irisin, would work by activating brown fat which could potentially lead to weight loss. The company hopes to test irisin in humans in two years.

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Healthcare

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