Fat chance

Obesity sector

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Over the past few years obesity has been labelled a global 'epidemic' responsible for rising healthcare costs, but current treatments have been beset with side effects or have shown insufficient efficacy. With several new treatments now in late-stage development, the obesity sector is likely to see significant interest from big pharma over the coming 18 months and could offer significant rewards for discriminating investors.

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COMPANIES IN THIS REPORT

Alizyme
Amylin
Arena
NeuroSearch
Orexigen
Vivus

A global problem

Obesity affects a large and increasing proportion of the population, including over 30% of Americans. Substantial health risks are associated, most importantly diabetes, although weight loss of as little as 5% can cut these risks by 50%. This report aims to compare the most promising late-stage anti-obesity projects on the basis of their safety and efficacy.

Key near-term indicators

The coming two years should determine the extent to which obesity is still a viable area for therapeutic intervention and big pharma involvement and, if so, which companies stand the most chance of achieving near-term success. 2008 is likely to see the first US filing of an anti-obesity project since rimonabant.

Failures of the past

The high-profile failures of Fen-Phen and rimonabant, a greater understanding of complex underlying pharmacological pathways and concerns about side effects have pointed the way towards new drug development. Current projects target multiple pathways, with an increasing focus on combination therapy.

Safety vs efficacy

A drug offering reasonable efficacy with limited side effects could easily become a blockbuster, and the greatest value for investors is contained in companies with late-stage products offering the best balance of safety and efficacy data. These are likely to attract the most lucrative deals with big pharma and capture the lion's share of the market.

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Exhibit 1: Companies profiled in this report

Notes: *closing price on 13 May 2008; **as of 31 Mar 2008.

Company	Country of listing	Share price ($)*	Market cap ($)*	2007 reported revenues ($)	Net cash ($)**	Obesity project(s)
Alizyme	UK	0.56	127m	0	20m	cetilistat
Amylin	US	29.15	3,932m	701m	100m	pramlintide combinations
Arena Pharmaceuticals	US	5.15	371m	19m	262m	lorcaserin
NeuroSearch	Denmark	57.03	878m	24m	171m	tesofensine
Orexigen Therapeutics	US	8.31	284m	0.9m	131m	bupropion + naltrexone bupropion + zonisamide
Vivus	US	5.24	307m	55m	156m	phentermine + topiramate

Source: Edison Investment Research

Investment summary: High-growth area

A range of projects under development

There are numerous anti-obesity agents in studies at present, with development being undertaken by a range of companies, including big pharma, speciality pharma and biotech. Several approaches are being investigated to treating the condition centrally, including cannabinoid receptor antagonism, neuropeptide Y and leptin to name a few, as well as using a peripheral approach by preventing the absorption of fat in the intestine. Following the high-profile withdrawal of fenfluramine and dexfenfluramine (part of the notorious 'Fen-Phen' diet combination) in 1997, and the recent failure of rimonabant to gain US approval, there is a perceived high barrier to approval for novel anti-obesity drugs and a major focus on new agents' side effect and tolerability profiles. Nevertheless, products with an acceptable risk-benefit profile should be able to gain a significant share of this blockbuster, fast-growing and significantly under-served market.

Co-morbidities

Numerous medical conditions – co-morbidities – have been associated with being overweight, and it is largely because of this that the sharp rise in obesity has started to be seen as such a significant global health problem. Most important among the co-morbidities is type 2 diabetes, but they also include hypertension, stroke and heart disease, and even the risk of malignancies and psychological disorders. This is a particularly interesting issue because obesity treatments can be seen as more than just 'lifestyle drugs', given that a reduction in weight of as little as 5% has been associated with a 50% decrease in co-morbidities (American Heart Association). Accordingly this is an area that has potential for reimbursement.

Key conclusions

We expect the following considerations to shape the anti-obesity sector:

- A number of important near-term triggers will determine the future course of the sector and indicate whether treatment of obesity with therapeutic intervention remains a possible blockbuster area worthy of multi-million dollar investment.
- The success or failure of one or more projects currently in late-stage development will shape the level of interest shown by big pharma in the obesity sector. At present, most of the late-stage projects remain unpartnered.
- We expect a growing focus on the development of therapies comprising a combination of two or more products. Projects currently in standalone development could ultimately be developed for combination use or prescribed in combination off label.
- Safety will remain the number one concern for the US FDA. As such, we believe that treating obesity with a CB1 antagonist is no longer a viable strategy.
- We expect 5-10% placebo-adjusted weight loss from baseline over 52 weeks to represent sufficient efficacy to warrant US approval, with activity below 5% acceptable only in the presence of significant safety/side-effect advantages.

BMI benchmark

The standard measure of obesity is the body mass index (BMI) – the individual's weight in kilograms divided by the height in metres, squared. For adults, a BMI of 18.5–25kg/m^2 is considered healthy and 25–30kg/m^2 overweight, 30–35kg/m^2 is denoted class 1 obesity, 35–40kg/m^2 class 2 obesity and 40kg/m^2+ class 3 obesity (also extreme or morbid obesity).

Regulatory stance

In 2007 the US FDA issued a draft guidance document for developers of weight management products. Among other recommendations, this suggested that Phase III studies should comprise 12 months of placebo-controlled exposure in 1,500 patients, followed by a second year of open-label exposure in 500 patients – a significant undertaking costing over $100m. Patients should be at significant risk of weight-related morbidity and mortality, including those with a BMI of above 30kg/m^2, or with a BMI of over 27kg/m^2 with co-morbidities, as well as a representative sample of the morbidly obese. In terms of efficacy criteria, the guidance suggests as co-primary endpoints the difference in mean percentage body weight loss in active vs placebo group and the percentage of subjects losing 5% or more of their baseline weight. Secondary endpoints should include changes in waist circumference and parameters relating to co-morbidities, such as blood pressure and lipids, lipoprotein lipids, fasting glucose and insulin, and HbA1c (in type 2 diabetics).

FDA approvals

Although prescription pharmaceuticals for treating obesity have been available for most of the 20th century, their development has been beset with problems. Most have been associated with limited efficacy – typically 5kg of placebo-adjusted weight loss – and significant side effects, including addiction potential and effects on the CNS and cardiovascular system.

Historically, the potential for abuse of approved drugs has been a major source of concern for regulators, especially in the case of those with an amphetamine-like profile, such as phentermine, phendimetrazine, benzphetamine and diethylpropion. Phentermine, a class IV controlled substance indicated for short-term use, appears still to be the most widely used anti-obesity agent. These older, short-term treatments are generally associated with a weight loss plateau, which is also typically seen with diet alone.

As the medical perception of obesity has changed, regulators have refined their criteria for approval, but the lack of a relatively safe and efficacious treatment for the subsection of patients who would most benefit from it has left a significant opportunity, and one that many pharmaceutical and biotech companies are attempting to capture.

Before 1996 all obesity drugs were approved for short-term treatment (ie, a few weeks) – a standpoint that contrasts with the current view of obesity as a chronic disease that needs to be treated chronically. Until current FDA guidance was adopted, anti-obesity drugs typically went through relatively short clinical studies of under 12 weeks' duration in only 200 to 400 patient exposures.

The current landscape

The landscape was shaken in the mid-1990s by two events: firstly, in 1996 the FDA issued draft guidance (since updated, in 2007) that introduced the concept of drugs for the chronic treatment of obesity, established BMI criteria and set standards for long-term safety and efficacy studies. It also made a clear link between obesity and various related co-morbidities, and recognised that maintenance of weight within reasonable boundaries was vital to reducing these co-morbidities.

This view has been borne out by subsequent studies showing that type 2 diabetes in certain obese patients could be treated by gastric banding, a surgical procedure in which a hollow band is inserted around the stomach, restricting gastric filling capacity and forcing the patient to lower his/her food intake. A recent study following patients with a BMI of 30–40kg/m^2 for two years after gastric banding surgery found that 73% achieved remission of type 2 diabetes, and that this remission was related to weight loss and lower baseline HbA1c levels ($p<0.001$; JAMA, 23 January 2008).

The second event occurred in 1997, with the worldwide market withdrawal of Wyeth/Servier's fenfluramine and dexfenfluramine, the so-called "Fen-Phen" diet drug combination (the name refers to the drugs' widely used off-label combination with phentermine, an earlier anti-obesity agent which is still sold). This combination treatment was something of a breakthrough in treating obesity in that it achieved a placebo-adjusted weight loss (around 10kg) that had never before been seen and has yet to be matched by any approved treatment. Dexfenfluramine was the first drug approved by the FDA for the long-term treatment of obesity. Fenfluramine and dexfenfluramine were withdrawn after being associated with heart valve damage, and the fallout resulted in years of product liability litigation costing the originator, Wyeth, billions of dollars.

Exhibit 2 outlines post-war FDA approvals of drugs for treating obesity. There have only been three drugs approved for long-term treatment – dexfenfluramine (withdrawn in 1997), Abbott's sibutramine (Meridia) and Roche's orlistat (Xenical).

Exhibit 2: US FDA approvals of anti-obesity drugs

Year approved	Drug name	Notes
1947	desoxyephedrine/methamphetamine	
1956	phenmetrizine (Preludin)	
1959	phendimetrazine (Bontril)	
1959	phentermine (Fastin, Ionamin)	Withdrawn by CPMP in 2000 – decision overturned 2003
1959	diethylpropion (Tenuate)	
1960	benzphetamine (Didrex)	
1972	fenfluramine (Pondimin)	Withdrawn 1997
1973	mazindol (Sanorex)	
1996	dexfenfluramine (Redux)	First approval for long-term use; withdrawn 1997
1997	sibutramine (Meridia)	Approved for long-term use
1999	orlistat (Xenical)	Approved for long-term use

Source: Presentation by Dr David Orloff

Market potential

It is generally recognised that the global market for obesity medications could be worth billions of dollars, given the large and growing population of the overweight and obese, and the recognition that the condition often leads to a range of co-morbidities which themselves are a significant drain on healthcare spending.

However, because of the side effects and limited efficacy of currently approved drugs, as little as 2% of the obese population in the US was treated with a pharmaceutical intervention in 2005 (Frost & Sullivan report), and no currently marketed anti-obesity treatment generates blockbuster sales; phentermine has been off-patent for years, and the two products that do have IP protection will shortly lose it (Xenical in 2009).

Current treatment approaches

Treatments for obesity consist of behavioural modification, pharmaceutical therapies and surgery, largely dependent on how obese the patient involved is. Modifications to diet and exercise are the preferred initial treatment, although on their own these measures tend only to be effective in the longer term among those with a relatively low BMI.

Surgery, including gastric bypass and gastric banding, is the approach taken in extreme cases, typically for obese individuals with a BMI of over 40kg/m^2. Surgery can be highly effective – sometimes helping patients lose 50% or more of their total body weight – but can be associated with potential complications including a long recovery time, substantial costs and death.

Pharmaceutical therapies, therefore, can be seen as targeting a large subsection of the obese patient population with a BMI of under 40kg/m^2 and generally those in whom behavioural modification alone has failed.

History of underachievement

After the high-profile withdrawal of Fen-Phen, the next drug to gain US approval was Abbott's Meridia (sibutramine), and this has now been on the market for over 10 years.

A meta-analysis of various studies published in 2005 indicated that sibutramine produces an average placebo-adjusted weight loss of around 4.5kg, but patients typically experience a plateau after 12 weeks. In addition, the drug has been associated with increased risk of hypertension and tachycardia – a significant risk for obese patients already susceptible to heart disease. No current figures are available for the product's sales, and given that Abbott no longer breaks these out in its analysis of key product revenues it can be assumed that Meridia generates a negligible amount of revenue.

Xenical – loose, oily stools; now OTC

Xenical (orlistat), meanwhile, was launched by Roche with much fanfare in 1999 and its initial revenues far exceeded the company and the market's expectations, nearly reaching SwFr1bn in the product's first full year on the market. However, despite an aggressive promotion campaign sales slowed sharply and the initial year of revenue has not been matched since; this is widely put down to patients discontinuing treatment owing to Xenical's unpleasant gastrointestinal side effects, which include flatulence, loose, oily stools and faecal incontinence. These are due to the drug's mechanism of action – it acts by binding fat in the gut and preventing its absorption, with the consequent egestion of unabsorbed fat in the faeces.

An over-the-counter version of orlistat has recently been launched by GlaxoSmithKline in a low-dose form under the brand name Alli. In the six months since it was launched in June 2007, Alli generated sales of £150m, but there was a strong stocking effect and Q108 revenue was £9m.

Rejection of rimonabant

Against this backdrop of historical safety/tolerability issues and relative lack of efficacy, the market launch of Sanofi-Aventis's rimonabant, a first-in-class selective CB1 (cannabinoid 1) antagonist, was eagerly awaited, the drug having been billed by some as the most promising weight loss treatment since Fen-Phen. However, in June 2006 an expert advisory panel to the US FDA voted against approving rimonabant, citing unresolved safety concerns.

This view was echoed by the FDA, which subsequently refused to approve the product. Rimonabant has been available in Europe (as Acomplia) since its approval by the EMEA in June 2006. The drug had undergone an extensive pivotal study programme, and US regulators were satisfied that it had demonstrated statistically significant efficacy – an average placebo-adjusted weight loss of around 5kg – but of concern was the effect that it was having on the central nervous system. In its review of rimonabant, the FDA experts described the drug's potential for causing suicide, suicide attempts or suicidal ideation; in 14 studies, the risk of suicidality was nearly double for subjects on rimonabant compared with those on placebo.

While Sanofi-Aventis has not given up on developing rimonabant in the US, it appears unlikely that the drug will be approved there in the near future, especially given the continued caution with which the FDA is progressing.

Effect on competitors

Of particular interest will be the effect that the rejection might have on other, competing anti-obesity projects. Approval for treating obesity has not yet been sought for any other drug since rimonabant, although a number are in mid- to late-stage clinical studies (see Exhibit 4).

Accordingly, the FDA's response to the next filing for an anti-obesity agent is likely to be seen as a key determinant of the future of treating the condition with pharmaceutical intervention. A number of other projects targeting cannabinoid receptors are in development, and it is possible that regulators will require significant additional safety data before approving a product with this mechanism of action, given the concerns over rimonabant. In particular, taranabant, a product under development by Merck & Co, acts on the endocannabinoid system (as a CB1 receptor inverse agonist) and is likely to be the next to test the FDA – its US filing is slated for the second half of 2008.

Other CB1 antagonists in development at Phase II or above include Pfizer's otenabant (in Phase III, with no date set yet for data publication), Sanofi-Aventis's rimonabant back-up AVE1625 (Phase IIb completed; no data published), and Bristol-Myers Squibb/Solvay's ipinabant (BMS-646256; Phase II/III study was planned to begin in March 2008, but has been withdrawn from Clinicaltrials.gov). Also worthy of note is Vernalis's CB1 antagonist V24343, which produced placebo-adjusted weight loss of up to 5kg with statistical significance in a small Phase I study of only 16 days' duration, and will shortly be tested in Phase I at much lower doses in an attempt to minimise side effects that might arise in larger studies of longer duration. However, following the failure of rimonabant in the US, the future of all of these agents has to be considered to be in considerable doubt.

The rimonabant rejection, in the wider context of the FDA's growing focus on drugs' safety profiles and perceived increased caution in approving new treatments, will likely have effects that reach beyond products targeting the endocannabinoid system. The agency is likely to hold all centrally acting anti-obesity agents to a relatively high safety standard, given their perceived potential for abuse and need to dose chronically.

Comparison of clinical data

In Exhibit 3 we present a summary of Phase II data with key obesity drugs at Phase II and III, where such data are available, as well as some of the major obesity treatments that have been marketed or investigated in the past but have since been discontinued.

An important caveat is that long-term data (ie, at least six months, but preferably a full year of treatment) are available for only some of the products, meaning that the placebo-adjusted weight loss figures need to be interpreted with caution; the anti-obesity effect of a drug can reasonably be expected to continue beyond 12 weeks of treatment, so for instance it would be reasonable to expect the effect of cetilistat to be more in line with orlistat over a longer treatment period. However, the effects of many anti-obesity agents plateau after a certain amount of time.

Exhibit 3: Comparison of clinical data for marketed and developmental anti-obesity drugs

Note: *average placebo-adjusted weight loss (because treatment periods differ from study to study, caution must be exercised in interpreting these results); **no "placebo-only" arm, so a 3kg placebo response has been estimated to preserve uniformity. Some, but not all, studies included some level of diet/dietary instruction and/or exercise across all groups tested. N/A=not available.

Product	Company	Study duration (wks)	Dose/study details	Weight loss*		
				active	placebo	adjusted
cetilistat	Alizyme	12	612 pts, cetilistat 40mg, 80mg and 120mg, placebo and Xenical 120mg. 80mg and 120mg cetilistat active, highest most active.	4.32kg	2.86kg	1.46kg
orlistat	Roche	52		N/A	N/A	2.75kg
velneperit	Shionogi	12	Phase IIa study in 342 patients with BMI 30–40. Four-week diet run-in arm showed 5.3kg weight loss, but immediate weight reduction arm showed no statistical significance.	5.3kg	2.5kg	2.8kg
lorcaserin	Arena	12	6.8lbs weight loss at highest dose (20mg). (3.7lbs at 10mg, 4.8lbs at 15mg.)	3.08kg	0.18kg	2.9kg
pramlintide	Amylin	16	120µg, 240µg or 360µg, given two or three times/day before meals.	6.1kg	2.8kg	3.3kg
phentermine	(various)	2 to 24		N/A	N/A	3.6kg
liraglutide	Novo Nordisk	20	564 patients. Study compared liraglutide vs placebo and Xenical (4kg weight loss).	7kg	3kg	4kg
taranabant	Merck & Co	52	Phase III study in 2,500 pts with BMI 30-43 (or 27–43 with co-morbidities); 2mg, 4mg and 8mg doses. Higher doses associated with increased psychiatric adverse events.	6.6kg	2.6kg	4kg
sibutramine	Abbott	52		N/A	N/A	4.45kg
otenabant	Pfizer	24	Phase II, testing otenabant 5-25mg. 4.8% reduction with 15mg (cf 4.5% for rimonabant historical data).	N/A	N/A	4.8%
bupropion SR	GlaxoSmithKline	24	2002 study in 327 subjects on placebo, 300mg/day and 400mg/day.	10.1%	5.0%	5.1%
Contrave	Orexigen	48	Phase IIb. 361 obese patients randomised to placebo, bupropion SR 400mg, naltrexone IR 48mg, or combination (400mg + 32mg was optimal).	6.6%	0.8%	5.8%
rimonabant	Sanofi-Aventis	52	RIO-Lipids study, 1,036 patients with BMI 27–40 and dislipidaemia. 20mg dose optimal.	8.6kg	2.3kg	6.3kg
pramlintide + metreleptin	Amylin	24	177 overweight and obese pts, BMI 27–35. Patients given pramlintide 360µg + leptin 5mg, pramlintide 360µg + placebo, or leptin 5mg + placebo. Leptin alone gave no significance, while pramlintide alone gave 7.7kg weight loss.	11.4kg	(3kg)**	(8.4kg)
Qnexa	Vivus	24	200-pt study, four arms: placebo, phentermine 15mg, topiramate 100mg, and Qnexa (phentermine 15mg + topiramate 100mg). Combination gave 11.4kg weight loss.	11.4kg	2.2kg	9.2kg
phentermine + fenfluramine	Wyeth	34		N/A	N/A	10kg
topiramate	J&J	60	192mg/day (215 patients started, 122 completed), 256mg/day (210 patients started, 124 completed). Higher dose most active.	12.9kg	2.8kg	10.1kg
tesofensine	NeuroSearch	24	Phase IIb. 203 patients with BMI 30-40. 4 arms: tesofensine 0.25mg, 0.5mg, 1.0mg and placebo. Highest dose most active.	12.8kg	2.2kg	10.6kg
Empatic	Orexigen	48	599-pt Phase IIb, bupropion 280mg, 360mg + zonisamide 120mg, 240mg, 360mg. Highest dose most efficacious	14.0%	1.1%	12.9%

Source: Edison Investment Research

Although the data have to be treated cautiously (and some extrapolation is necessary in the case of relatively short studies) the table indicates a few obvious trends. The lipase inhibitors (orlistat and cetilistat) tend to exhibit activity at the lower end of the spectrum, but have the benefit of no issues on the CNS. Activity of the CB1 antagonists (rimonabant, taranabant, otenabant etc) appears to be in the mid-range, while possibly the most interesting agents – reformulations of established drugs – show impressive activity towards the upper end of the scale of placebo-adjusted weight loss.

While some agents with novel mechanisms of action have shown extremely impressive activity this too has to be treated with caution as side effects are likely to prove a limiting factor in the future. It is particularly worthy to note that the side effects of rimonabant did not become fully apparent until the product was studied in long-term trials in thousands of patients; accordingly, companies with novel products are likely to tread cautiously, probably opting to test lower doses of their agents in longer studies, preferring to see somewhat reduced efficacy than risking potential side-effect issues at more active doses.

It is important to note that a reduction in weight of as little as 5% has been associated with a 50% decrease in co-morbidities, and this will likely be a key consideration with regulators. Accordingly, although weight loss of 5–10kg does not immediately appear impressive, there is a strong business rationale for developing agents with activity in this range. Because of the many subtle moving parts in this analysis, we are providing an overview of the various mechanisms of action, as well as more in-depth profiles of several companies.

Mechanisms of action

While obesity is clearly the result of over-eating, on a pharmacological level the mechanisms governing what causes people to eat to excess and what further happens once a long-term pattern of excessive food intake becomes established are extremely complex. Mechanisms regulating eating/satiety involve multiple feedback loops, meaning that there are numerous ways of targeting the pathways involved, and some therapeutic approaches are aimed at multiple targets.

Involvement in control of food intake of the brain region known as the hypothalamus has been known for over 50 years, although it was not until 1994, with the discovery of leptin, that current thinking about appetite and satiety – and the involvement of multiple pathways – was formed. Essentially, appetite control has been localised to a region of the hypothalamus known as the arcuate nucleus, and this contains AgRP/NPY neurons (those that produce agouti-related peptide and neuropeptide Y) and α-MSH/CART neurons (producing α-melanocyte-stimulating hormone and cocaine and amphetamine-regulated transcript (CART)).

Targets for anti-obesity agents include the cannabinoid receptor, 5HT, leptin, neuropeptide Y, peptide YY, ghrelin, α-melanocyte-stimulating hormone, corticotropin-releasing hormone, urocortin, galantine, amylin, orexin, GLP-1 and bombesin.

Because of the condition's complex nature and presence of feedback loops, many drugs that operate via single mechanisms have shown limited benefits in terms of efficacy, and a combination approach is increasingly being seen as a promising one to follow. A number of companies are attempting this, some with patent-protected agents, such as Amylin's pramlintide plus metreleptin, and others with combinations of off-patent drugs – Orexigen and Vivus specialise in this.

Furthermore, it could be the case that many of the drugs currently being developed as single agents end up being prescribed in combination (possibly off-label), as happened in the 1990s with fenfluramine and dexfenfluramine, and as it has been suggested might end up being the case with Arena's lorcaserin, although the company has repeatedly refused to be drawn on this issue.

The only late-stage project that acts peripherally (ie, non-centrally) is Alizyme's cetilistat, which has completed Phase II. This uses the same mechanism of action as orlistat and appears to result in a similar (ie, relatively low) level of placebo-adjusted weight loss, but does hold the promise of no CNS-related side effects. In terms of tolerability, however, cetilistat is likely to be associated with similar side effects as orlistat owing to its action of fat binding in the intestine, although early studies have suggested that this effect is less pronounced. More evidence as to the extent of this unpleasant side effect will be sought from a six-month Phase II trial that was carried out by Alizyme's Japanese partner, Takeda. This trial is due to be reported in 2008, and will indicate for the first time how cetilistat performs over more than 12 weeks.

The mechanisms of action of the key anti-obesity projects in Phase II and III studies are described in detail below:

CB1 receptor antagonism

The role of cannabinoid receptors in obesity is based on the finding that cannabis intake was often associated with an increase in appetite. Endocannabinoids are endogenous lipids capable of binding to cannabinoid receptors, part of the G protein-coupled family of receptors discovered while investigating the mode of action of Δ9-tetrahydrocannabinol, a component of *Cannabis sativa*, which binds to them with high affinity.

CB1 receptors are present in the hypothalamic nuclei involved in the control of energy balance and body weight, as well as in neurons of the mesolimbic system, which is believed to mediate the incentive value of food. At central nervous system level, CB1 activation is necessary to induce food intake after a short period of food deprivation. Genetically induced obesity in animals has been shown to lead to long-lasting overstimulation of endocannabinoid synthesis, resulting in permanent overactivation of CB1, which may then contribute to the maintenance of this disease. CB1 has been shown to be upregulated in adipocytes derived from obese rodents. These findings pointed a clear way to CB1 blockade as a possible means of treating obesity.

Leptin

Leptin, an adipose-derived hormone, plays a key role in the long-term regulation of food intake and energy expenditure, its release being associated with a decrease in appetite and an increase in metabolism. Leptin binds to receptors present in the hypothalamic arcuate nucleus (the 'appetite centre' of the hypothalamus), bringing about the feeling of satiety. A small number of people have a rare condition in which the gene coding for leptin is mutated, and who consequently are unable to produce the hormone; these individuals experience constant craving for food and are typically severely obese, but can be treated by the administration of recombinant leptin. Leptin release has been associated with downregulation of the expression of endocannabinoids.

However, simply administering leptin alone to treat obesity is not thought to be practical because many obese people are found already to have high levels of circulating leptin, having developed so-called leptin resistance, perhaps through prolonged intake of food in spite of normal brain satiety signals. Leptin works by inhibiting the activity of AgRP/NPY neurons – neurons that produce neuropeptide Y (see below) and agouti-related peptide, and by increasing the activity of neurons producing α-melanocyte-stimulating hormone (α-MSH/CART neurons). α-MSH is another important mediator of satiety, and differences in the gene coding for the receptor at which α-MSH acts in the brain are linked to obesity in humans. Leptin is also downregulated by melatonin during the night. Melatonin is believed to interact with insulin and upregulate insulin-stimulated leptin expression.

Neuropeptide Y

Neuropeptide Y is a neurotransmitter that has been linked with several physiological processes in the brain, including the regulation of energy balance, being associated with increased food intake and decreasing physical activity. It is produced along with agouti-related peptide by the AgRP/NPY neurons in the hypothalamic arcuate nucleus. Neuropeptide Y forms part of the lipostat system along with leptin (see above) and corticotropin-releasing hormone. Small doses of neuropeptide Y injected into the brains of experimental animals were found to stimulate feeding, while selective destruction of the neuropeptide Y neurons in mice causes anorexia.

Peptide YY

This is also known as peptide tyrosine tyrosine, or peptide YY_{3-36} and is produced in the intestine in response to feeding, acting in a negative feedback loop to reduce appetite. It exerts its action through neuropeptide Y receptors on AgRP/NPY neurons, inhibiting gastric motility and increasing water and electrolyte absorption in the colon. The obese have been found to secrete less peptide YY than normal people, and administration of peptide YY has been shown to reduce food intake.

Amylin

Amylin, also known as amyloid polypeptide, is a small (32-amino acid) peptide secreted by pancreatic β-cells at the same time as insulin, in response to the intake of food, possibly acting synergistically with insulin. It contributes to glycaemic control and exerts an anorectic effect via regulation of appetite, slowing gastric emptying, reducing food intake and lowering post-prandial glucose concentration (slowing appearance of new glucose by inhibiting secretion of glucagon). Rodent amylin knockouts have been shown to fail to lose appetite after normal food consumption.

GLP-1

GLP-1 (glucagon-like peptide-1) is a gut hormone secreted by intestinal L-cells in response to carbohydrate, protein and lipid. The known physiological functions of GLP-1 include increased insulin secretion from the pancreas in a glucose-dependent manner, decreased glucagon secretion from the pancreas, increased β cells mass and insulin gene expression, inhibition of acid secretion in the stomach and gastric emptying, and lowering food intake by increasing satiety.

Also worthy of note, given orlistat's recent approval for use OTC, is the approach being pursued by Phytopharm in a collaboration with Unilever. The companies are developing an extract of the *Hoodia gordonii* plant as a satiety-inducing functional food, and this could be launched (eg, as part of a widely available dietary supplement) in 2009. Phytopharm retains rights to develop the extract as a prescription product for treating Prader-Willi syndrome – a very rare genetic disorder characterised by uncontrolled appetite – after it is launched as a functional food.

Late-stage anti-obesity projects

In this report we profile six companies which we believe could capitalise in the near term on the significant unmet medical need that obesity represents in light of currently approved treatments lacking efficacy and/or being associated with side effects.

The six companies profiled in detail (Alizyme, Amylin, Arena, NeuroSearch, Orexigen and Vivus) each have Phase II data, some of significant duration, and each offer a relatively high-risk, but also potentially high-reward investment opportunity if Phase III data are positive and their respective products can be licensed to significant big pharma players.

Exhibit 4 profiles the most important anti-obesity projects currently in development in Phase II or higher. Many of the additional projects presented here could prove equally or even more promising, capturing a significant share of the market, but are not profiled in detail mainly because they are relatively further away from launch. Many lack significant Phase II data, and some are in development by big pharma companies, meaning that investors would be less exposed to the success or failure of the anti-obesity project in question.

Exhibit 4: Anti-obesity drugs in development at Phase II and above

Notes: *privately owned company.

Drug name	Company	Status	Mech of action	Notes
Acomplia (rimonabant)	Sanofi-Aventis	marketed in Europe	CB1 antagonist	US filing withdrawn after being rejected by FDA. EMEA reviewing data.
taranabant	Merck & Co	Phase III	CB1 inverse agonist	Due to be filed in US in H208. Latest Phase III study in 2,500 patients gave statistical significance, and 2mg chosen as best dose. Higher doses associated with increased psychiatric adverse events.
Contrave (naltrexone + bupropion)	Orexigen	Phase III	bupropion = dopamine & noradrenaline reuptake inhibitor; naltrexone = opioid antagonist.	Last of four Phase III studies initiated in November 2007; two are now fully recruited. Total pivotal programme comprises 4,500 patients.
lorcaserin	Arena	Phase III	selective $5HT_{2C}$ receptor agonist	'Safer fenfluramine' thanks to 2C receptor selectivity. Complete Phase III programme to enrol 7,000 patients.
otenabant	Pfizer	Phase III	CB1 antagonist	Four active long-term Phase III trials in a total of over 5,500 patients. Completion due between early 2009 and early 2010.
Qnexa (phentermine + topiramate)	Vivus	Phase III	topiramate = GABA and other agonist properties	Full Phase III programme (three studies, 4,500 patients) underway. Additional formulation in development.
Empatic (zonisamide + bupropion)	Orexigen	Phase IIb	bupropion = dopamine & noradrenaline reuptake inhibitor; zonisamide = GABA agonist	Recently initiated Phase IIb matrix design study in over 600 patients to determine optimal dose ratio(s) for further development. Phase III to begin in H109.
pramlintide	Amylin	Phase IIb	amylin analogue	Injectable. Marketed for types 1 and 2 diabetes. Also in combination with metreleptin, peptide YY_{3-36} and other agents.
AVE1625	Sanofi-Aventis	Phase IIb	CB1 antagonist	Surinabant also tested in obesity, but that is now a smoking-cessation project.
tesofensine	Neuro-Search	Phase IIb	dopamine/noradrenalin/ 5HT reuptake inhibitor	Phase IIb proof-of-concept study in 203 obese patients showed statistical significance after 24 weeks. Open-label extension under way. Previously studied for Alzheimer's and Parkinson's diseases.
velneperit	Shionogi	Phase IIb	neuropeptide Y5 receptor antagonist	12-week Phase IIa study gave statistical significance after four-week diet run-in. No statistical significance in second arm.
obinepitide	7TM Pharma	Phase II	neuropeptide Y agonist	In Phase IIa study to evaluate weight loss after subcutaneous treatment for 28 days. Will enrol 180 patients with BMI of 30–40.
liraglutide	Novo Nordisk	Phase II	GLP-1 analogue	Injectable project, in Phase III for diabetes, with filing possible in 2008. Phase II obesity data showed 7kg loss in liraglutide group vs 3kg (placebo) and 4kg (orlistat).
betahistine	Obecure*	Phase II	histamine receptor activation	Phase II study in 281 patients failed to show statistical significance. Betahistine marketed outside the US for vertigo.
cetilistat	Alizyme	Phase II	lipase inhibitor	Phase III dependent on signing a partner.
CP-866087	Pfizer	Phase II	not disclosed	In 12-week Phase II trial in 96 obese subjects. Also in development for alcohol dependence and female sexual arousal disorder.
ibipinabant	BMS/ Solvay	Phase II	CB1 antagonist	600-patient Phase II/III study was to start in March 2008. Trial withdrawn from Clinicaltrials.gov.
N-5984	Nisshin Kyorin	Phase II	selective β3 antagonist	May improve obesity and have less cardiac effect than previous compounds.
peptide YY_{3-36} nasal spray	Nastech	Phase II	peptide YY_{3-36}	Six-month, dose-ranging trial has recruited 551 obese subjects and will compare the nasal spray with placebo and sibutramine.
CE-326597	Pfizer	Phase II	CCK receptor antagonist	200-patient study due to be completed in September 2008.
JNJ28431754	Johnson & Johnson	Phase II	SGL T2 inhibitor	12-week study in 400 patients testing 50mg, 100mg and 300mg doses started February 2008.
R256918	Johnson & Johnson	Phase II	gut-selective MTP inhibitor	12-week study in 320 patients testing 5mg, 10mg and 15mg doses due to complete June 2008.
SCH-497079	Schering-Plough	Phase II	histamine H3 receptor antagonist	12-week study in 300 patients started in April 2008.
THR-4109	Theracos*	Phase II	venlafaxine = norepinephrine and 5HT uptake inhibitor; rivastigmine = cholinesterase inhibitor	Combination of venlafaxine and rivastigmine. 24-week study in 220 patients due to be completed July 2008.
Adyvia	Innodia*	Phase IIa	adipose triglyceride lipase & PI3 kinase activator	Results of 12-week trial in 100 patients were due by end of 2007.

Source: Edison Investment Research

CB1-targeting agents

We are of the view that agents targeting the endocannabinoid system are unlikely to gain US FDA approval in the near term, following the agency's refusal to approve rimonabant and the continued association of this drug class with psychiatric adverse events. Nevertheless, a few are in development and one of these, taranabant, is scheduled to be filed in 2008; the FDA's response to this filing could be a strong indicator of the agency's views towards this drug class.

taranabant

In March 2008 Merck & Co reported 52-week data from a two-year, 2,500-patient Phase III trial of taranabant, showing that the 2mg dose was associated with a 6.6kg reduction in weight, compared with 2.6kg for placebo recipients. 57% of 2mg taranabant recipients lost 5% or more of baseline body weight, compared with 27% of those on placebo. 4mg and 6mg doses were also tested, but the results were described as not being substantially better than with the 2mg dose, which has been chosen for continued evaluation and, presumably, filing. However, the higher doses were associated with a higher incidence of psychiatric adverse events (28% on 2mg, 40% on 4mg and 38% on 6mg) compared with placebo (20%).

We feel that in light of the FDA's likely concern regarding the possibility for abuse of anti-obesity medicines, this association with psychiatric events at higher doses is likely to present a significant hurdle to gaining regulatory approval for taranabant.

otenabant

One other CB1 antagonist is in Phase III studies – otenabant – although its originator, Pfizer, has so far presented little data from earlier studies. In a Phase II trial whose results were presented in November 2006, 5mg, 15mg and 25mg doses of otenabant resulted in six-month placebo-adjusted percentage changes in body weight of –2.4%, –4.8% and –4.4% respectively. There has been little mention so far of possible side effects. Clinicaltrials.gov lists four active Phase III studies of the product (previously known as CP-945598): a one-year trial in 974 obese patients with type 2 diabetes, due to be completed in February 2009; a two-year trial in 2,500 obese patients and those with co-morbidities, due to be completed in August 2009; a two-year trial in 1,253 obese patients with no co-morbidities, due to be completed in October 2009; and a 14-month study in 850 obese patients and those with co-morbidities, examining prevention of weight regain, due to be completed in January 2010. Pfizer estimates that the earliest date for filing could be 2010.

ibipinabant

Another CB1 antagonist, Bristol-Myers Squibb/Solvay's ibipinabant (previously known as BMS-646256), completed a randomised, double-blind, placebo-controlled study in 434 obese and high-risk overweight subjects, although data from this have not yet been presented. A Phase II/III study in 600 patients was due to begin in March 2008, but has not commenced while the companies analyse Phase II results, and is listed on Clinicaltrials.gov as "withdrawn prior to recruitment".

GLP-1 analogue

liraglutide

Novo Nordisk's once-daily injectable product, liraglutide, appears to be the only GLP-1 analogue in mid-stage development. In November 2007 the company reported data from a 20-week, double-blind, placebo-controlled Phase II study comparing liraglutide with orlistat in 564 patients. At the highest dose liraglutide resulted in a weight loss from baseline of 7kg, compared with 3kg in the placebo and 4kg in the orlistat groups.

More than 75% of patients on the highest dose experienced a weight loss of over 5%, and the trial showed a beneficial effect on systolic blood pressure after treatment with liraglutide; this means liraglutide and Vivus's Qnexa appear to be the only two anti-obesity projects to show an effect on blood pressure – an important risk factor contributing to metabolic syndrome.

Around 30% of patients showed signs of prediabetes at randomisation and, after 20 weeks of treatment with any liraglutide dose, 80–90% of these no longer showed any sign of prediabetes, as opposed to around 40% in the placebo and orlistat-treated groups. The most common adverse events were related to the gastrointestinal systems and were mild to moderate, and 20–50% of patients on liraglutide reported dose-dependent nausea. Around 85% of all participants volunteered to continue into an open-label extension. A Phase III programme with liraglutide in obesity is planned, and the product could be filed in the US and EU in 2008 for treating diabetes.

Neuropeptide Y receptors

protein YY_{3-36}

Two companies – Amylin and Nastech – are using protein YY_{3-36} as an approach to treating obesity. While Amylin is combining protein YY_{3-36} with its amylin analogue, pramlintide, in an effort to increase the activity of the latter, Nastech's approach involves the standalone administration of a nasal spray formulation of the protein YY_{3-36} hormone, which is normally produced by specialised endocrine cells (L-cells) in the gut in proportion to the calorie content of a meal. Protein YY_{3-36} exerts its action on neuropeptide Y receptors.

In January 2008 Nastech completed the recruitment of 551 obese patients into a six-month, US, dose-ranging Phase II study. This will test three doses of the nasal spray, and compare it with placebo and sibutramine. The nasal spray formulation aims to improve on the iv delivery route, which was the focus of Nastech's earlier studies. An earlier dose-ranging study in 24 obese subjects with a BMI of 30–40kg/m^2 included iv and placebo arms and showed that the nasal spray produced a statistically significant dose-dependent treatment effect.

Three Phase I trials of iv protein YY_{3-36} in over 60 subjects indicated that the product was well tolerated and showed evidence of reducing calorie intake, moderating appetite and demonstrating weight loss.

obinepitide

Meanwhile, a third company, the Danish firm 7TM Pharma, has a number of anti-obesity projects in its pipeline, the most advanced of which, obinepitide, is a synthetic analogue of protein YY_{3-36} and pancreatic polypeptide; the latter is also a naturally occurring hormone released during food intake. Obinepitide, a potential subcutaneous injectable therapeutic, is believed to exert agonist activity at neuropeptide Y2 and Y4 receptors, with selectivity over the Y1 receptor, which is believed to be involved in cardiovascular side effects (protein YY_{3-36} targets the Y2 receptor only).

Obinepitide is in a Phase IIa study that was to have been completed in Q108, but no announcement has been made on this and the company says it has not yet set a date for release of the data. In Phase I/II, the product delivered subcutaneously once daily resulted in statistically significant inhibition of food intake up to nine hours after dosing.

velneperit

Shionogi is also targeting the neuropeptide receptor with a small-molecule, oral product, velneperit (previously known as S-2367), which is a neuropeptide Y5 receptor antagonist. A Phase IIa US study in 342 obese subjects with a BMI of 30-40kg/m^2, velneperit produced mixed results. The trial involved two separate treatment regimens: the first, in which patients were first assigned to a four-week low calorie diet run-in before starting two doses of velneperit (or placebo), yielded a statistically significant reduction in weight; however, the second, in which patients were randomised to treatment directly without the low calorie run-in, failed to reach statistical significance, with valneperit recipients losing 3.6kg on average over 12 weeks versus 2.4kg with placebo.

Discontinuations

In addition to the high-profile withdrawal of Fen-Phen (with its resulting multi-year, multi-billion dollar product liability litigation battle) and failure to gain US approval for rimonabant, the obesity sector is notable for a high number of discontinuations of products that have undergone clinical testing, some at a late stage of development.

One of the more prominent discontinuations was that of Merck & Co's **neuropeptide Y5 receptor antagonist** MK-0557 around three years ago. The compound underwent a two-year Phase II/III study in 1,661 patients that started in September 2003; although it produced statistically significant results at 52 weeks, the amount of weight loss it induced was deemed not to be clinically meaningful. The trial provided the first insight into the human neuropeptide Y homoeostatic pathway in a large clinical setting, and the researchers concluded that solely targeting the neuropeptide Y5 receptor in future was unlikely to produce therapeutic efficacy (Cell Metabolism, October 2006, pp 275-282). This appears to have been borne out by Shionogi, whose neuropeptide Y5 receptor antagonist velneperit has so far produced mixed data in Phase II, while results of a Phase IIa trial of 7TM Pharma's obinepitide have yet to be reported, although this compound does not appear to be specific for the Y5 receptor subtype.

In the 1990s, shortly after the discovery of leptin's involvement in appetite/satiety, Amgen studied native **leptin** as an anti-obesity agent, and took this as far as Phase II studies in around 800 patients. The product was found to induce only modest weight loss, and Amgen decided to focus on second-generation molecules instead. Leptin's lack of activity in the clinical setting was likely due to the fact that many obese patients become resistant to leptin, and already have high circulating levels of it.

Agonist activity at the **$5HT_{2C}$ receptor**, a strategy currently being pursued by Arena Pharmaceuticals with lorcaserin, was also the target of BVV-933, a project under joint development by GlaxoSmithKline and Biovitrum. A Phase IIb study in 300 patients was completed, but the companies decided to terminate it early and focus on 5HT agonists with even greater activity at the 2C receptor subtype. This was likely linked to the fact that Fen-Phen's non-selective action at $5HT_2$ receptors was blamed for the cardiovascular side effects that led to its withdrawal, and resulting concerns that an agent with insufficient selectivity could give rise to similar side effects in later studies. Likewise, Arena is putting great stress on lorcaserin's 2C selectivity, saying its agent has 100-fold selectivity for $5HT_{2C}$ vs $5HT_{2B}$, and 15-fold selectivity for $5HT_{2C}$ over $5HT_{2A}$.

Inhibition of **pancreatic lipase** – the mechanism of action of Roche's orlistat and Alizyme's cetilistat – was also pursued by the private company Peptimmune, which in 2004 licensed rights from Genzyme to GT389-255, a novel conjugate of a pancreatic lipase inhibitor and a fat binding hydrogel polymer. This product entered a Phase I single ascending dose study in 48 volunteers, and a subsequent Phase II trial in obese patients was planned for 2005; however, this was not carried out and the product is no longer listed in Peptimmune's R&D portfolio.

In early 2008 GlaxoSmithKline and Kissei discontinued development of sergliflozin, a **sodium-dependent renal glucose transporter-2 inhibitor**, which had undergone Phase II studies but failed to

show sufficient efficacy. The companies have remogliflozin, a back-up compound with a similar mechanism of action, in Phase I studies, and this appears to be GSK's only anti-obesity project currently in clinical development.

Of the late-stage development candidates in Exhibit 4, Solvay/Bristol-Myers Squibb's **CB1 antagonist** ibipinabant appears to be moribund, although the companies have said that they are continuing to evaluate Phase II data in full before deciding whether and under what protocol to proceed into Phase III.

Early-stage anti-obesity agents

Exhibit 5 outlines anti-obesity projects that are at present at an earlier stage of clinical development.

Exhibit 5: Obesity projects in early-stage development

Notes: *privately owned company.

Drug name	Company	Mech of action	Notes
TM30339	7TM Pharma	neuropeptide Y4 receptor agonist	Entered Phase I/II in early 2007. Mimics action of pancreatic polypeptide, a natural satiety hormone.
oral protein YY_{3-36}	Emisphere	protein YY_{3-36}	Phase I results due Q208.
AZD-1175	AstraZeneca	CB1 antagonist	Phase I.
V-24343	Vernalis	CB1 antagonist	16-day Phase I study of 5–100mg/day doses in 32 volunteers showed placebo-adjusted weight loss of up to 4.5kg.
THCV	GW Pharmaceuticals	Tetrahydrocannabivarin	Multidose proof-of-principle Phase IIa trial in type 2 diabetics due to begin in 2008.
PF-04415060	Pfizer	DGAT-1 inhibitor	Licensed from Bayer. Phase I.
JTT-553	Japan Tobacco	DGAT-1 inhibitor	Phase I.
ATHX-105	Athersys	$5HT_{2C}$ agonist	Phase II trial is planned for 2008.
BVT-74316	Biovitrum	$5HT_6$ receptor antagonist	Safety and tolerability seen in Phase I trial in 98 healthy volunteers.
TTP435	TransTech Pharma*	AgRP inhibitor	Phase I.
trodusquemine	Genaera	inhibition of protein tyrosine phosphatase and dopamine and norepinephrine reuptake transporters; downregulation of AgRP and NPY hormone expression	Six-month Phase I trial in 28 obese patients with type 2 diabetes testing single ascending doses 3-15mg/m^2. Completion expected in June 2008.
TKS-1225	Thiakis*	oxyntomodulin analogue	Injectable. Previous Phase I 28-day trial at Imperial College, London, showed 1.8kg placebo-adjusted weight loss in volunteers.
NGD-4715	Neurogen	melanin concentrating hormone-1 receptor antagonist	Phase II proof-of-concept trial requires a licensing partner.
AP1030	Action Pharma*	targets MCR4	Phase I.
remogliflozin	GlaxoSmithKline/ Kissei	sodium-dependent glucose transport inhibitor	Phase I.
PF-2575799	Pfizer	not disclosed	Phase I.
PF-4325667	Pfizer	not disclosed	Biological product in Phase I.

Source: Edison Investment Research

Newsflow

Expected newsflow that might influence investment decisions in companies with a large interest in the obesity sector includes the following:

- 2008 – publication of 12-week data for Innodia's Adyvia.
- 2008 – completion of Phase IIa study of 7TM Pharma's obinepitide.
- 2008 – publication of six-month cetilistat data by Takeda.
- 2008 – data for Amylin's pramlintide combinations with phentermine and PYY_{3-36}.
- June 2008 – data from open-label Phase IIb extension study of NeuroSearch's tesofensine.
- H208 – possible further Phase III data for taranabant.
- H208 – US filing of taranabant.
- September 2008 – completion of Phase II study with Pfizer's CE-326597.
- H1 2009 – start of Phase III for Orexigen's Empatic.
- H1 2009 – possible first Phase III data for Pfizer's otenabant.
- 2009 – expiry of US patent on orlistat.
- H209 – pivotal data and possible filing for Vivus's Qnexa.
- Late 2009 – possible filing for Orexigen's Contrave.
- 2010 – earliest possible filing date for Pfizer's otenabant.

Alizyme

Year End	Revenue (£m)	PBT (£m)	EPS (p)	DPS (p)	PE (x)	Yield (%)
12/06	1.1	(18.0)	(9.3)	0.0	N/A	N/A
12/07	0.0	(32.0)	(15.3)	0.0	N/A	N/A
12/08e	1.1	(6.6)	(2.7)	0.0	N/A	N/A
12/09e	0.1	(3.9)	(1.5)	0.0	N/A	N/A

Investment summary: Partner needed

In cetilistat Alizyme has the only peripherally acting anti-obesity project in late-stage development, which it believes could offer considerable safety benefits in light of the US FDA's rejection of Sanofi-Aventis's centrally acting agent rimonabant. Although cetilistat is ready to enter Phase III studies and this programme has been agreed with the FDA, Alizyme needs a partner to fund it, and its negotiation position was recently strengthened by a £10m fund-raising.

Peripheral advantage

Cetilistat acts peripherally, inhibiting gastrointestinal lipase thus preventing fat absorption in the gut, and Alizyme sees the fact that it exerts no action on the CNS as a key advantage. It has the same mechanism of action as Roche's Xenical (orlistat), which had a high-profile launch in 1998 but whose sales faltered because of unpleasant side effects – loose, oily stools caused by the egestion of unabsorbed fat.

Underway in Japan…

Japanese cetilistat rights were licensed to Takeda in 2004, and this partner is carrying out a 450-patient Phase II trial, results of which are due this year – this will be the first time that cetilistat's effect will be seen over six months, and could spur partnering interest. Takeda is solely funding Japanese development, and the deal comprises $42m in milestones ($7m paid so far) and double-digit royalties.

…but no US studies since 2005

Despite the fact that a Phase III programme has been agreed with the US FDA, including a special protocol assessment for the first pivotal study, Alizyme has as yet been unable to sign up a partner for cetilistat outside Japan. Given the likely $150m–175m cost of Phase III, Alizyme is unable to carry this out in-house, and accordingly cetilistat has not been studied in a US clinical setting since late 2005.

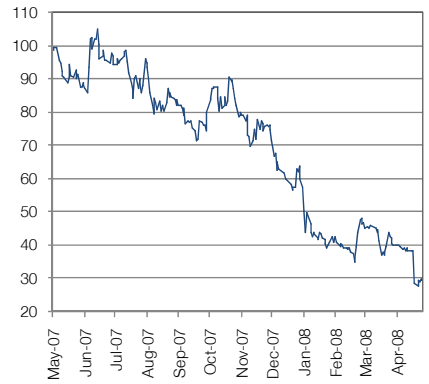
Side effects vs efficacy

In Phase IIb there was no difference in treatment discontinuations between cetilistat and placebo, while orlistat had a higher discontinuation rate. The highest cetilistat dose was associated with more GI side effects than placebo (but less than orlistat), and given the agents' similar modes of action the balance between efficacy and tolerability should be a key focus in larger studies.

Price	28.75p*
Market Cap	£63m*

**as at close on 13 May 2008*

Share price graph



Share details

Code	AZM
Listing	Full
Shares in issue	221m

Price

52 week	High	Low
	105.00p	26.25p

Business

Alizyme is a UK biotech company developing potential treatments for obesity, diabetes, irritable bowel syndrome, ulcerative colitis and mucositis.

Recent newsflow

Apr 2008 – Renzapride discontinued

Mar 2008 – £10m fund-raising

Dec 2007 – Colal-Pred licensed to TSD Japan

Nov 2007 – Colal-Pred licensed to Prometheus

Jul 2007 – Interim financials published

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Phase III protocol

The pivotal programme that was agreed with the US FDA in August 2006 for registration of cetilistat will involve dosing around 4,000 patients for one year in three or four placebo-controlled studies, in order that up to 1,500 patients who will have undergone one year's treatment are included in the safety database.

The primary endpoint in the trials would be the proportion of patients who lose at least 5% of their body weight. Secondary endpoints will include absolute weight loss and the proportion of patients who lose over 10% of their body weight compared with placebo. Key endpoints for the trials focusing on co-morbidities, such as with type 2 diabetes, will include reduction in levels of HbA1c, a marker of diabetic control.

The US FDA has agreed to review the first pivotal Phase III study of cetilistat under a special protocol assessment, meaning that the protocol design, clinical endpoints and statistical analyses are acceptable to support approval.

Phase IIb data

Study design: 12-week, double-blind, multicentre trial in five EU countries in 612 patients with BMI of 28-45. Five arms – cetilistat 40mg, 80mg and 120mg, Xenical 120mg, and placebo, each dosed orally 3x/day.

Efficacy: cetilistat 80mg and 120mg gave statistically significant weight loss (primary endpoint; 3.85kg, p=0.01; 4.32kg, p=0.0002) cf placebo (2.86kg). Xenical 120mg caused comparable weight loss (3.78kg, p=0.008). No statistical significance at 40mg. 80mg and 120mg also gave statistically significant reduction in HbA1c (0.5-0.6% from a baseline of 7.2%). Similar result with Xenical.

Tolerability: Discontinuations due to adverse events were 2.5%, 5.0% and 2.5% for cetilistat 40mg, 80mg and 120mg respectively, 6.4% for the placebo group and 11.6% for the Xenical group. Discontinuation due to GI adverse events was 0.8%, 2.5%, 1.7% for cetilistat, 4.0% for placebo and 11.6% for Xenical. The total number of GI adverse events was 294, 282 and 339 for cetilistat, 153 for placebo and 431 for Xenical.

Alizyme pipeline

Cetilistat – lipase inhibitor in Phase II studies for obesity.

Colal-Pred – in Phase III for ulcerative colitis. EU filing due in H208, with potential to become Alizyme's first marketed product. Colal-Pred was recently licensed to Prometheus Laboratories for North America and TSD Japan for co-development in Japan.

ATL-104 – Phase IIa mucositis study completed in 64 patients with lymphoma and myeloma.

Renzapride – discontinued after showing mixed/ inconclusive data in Phase III for treating constipation-predominant irritable bowel syndrome.

Senior management

CEO – Tim McCarthy

Finance director – David Campbell

R&D director – Roger Hickling

Bull

- £10m fund-raising announced in March 2008 could strengthen Alizyme's hand in licensing discussions and gives it sufficient cash to last well into 2009.
- Cetilistat exerts its action peripherally rather than on the central nervous system, and this could give it an advantage in light of the US FDA's growing caution and last year's rejection of Sanofi-Aventis's rimonabant. The decision by the FDA panel against approval was a unanimous one, based on findings of psychological and neurological adverse events with rimonabant, a cannabinoid CB1 receptor antagonist. The product's NDA was subsequently withdrawn.
- The recent launch of low-dose orlistat for OTC use (under the brand name Alli) illustrates the regulatory attitude to peripherally acting agents, ie lack of significant safety concerns.
- The Phase III protocol has been agreed with the FDA, along with SPA for the first pivotal study. This makes the regulatory pathway clear for a licensee; although a partner might want to repeat some studies, we do not view this as likely.
- US FDA has told Alizyme that it can open a separate IND for cetilistat in diabetes, given that the agency no longer requires a drug's effect on glycaemic control to be independent of its effect on body weight in order to be considered for a standalone diabetes indication.

Bear

- The discontinuation of renzapride has eliminated a second possible partnering project and in our view makes the signing of a licensing deal for cetilistat even more vital for Alizyme.
- As cetilistat has not been studied in a US clinical setting since Phase IIb data were presented in Dec 2005, it has given competitors a two-year catch-up period.
- Cetilistat's placebo-adjusted efficacy is low relative to competing agents in clinical development, although it has so far only been studied for up to 12 weeks. Longer-term studies should be expected to show increased efficacy, and this will be a major focus of the Takeda Phase II trial due to be reported this year.
- Although patient withdrawals due to adverse events were considerably lower with cetilistat than with Xenical, GI adverse events experienced did increase with dose, and since both drugs share the same mechanism of action this issue is likely to remain a focus of future clinical studies.
- Orlistat going OTC and facing potential patent expiry in 2009 could put pressure on the pricing of cetilistat and other anti-obesity agents unless a clear efficacy/side effect benefit can be demonstrated.

Amylin Pharmaceuticals

Year End	Revenue ($m)	PBT ($m)	EPS ($)	DPS (c)	PE (x)	Yield (%)
12/06	474.0	(26.4)	(1.78)	0.0	N/A	N/A
12/07	701.4	(31.8)	(1.59)	0.0	N/A	N/A
12/08e*	921.1	(271.9)	(1.94)	0.0	N/A	N/A
12/09e*	1,073.2	(216.7)	(1.50)	0.0	N/A	N/A

*consensus forecasts.

Investment summary: Now with added leptin

Amylin is unique in our sample of biotech companies in that it already markets two significant diabetes treatments and is developing injectable treatments for obesity, while all late-stage competitors are using the oral route of administration. Having obtained promising efficacy with pramlintide in treating obesity, Amylin is now looking at combining it with other molecules, and its combination with metreleptin recently showed synergistic efficacy in a 24-week study.

Already on the market

Pramlintide, an analogue of the naturally occurring pancreatic hormone amylin, has been marketed in the US since 2005 as Symlin as an adjunct to insulin treatment in types 1 and 2 diabetes, and Amylin also markets Byetta (exenatide), for treating type 2 diabetes. Amylin has a US field force of some 550 reps, and Lilly is its co-promotion partner for Byetta in the US.

Metreleptin combination

In a 52-week, Phase II study, pramlintide alone gave an average weight reduction of 7–8%, compared with 1% for placebo, but Amylin is combining it with other agents, most notably metreleptin, in an attempt to increase the resulting efficacy. Metreleptin is an analogue of human leptin, a hormone discovered in 1994 to play a role in regulating energy homoeostasis and fat and glucose metabolism.

Multiple anti-obesity projects

Amylin is pursuing what it terms a novel integrated neurohormonal treatment of obesity (INTO), involving the combination of pramlintide with several other molecules. In addition to leptin, the company is combining pramlintide with PYY3-36, and PYY3-36 plus leptin, and has a stand-alone amylin mimetic in early studies.

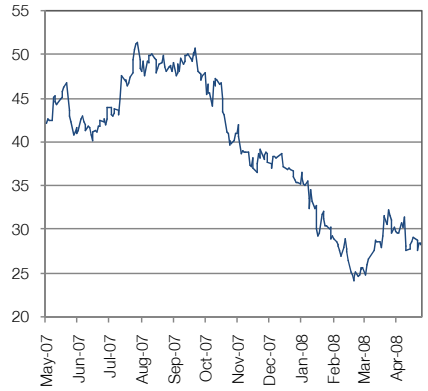
Newsflow

In the coming months Amylin should report Phase I data of the pramlintide/PYY3-36 combination, which should show the first indication of the viability of this approach. A Phase IIb study of pramlintide combined with phentermine has been completed, but its results have yet to be reported. A decision could also be taken shortly on which combination to take into Phase III.

Price	$29.15*
Market Cap	$3.9bn*

as at close on 13 May 2008

Share price graph



Share details

Code	AMLN
Listing	Nasdaq
Shares in issue	134.9m

Price

52-week	High	Low
	$53.25	$23.75

Business

Amylin markets two diabetes treatments, Byetta and Symlin (pramlintide), and has R&D projects in diabetes, obesity and cardiovascular disease. Byetta and Byetta LAR are partnered with Lilly. Pramlintide is in several Phase II studies for obesity, alone and in combination.

Recent newsflow

May 2008 – Phase IIb dose-finding study starts with pramlintide+leptin

Nov 2007 – Phase IIa results of pramlintide+leptin

Oct 2007 – Byetta vs LAR formulation study results

Oct 2007 – FDA approves Symlin pen injector

June 2007 – $575m senior debt placement

Analyst

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Multi-pronged anti-obesity approach

In early 2006, Amylin reported positive data from a Phase IIa dose-ranging study evaluating the safety and weight effects of pramlintide in obese subjects; after 16 weeks of treatment, subjects on pramlintide lost an average of 8.4–13.4lbs cf 6.2lbs weight loss for placebo recipients. In a 52-week study pramlintide alone gave an average weight reduction of 7–8%, compared with 1% for placebo.

However, Amylin has focused on move towards a combination approach, turning to trials of pramlintide plus metreleptin, protein YY3-36 (PYY3-36) and approved obesity agents. Presumably this aims to improve pramlintide's efficacy at comfortably tolerated doses, based on early findings of synergistic effects.

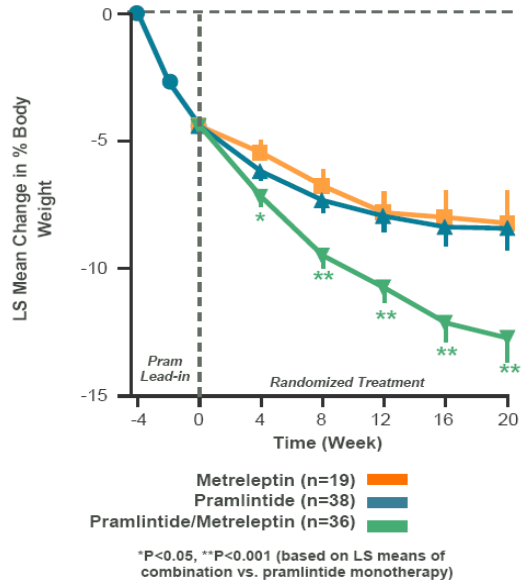
Results from a Phase IIa trial of pramlintide combined with metreleptin were reported Nov 2007 (see below). A six-month, Phase IIb, dose-finding study of pramlintide + metreleptin started in May 2008.

A Phase IIb study of pramlintide in combination with two approved oral obesity agents, phentermine and sibutramine, is under way, designed to show whether additive weight loss can be achieved.

A Phase I safety study evaluating pramlintide and PYY3-36 is under way, to support a triple combination study with pramlintide, leptin and PYY3-36 if the combination of pramlintide and leptin shows potential.

Phase IIa results of metreleptin combination

In a 24-week proof-of-concept study that enrolled an initial 177 patients with a BMI of 27–30, pramlintide+metreleptin treatment reduced body weight on average by 25lbs, significantly more than treatment with pramlintide alone (17lbs; p<0.001).



Source: Amylin presentation

Tackling obesity's neurohormonal basis

Amylin's approach is based on the role of neurohormones in regulating appetite and energy balance, and in investigating the interaction between these hormones.

Pramlintide is an analogue of the naturally occurring pancreatic hormone amylin, which contributes to glycaemic control and exerts an anorectic effect via regulation of appetite, food intake and post-prandial glucose concentration. Leptin is a hormone produced by adipose tissue and involved in energy homoeostasis and fat and glucose metabolism; it acts on the hypothalamus as a signal of satiety. Early preclinical work suggested that combinations of neurohormones can produce a synergistic weight loss effect, hence Amylin's 'integrated neurohormonal' strategy.

Obese people sometimes develop a resistance to leptin, and Amylin is also combining pramlintide with PYY3-36, a peptide produced in the ileum and colon that reduces appetite in response to feeding. PYY3-36 is separately under development for obesity by Nastech, which recently started a 551-patient Phase II monotherapy study. Merck & Co earlier terminated a licence with Nastech after a proof-of-concept study did not show efficacy.

Bull

- Good efficacy relative to competing products, and suggestion of further activity in the longer term.
- Pramlintide has been on the market for three years and has an established record of safety (side effects have included nausea and injection site reactions). Clearly, safety will be a focus in combination studies.
- Several shots at goal, with a number of projects in studies, including pramlintide, another amylin mimetic, and pramlintide combinations with metreleptin, PYY (peptide tyrosine tyrosine) 3-36 and established anti-obesity agents.

Bear

- Injectable product. All competitors in late-stage development for treating obesity are orally administered. (However, work is under way on a single-injection pen delivery system.)
- The amylin hormone is thought to induce satiety and cause a feeling of nausea if excessive food is eaten; nausea, albeit mild and transient, has been the most common side effect observed in clinical trials. 93 of 139 eligible patients in Phase IIa pramlintide + metreleptin study completed the 24-week treatment.

Arena Pharmaceuticals

Year End	Revenue ($m)	PBT ($m)	EPS ($)	DPS (c)	PE (x)	Yield (%)
12/06	30.6	(86.2)	(1.89)	0.0	N/A	N/A
12/07	19.3	(143.2)	(2.31)	0.0	N/A	N/A
12/08e*	15.1	(206.0)	(2.85)	0.0	N/A	N/A
12/09e*	39.4	(151.1)	(2.21)	0.0	N/A	N/A

*consensus forecasts.

Investment summary: A safe fen-phen?

Having received the go-ahead from a second data safety monitoring board (DSMB) in March, Arena's lead project, lorcaserin, is now in one of the biggest anti-obesity Phase III programmes, enrolling almost 7,000 patients. The molecule works by a similar mechanism to fenfluramine, but aims to circumvent the side-effects that led to its withdrawal in 1997. During the past year, however, Arena has lost over half its market capitalisation, and the stock currently trades near its 12-month low.

Heart valve scrutiny

Fen-phen was withdrawn owing to an association with heart valve damage, and demonstrating an absence of this effect is a key hurdle that Arena will have to overcome. However, neither human trials nor animal studies (at 50x the human exposure of drug) have so far shown significant increases in this side effect.

Safety review gives all-clear

The DSMB is specifically looking at heart valve effects, and reviewed unblinded echocardiograms in patients from the first six months (September 2007) and 12 months (March 2008) of BLOOM, lorcaserin's first Phase III trial. It ruled at each point that there was no increase in heart valve abnormalities sufficient to stop the study, thus allowing the remaining two Phase III trials to start. The second all-clear completes the DSMB's planned reviews of this study.

Serotonin receptor selectivity

Fenfluramine's mechanism of action involved general agonist activity at $5HT_2$ receptors, while lorcaserin is specific for the $5HT_{2C}$ receptor subtype. Arena believes that the $5HT_{2B}$ receptor is primarily implicated in the heart valve side effects, and argues that lorcaserin's 100-fold selectivity for $5HT_{2C}$ over $5HT_{2B}$ should therefore enable its project to avoid fenfluramine's side effects.

Cash raised

Arena's recently completed $125m share offering gives it sufficient cash to fund near-term development of lorcaserin, as well as other clinical and earlier-stage projects. The R&D pipeline includes programmes for insomnia, arterial thrombosis, diabetes (licensed to Ortho-McNeil (J&J)) and atherosclerosis (Merck & Co).

Price	$5.15*
Market Cap	$371m*

as at close on 13 May 2008

Share price graph

Share details

Code	ARNA
Listing	Nasdaq
Shares in issue	72m

Price

52-week	High	Low
	$14.78	$4.92

Business

Arena is a US biopharmaceutical company with a pipeline of compounds that act on G protein-coupled receptors. Its lead development product is lorcaserin for obesity, and it is also developing treatments for insomnia, diabetes and thrombosis.

Recent newsflow

Mar 2008 – Second all-clear from DSMB review

Jan 2008 – Phase I starts with joint Merck project

Jan 2008 – Phase Ia atherosclerosis study results

Dec 2007 – second and third pivotal lorcaserin trials start

Nov 2007 – $125m fund-raising

Analyst

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Phase III study programme

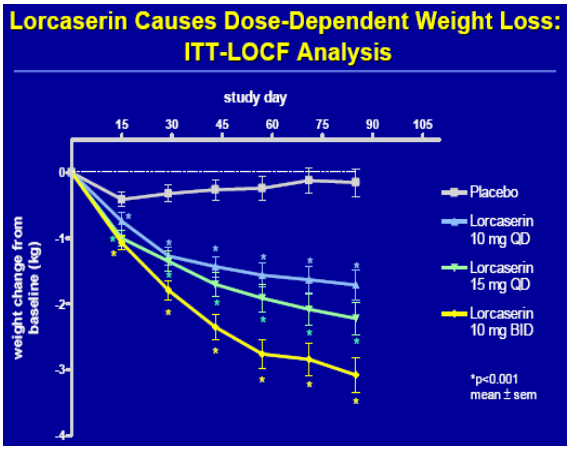
BLOOM – a two-year study started in Sep 2006 in 3,100 patients with BMI of 27–45 and at least one co-morbidity, dosing lorcaserin 10mg twice daily. Primary endpoints are percentage of patients achieving ≥5% weight loss at 52 weeks and at 104 weeks. All patients to receive echocardiograms at baseline and follow-up at 6, 12, 18 and 24 months; echocardiograms were reviewed by an independent data safety monitoring board at 6 and 12 months.

BLOSSOM – a 52 week trial started in Jan 2008 in 3,000 patients with BMI of 27–45 and at least one co-morbidity, dosing lorcaserin 10mg once and twice daily. Primary outcome measure is the percentage of patients achieving ≥5% weight loss at week 52.

BLOSSOM-DM – a 52 week study started in Dec 2007 in 750 patients with BMI of 27-45 and type 2 diabetes managed with oral anti-hyperglycaemic agents. Lorcaserin dosed 10mg once and twice daily, looking at percentage of patients achieving ≥5% weight loss at week 52 as the primary outcome measure.

Phase IIb study data

Data from a 12-week, 469-patient, Phase IIb trial showed that patients who received lorcaserin experienced significantly greater weight loss than those who received placebo. Summary below.



Source: Arena presentation

Overcoming fen-phen

Lorcaserin has been developed to exert its action selectively at the $5HT_{2C}$ receptor because Arena believes that this can avoid the cardiovascular side effects associated with fenfluramine and dexfenfluramine (which were often used in combination with phentermine as "fen-phen"). Both were highly efficacious but were withdrawn from the market in 1997 after reports of heart valve disease and pulmonary hypertension associated with their use.

The withdrawn drugs targeted $5HT_2$ non-selectively, and their action at $5HT_{2B}$ was thought to be responsible for the side effects. Lorcaserin has 100-fold selectivity for $5HT_{2C}$ vs $5HT_{2B}$, and 15-fold selectivity for $5HT_{2C}$ over $5HT_{2A}$, a subtype thought to be responsible for many of the CNS adverse effects of non-selective agents.

Senior management

CEO – Jack Lief

Chief scientific officer – Dr Dominic Behan

Chief financial officer – Robert Hoffman

Bull

- While lorcaserin's efficacy does not appear so far to match some of its competitors, the longest treatment duration studied so far is only 12 weeks. Current Phase III studies will be expected to show increased efficacy, and there is a suggestion from the Phase IIb graph (above) that at 12 weeks the treatment effect of lorcaserin has yet to reach a plateau.
- One logical way to achieve added efficacy would be to combine lorcaserin with phentermine. However, management has made no comment on whether this is being considered, perhaps owing to continuing concerns following the 1997 withdrawal of Fen-Phen. It is noteworthy that only in combination with phentermine did fenfluramine and dexfenfluramine show efficacy at the top end of the spectrum of obesity treatments.

Bear

- Lorcaserin faces a huge perceived regulatory hurdle owing to the withdrawal of Fen-Phen. However, the 7,000-patient Phase III programme is specifically monitoring heart valve effects and no significant increase has been seen so far.
- While lorcaserin's selectivity profile might avoid the side effects, the relationship between its mechanism of action and that of fenfluramine and dexfenfluramine is likely to result in increased scrutiny from the US FDA and other regulators. Furthermore, potential adverse publicity could affect clinical trial enrolment or eventual sales.
- Lorcaserin's Phase III programme is one of the largest ever, planning to enrol almost 7,000 patients. Its total budgeted cost was recently increased from $125m to $160m, although Arena maintains that its current cash position will be sufficient to fund this.

NeuroSearch

Year End	Revenue (DKKm)	PBT (DKKm)	EPS (DKK)	DPS (DKK)	PE (x)	Yield (%)
12/06	66.3	(212.2)	(24.17)	0.0	N/A	N/A
12/07	115.2	(294.7)	(21.17)	0.0	N/A	N/A
12/08e*	178.4	(257.5)	(12.8)	0.0	N/A	N/A
12/09e*	133.3	(287.9)	(19.0)	0.0	N/A	N/A

*consensus forecasts

Investment summary: Top-level efficacy

Published literature indicates that NeuroSearch's tesofensine has shown some of the most impressive weight loss data of an anti-obesity agent in a clinical study to date – 10.6kg. Release of the study data in September 2007 caused a sharp uplift in the company's share price, although the stock has since drifted back down. NeuroSearch also has a large R&D pipeline of projects focused on CNS disorders.

Longer-term data due

An open-label Phase IIb extension study evaluating tesofensine's safety profile, tolerability and weight reduction effect for up to 12 months is due to generate data in June 2008. This could boost the investment case and is likely to determine the programme for Phase III, including study design, cost and partnering strategy. A Phase I study investigating tesofensine's liability for abuse is ongoing.

Likely to seek a licensee

NeuroSearch is well funded, having reported DKK823.5m of cash on 31 March 2008 after raising DKK771m before costs. Nevertheless, it has a broad pipeline of clinical projects to support (some already being funded by big pharma partners), and Phase III studies of tesofensine do not feature in its current budget. Tesofensine will need to be licensed out to an industry partner with a substantial US sales presence.

Large database of patient exposures

Thanks to previous Phase II/III studies of tesofensine in Alzheimer's and Parkinson's diseases, NeuroSearch has a safety database from around 1,000 patient exposures – a significant number for a Phase II anti-obesity project. This means that a slightly smaller pivotal programme than normal might satisfy regulators, and this could spur partnering interest. NeuroSearch has existing broad licensing deals for other pipeline compounds with GlaxoSmithKline and Abbott – companies with a presence in obesity – and we expect these to show some level of interest in tesofensine.

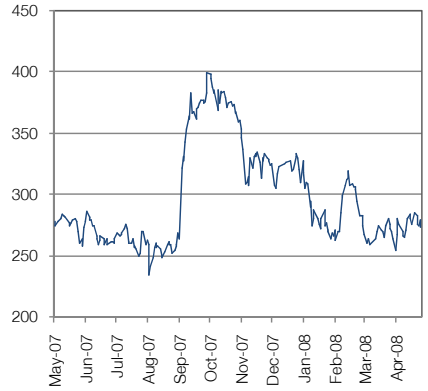
Safety?

As is the case with all centrally acting agents, tesofensine's safety profile is likely to be scrutinised thoroughly by regulators. Anticipating this, NeuroSearch has decided to focus on the 0.5mg dose in future studies – this produced slightly, but not statistically, lower efficacy in Phase IIb than the 1mg dose, with a better side-effect profile. Potentially, 0.25mg could be used as a maintenance dose.

Price	DKK275*
Market Cap	DKK4.2bn*

as at close on 13 May 2008

Share price graph



Share details

Code	NEUR
Listing	Copenhagen
Shares in issue	15.4m

Price

52-week	High	Low
	DKK432.5	DKK239.0

Business

Neurosearch is an $800m market cap Danish biopharmaceuticals company with a focus on central nervous system diseases. It has 11 projects in Phase I or II, and expects its obesity project, tesofensine, to start Phase III this year before being licensed out to a partner.

Recent newsflow

Mar 2008 – Top-line data from tesofensine metabolic study (TIPO-2)

Dec 2007 – Start of Phase I Parkinson's study

Dec 2007 – Start of Phase Ib Alzheimer's trial

Nov 2007 – Completion of DKK771m rights issue

Sep 2007 – Data from Phase IIb obesity trial

Analyst

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Current tesofensine studies

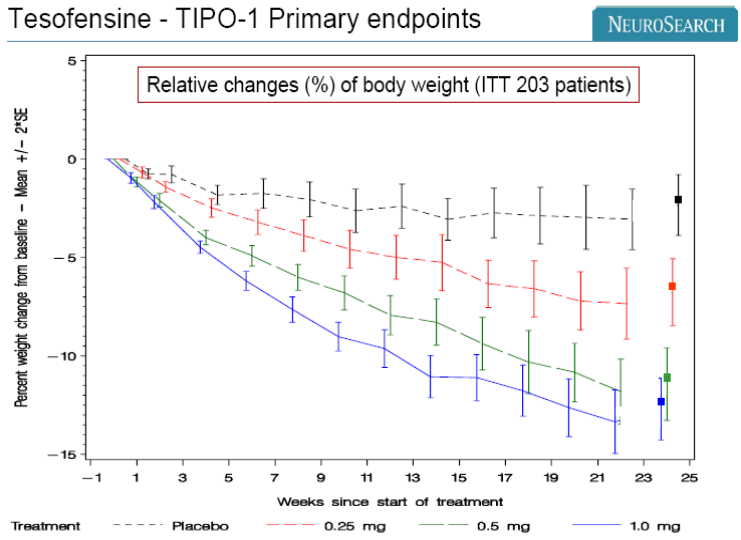
Tesofensine was previously in Phase II/III development for treating Alzheimer's and Parkinson's diseases, but this was discontinued owing to poor efficacy. Two Phase II obesity studies are due to report data this year:

TIPO-2 – 14-day study evaluating tesofensine's direct effect on metabolic parameters such as insulin, glucose and cholesterol levels in 32 overweight patients. Headline data showed no changes in energy expenditure, metabolic rate or respiratory quotient, and an increase in fat oxidation. Full results are due in May/June 2008.

TIPO-4 – an open-label Phase II extension study initiated in June 2007. This is offering all patients who concluded 24 weeks' treatment in TIPO-1 another six months of treatment (over 90% of TIPO-1 patients elected to continue into TIPO-4), and patients will follow the same diet and exercise programme as in TIPO-1. Tesofensine is being dosed at 0.5mg daily (postulated to be the ideal dose for Phase III) with the possibility of increasing to 1.0mg daily according to tolerance and efficacy. The aim of TIPO-4 is to evaluate tesofensine's safety profile and tolerability and generate additional weight reduction data, with results expected in June 2008. An additional 24-week extension is possible afterwards.

Phase IIb (TIPO-1) results

In September 2007 NeuroSearch reported data from TIPO-1, a Phase IIb proof-of-concept and dose-finding study with tesofensine. Data from 203 patients (BMI 30–40) showed that 24 weeks' treatment with tesofensine 0.25mg, 0.5mg and 1mg resulted in a dose-dependent average weight loss of 6.7kg, 11.3kg and 12.8kg respectively (against a weight loss of 2.2kg in the placebo group). In all treatment groups, the primary endpoints were met with high statistical significance (p<0.0001).



Source: NeuroSearch presentation

NeuroSearch pipeline

Phase III
Huntington's disease – in-house

Phase II
Obesity – in-house
Depression – GSK
ADHD – Abbott
Neuropathic pain – Abbott
ADHD – GSK
Epilepsy and pain – in-house

Phase I
Schizophrenia – Astellas
Parkinson's/bipolar – in-house
Schizophrenia/dementia – Abbott
Cognitive dysfunction – Abbott
Neuropathic pain – GSK
Parkinson's disease – in-house

Preclinical
COPD – in-house
Anxiety – GSK option
CNS disorders – GSK option
CNS disorders – Abbott
Autoimmune diseases – GSK option
Epilepsy/pain – GSK option
Schizophrenia/cognitive – GSK option

Bull

- Efficacy (in a 203-patient, 24-week Phase IIb study) is higher than any marketed drug and appears better than any developmental product candidate.
- NeuroSearch already has significant big pharma partners in GlaxoSmithKline and Abbott as licensees for other pipeline projects, and we would expect these to show interest in the anti-obesity programme.
- Because tesofensine was previously in mid/late-stage development for other indications, NeuroSearch has safety data on hundreds of additional patient exposures (about 1,000 patients exposed in total so far to all therapeutic doses), meaning that the Phase III obesity programme need not necessarily be as large as for competitor companies' projects.
- Possible future use in combination (eg, with a GLP-1 analogue) could have the potential to lower the tesofensine dose further while retaining efficacy.

Bear

- As tesofensine is a centrally acting dopamine, noradrenaline and 5HT reuptake inhibitor it will likely face regulatory scrutiny over its safety profile. The most common adverse events in Phase IIb were dry mouth, nausea, constipation, diarrhoea and insomnia, and there were slight increases in pulse and blood pressure (mean changes were not statistically different cf placebo). The adverse events were dose dependent, however, hence NeuroSearch's decision to focus on the 0.5mg dose.
- Boehringer Ingelheim, NeuroSearch's former partner for tesofensine in Alzheimer's and Parkinson's diseases, retains rights to 10% of any future milestones on the project, plus a 2% royalty on sales.
- Funding Phase III development is not within NeuroSearch's current budget, and a partner is thus needed to complete pivotal trials. Failure to sign up a licensee could delay the study, while beginning Phase III without sufficient cash to finish it is risky.

Orexigen Therapeutics

Year End	Revenue ($m)	PBT ($m)	EPS ($)	DPS (c)	PE (x)	Yield (%)
12/06	0.9	(57.8)	N/A	0.0	N/A	N/A
12/07	0.9	(41.4)	(3.08)	0.0	N/A	N/A
12/08e*	0.1	(85.3)	(2.66)	0.0	N/A	N/A
12/09e*	6.4	(106.3)	(2.87)	0.0	N/A	N/A

*consensus forecasts.

Investment summary: Repositioning play

Orexigen's two lead anti-obesity projects – Contrave and Empatic – comprise new formulations of established drugs that have been approved for other indications and have established post-marketing safety records. Both have demonstrated efficacy in treating obesity, but off-label use of generics remains a potential risk to the business, and the patent-protected formulations will need to demonstrate strong evidence of safety, efficacy and convenience over generics.

Two shots at goal

Contrave is a fixed-dose formulation of bupropion and naltrexone and is in four Phase III trials (all now fully enrolled) comprising almost 4,500 patients over a year, while Empatic contains bupropion formulated with zonisamide, and recently saw data from a 48-week, Phase IIb study showing efficacy at the top end of the range in our comparison of competing products.

Both unpartnered

Contrave could be filed in late 2009, while with Empatic's Phase III programme not due to begin until H109 an NDA filing is unlikely before 2011. Both products are unpartnered, and Orexigen's strategy is to carry out further Contrave development in-house before seeking a US co-development/co-promotion deal. Talks on licensing out Empatic could start this year, but its Phase III development programme – closely mirroring that of Contrave – will proceed regardless.

Subtle positioning

In studies Empatic has shown greater efficacy than Contrave, but its label is likely to recommend birth control for women of childbearing age and it is likely to be contraindicated in women who are pregnant or breastfeeding. As a result, Contrave could be targeted at women with food craving, while Empatic may be reserved for heavier men and post-menopausal women who require greater weight reduction.

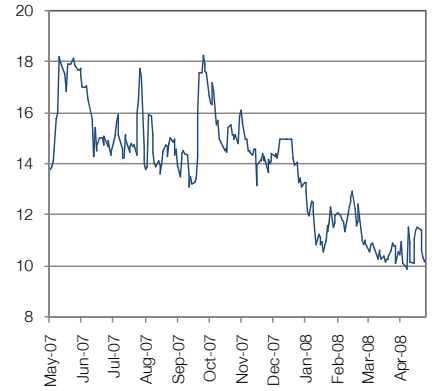
But safety and generics could be an issue

The overall tolerability of Empatic has yet to be determined, and while it appears to be relatively efficacious it contains zonisamide at its highest approved dose, at which the immediate-release version has been associated with nausea. Off-label use of the generically available constituent products remains a risk unless Orexigen can make a clear case regarding practicality, cost-effectiveness and clinical superiority.

Price	$8.31*
Market Cap	$284m*

as at close on 13 May 2008

Share price graph



Share details

Code	OREX
Listing	Nasdaq
Shares in issue	34.2m

Price

52-week	High	Low
	$19.15	$8.24

Business

Orexigen is a US biopharmaceutical company focused on treatments for central nervous system disorders, with an initial focus on obesity. Its work is based on an understanding of neural circuits and the selection of generic compounds approved for other indications and reformulating them for new uses.

Recent newsflow

Jan 2008 – $77m follow-on offering

Jan 2008 – 48-week results of Phase IIb Empatic trial

Dec 2007 – Fourth Phase III Contrave study begins

Oct 2007 – Phase IIb Contrave trial results

May 2007 – Flotation on Nasdaq

Analyst

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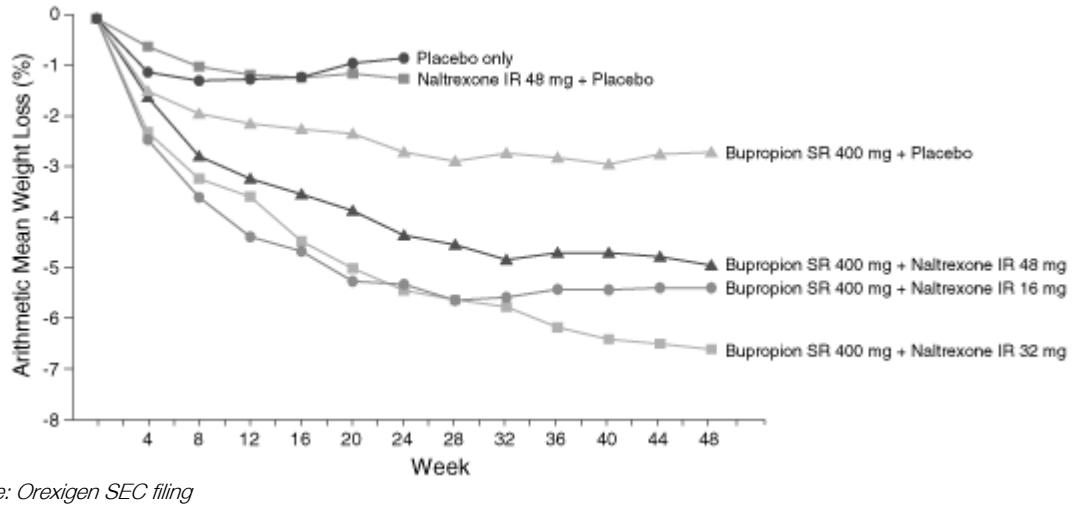
Contrave development rationale

Contrave employs a proprietary formulation of two marketed off-patent CNS molecules, bupropion SR (treating depression and smoking cessation) and naltrexone SR (alcohol dependence/opiate addiction).

Bupropion has been shown to activate pro-opiomelanocortin neurons in the hypothalamus, leading to the production of α-MSH and beta-endorphin. α-MSH leads to a reduction of appetite and an increase in energy expenditure through a pathway by which naturally occurring peptides such as leptin regulate body weight. However, in obese patients a resistance to leptin is present; bupropion is thought to circumvent leptin resistance and activate the weight loss pathway.

Beta-endorphin, meanwhile, is an opioid that serves as a brake on the above system. Naltrexone is a potent opioid antagonist which competes with beta-endorphin, thus limiting this negative feedback mechanism.

Contrave Phase IIb mean weight loss over 48 weeks (intent-to-treat population)



Source: Orexigen SEC filing

In this study, Orexigen saw a high early dropout rate (124 of 228 enrolled patients completed the 48-week extension), which it believes was related to the use of immediate-release naltrexone; for the Phase III programme the company has switched to a sustained-release (SR) formulation. Accordingly, the above data are affected by the use of the last observation carried forward, and this also led to the highest (48mg) naltrexone dose appearing less efficacious than the other two doses. If only completer data are considered, there is a dose-dependent effect (ie, naltrexone 48mg is the most efficacious), and the highest dose gives a placebo-adjusted weight loss of around 10% at week 48.

Nevertheless, the FDA will focus on the intent-to-treat population (with last observation carried forward), and that is the basis on which study data have been presented in this report

Contrave's Phase III programme comprises four studies, all fully recruited as of May 2008

An 800-patient, 56-week trial started in April 2007, comparing bupropion SR 360mg + naltrexone SR 32mg/day with placebo, including a behaviour modification programme. Patients with BMI 27–45; primary outcome measure is change in percentage of body weight.

A 525-patient, 56-week study began in May 2007, comparing bupropion SR 360mg + naltrexone SR 32mg/day with placebo. Patients with BMI 27–45 and type 2 diabetes; primary outcome measures are change in percentage of body weight and percentage of patients with ≥5% weight loss.

A 1,650-patient, 56-week trial began in September 2007, comparing bupropion SR 360mg + naltrexone SR 32mg/day with bupropion SR 360mg + naltrexone SR 16mg/day and with placebo. Patients with BMI 27–45; primary outcome measures are change in percentage of body weight and percentage of patients with ≥5% weight loss.

A 1,500-patient study started in November 2007, comparing bupropion SR 360mg + naltrexone SR 32mg/day with placebo. Patients with BMI 27–45; primary outcome measures are change in percentage of body weight and percentage of patients with ≥5% weight loss.

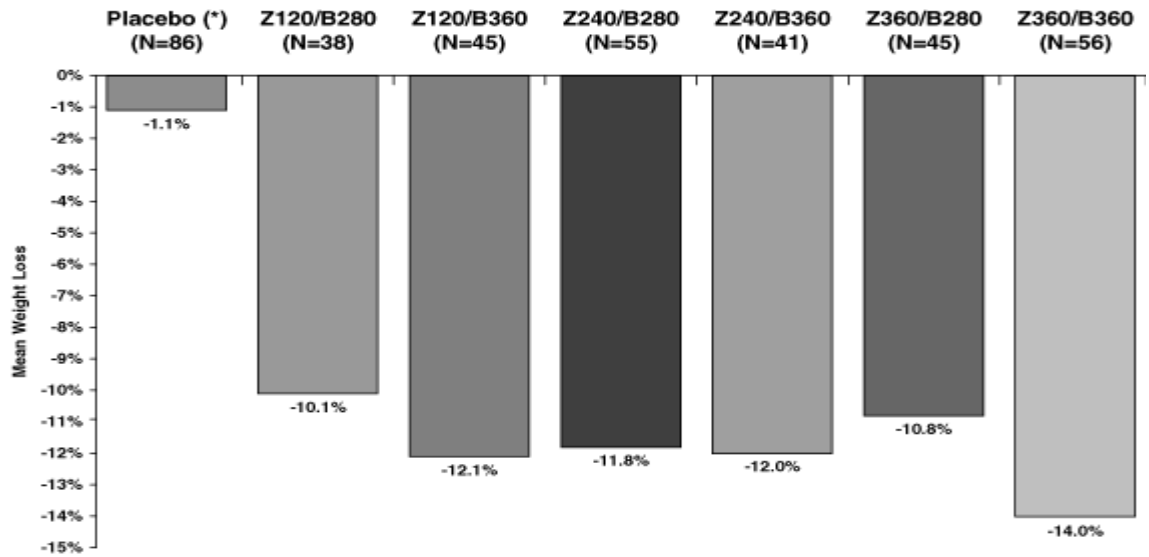
Empatic development rationale

Empatic is a proprietary formulation of bupropion SR and zonisamide SR (a marketed off-patent anti-epileptic). Bupropion and zonisamide each target reciprocal pathways in the hypothalamus that mediate appetite and energy expenditure and, as with Contrave's components, have been shown to act synergistically.

Like Contrave, Empatic employs bupropion to increase α-MSH secretion via pro-opiomelanocortin stimulation, and zonisamide increases the firing rate of these neurons in the presence of bupropion.

Zonisamide is also thought to inhibit the firing of neuropeptide Y/Agouti-related peptide neurons, whose stimulation results in the release of AgRP, which competes with α-MSH. By inhibiting these neurons it is postulated that zonisamide can prevent counteraction of the weight-promoting activity of α-MSH.

Empatic Phase IIb mean weight loss at 48 weeks (intent-to-treat population; double-blind extension)



Source: Orexigen SEC filing

There were fewer dropouts in this trial than in the study of Contrave: 599 patients were enrolled initially, with 480 completing 24 weeks' treatment; 366 elected to go into the 48-week extension, and 268 of these completed that study. Looking only at the completer population, the placebo-adjusted weight loss at 48 weeks with the highest Empatic dose (zonisamide 360mg/bupropion 360mg) was 13.9%. Empatic's Phase III programme is likely to mirror that of Contrave.

Bull	Bear
• Orexigen's two anti-obesity products comprise combinations of established active ingredients with established safety records and extensive patient exposure data. • Orexigen is well funded ($97m raised at IPO, $77m in a follow-on offering). • Threat of generic substitution could be overcome thanks to the pharmacokinetic profile of the SR formulations being used in Contrave and Empatic, which cannot be matched by generic versions. Also, doses used are not commercially available, and physicians might feel uncomfortable prescribing these types of drugs without an FDA label. • If priced astutely there could be little economic incentive for physicians to substitute. The Contrave and Empatic combinations would each cost around $10 per day to recreate with generics, while Orexigen plans to price at $5 to $7 per day.	• Regulatory/litigation risk. Because Orexigen's product candidates are combinations of marketed generics, its success hinges on an ability to prevent off-label generic substitution. The strength of its IP will be key. • Contrave is safe with limited efficacy, while Empatic has good efficacy but uses zonisamide at the highest approved dose (previous evidence of nausea side effects). • A relatively high number of early dropouts was seen in the Phase IIb study of Contrave. However, this used naltrexone IR, and use of the SR formulation (being studied in Phase III) could overcome this. • Big pharma has so far appeared reluctant to buy into fixed-dose combination treatment approaches.

Vivus

Year End	Revenue ($m)	PBT ($m)	EPS ($)	DPS (c)	PE (x)	Yield (%)
12/06	17.2	(21.6)	(0.45)	0.0	N/A	N/A
12/07	54.7	2.7	(0.04)	0.0	N/A	N/A
12/08e*	101.5	15.9	0.29	0.0	N/A	N/A
12/09e*	51.8	(18.5)	(0.28)	0.0	N/A	N/A

*consensus forecasts.

Investment summary: Now well funded

Receipt of a $140m milestone payment from KV Pharmaceutical has given Vivus sufficient funds to finance the entire late-stage development programme for Qnexa. Previous clinical studies have shown the project to have efficacy at the upper end of the spectrum of developmental anti-obesity agents and, as Qnexa is a combination of two established drugs, adverse events are unlikely to be a significant concern.

Old drugs, new formulation

Qnexa is a fixed-dose combination of phentermine and topiramate, designed to complement the former's appetite-reducing properties with the latter's satiety-increasing properties. Although development of standalone topiramate for obesity was stopped owing to CNS side effects, Qnexa contains a low dose of it, and combining it with phentermine is aimed at broadening its therapeutic window.

In three Phase III trials

The Phase III development programme for Qnexa comprises three studies, all of which are now underway and aiming to recruit a total of almost 4,500 patients. Enrolment is due to be completed in mid-2008, with pivotal data publication and NDA filing possible in H209. The highest Qnexa dose in Phase III contains less than a quarter of the highest approved topiramate dose and less than half the highest approved dose of phentermine.

Blood pressure benefits

In Phase II Qnexa also showed a reduction in certain risk factors contributing to metabolic syndrome, including a significant decrease in systolic and diastolic blood pressure in obese hypertensive patients. Qnexa appears to be one of only two anti-obesity projects (with Novo Nordisk's liraglutide) to show an effect on blood pressure.

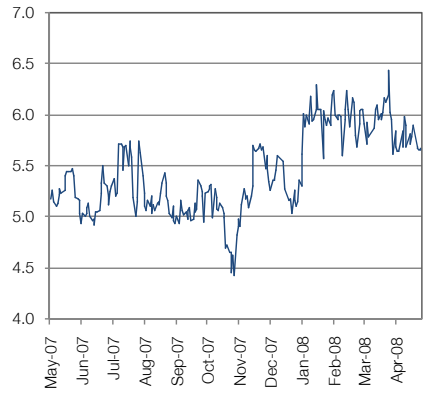
One product on the market

Vivus already markets one product, Muse, an intraurethral alprostadil formulation for erectile dysfunction, although this does not generate significant revenue. The in-house R&D pipeline comprises Qnexa for obesity and diabetes (Phase II), Luramist (testosterone metered-dose transdermal spray in Phase II for low sexual desire in women) and avanafil, a PDE5-inhibitor follow-up to Viagra (Pfizer's sildenafil) in Phase II development for erectile dysfunction.

Price	$5.24*
Market Cap	$307m*

as at close on 13 May 2008

Share price graph



Share details

Code	VVUS
Listing	Nasdaq
Shares in issue	58.6m

Price

52-week	High	Low
	$6.55	$4.28

Business

Vivus is a Nasdaq-listed biotechnology company developing therapeutics for treating obesity and sexual health. It markets an erectile dysfunction treatment, and last year licensed rights to EvaMist, an investigational metered-dose transdermal estradiol spray for menopause symptoms, to KV Pharmaceutical.

Recent newsflow

Apr 2008 – Third Phase III study of Qnexa completes enrolment

Apr 2008 – $30m funding for Phase III studies of avanafil for erectile dysfunction

Nov 2007 – Qnexa enters Phase III for obesity

Aug 2007 – $140m milestone received from KV

May 2007 – EvaMist licensed to KV

Analyst

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Qnexa development rationale

Phentermine has been available for treating obesity since 1950s, and is still the most widely prescribed weight loss therapy. Topiramate was approved in 1997 for treating epilepsy, having been studied and discontinued by J&J for obesity. Topiramate was shown at high doses (192–256mg/day) to be highly efficacious at treating obesity, but over 40% of patients withdrew owing to side effects, mainly CNS (depression and mood/memory problems). At lower doses topiramate was much more tolerable, but lacked efficacy vs placebo.

The rationale behind Qnexa is to expand topiramate's therapeutic window by using a very low dose of it and combining it with phentermine, which acts via a different mechanism. Topiramate works via GABA and other agonist properties and increases satiety, while phentermine is noradrenergic and non-serotonergic, and reduces appetite. A complementary, synergistic effect has been postulated and demonstrated in Phase II trials.

Phase III programme

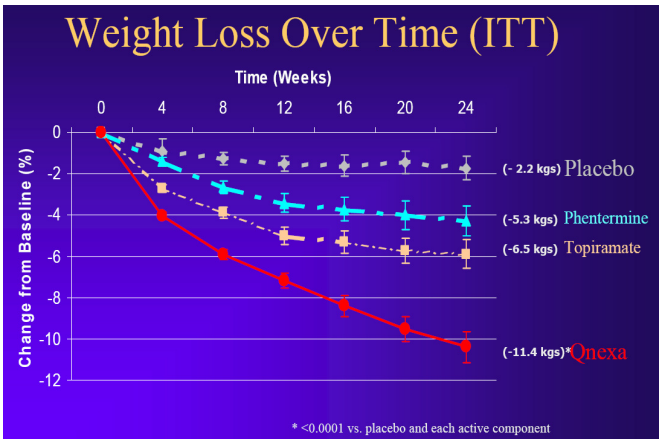
OB-301 – six-month study aims to repeat results of Phase II (improvement over individual components) but with a proprietary formulation; also looking at a half dose. Seven arms, 100 patients in each (BMI of 30-45 with and without metabolic co-morbidities. Co-primary endpoints are percentage weight loss at week 28, and percentage of subjects achieving weight loss ≥5%.

OB-302 – 56 week trial in 1,250 morbidly obese patients (BMI ≥ 35) without metabolic co-morbidities.

OB-303 – 56 week study in 2,500 overweight and obese patients (BMI 27–45) with at least two metabolic co-morbidities (eg triglycerides 200–400mg/dl, BP >140/90, impaired glucose tolerance, waist circumference >102cm [men] or >88cm [women]). The co-primary endpoints for OB-302 and OB-303 are percentage weight loss at week 56 and percentage of subjects achieving weight loss ≥5%.

Qnexa Phase II results

Results of a four-arm study to investigate Qnexa's effect vs placebo and its individual components were reported in May 2006. 50 patients (average BMI of 38.6) were randomised into each arm and treated for 24 weeks. Results below.



Source: Vivus presentation.

IP position

Because Qnexa will contain two generic ingredients (topiramate will come off patent in 2009) Vivus's IP position is an important consideration. Qnexa is a fixed-dose combination containing active ingredients at lower doses than currently available (eg topiramate 92mg cf 400mg available). Furthermore, the once-daily tablet releases phentermine in the morning, while the topiramate is control-released in the afternoon (ie after food intake) and at night.

Therefore attempting to mimic the formulation's action using generic tablets appears to be too complex to make it a realistic possibility.

Senior management

CEO – Leland Wilson

Chief Financial Officer – Timothy Morris

VP of Clinical Development – Dr Wesley Day

Bull

- Qnexa comprises two active ingredients whose standalone use at higher doses has been demonstrated over many years and patient exposures.
- Vivus is well financed, and thus able to fund Qnexa's entire Phase III programme. This means that it is likely to retain a considerable amount of the product's late-stage value and command a higher partnering deal value than would be possible if it were to license it out before Phase III.

Bear

- Continued demonstration of safety will be a key consideration for the US FDA, although topiramate is at a very low dose and phentermine was not implicated in the Fen-Phen withdrawal due to valvulopathy. Phentermine was suspended from the European market, but this decision has been annulled.
- Topiramate is about to come off patent (phentermine is already generic) so IP could in theory be an issue. But the fact that Qnexa contains low doses of active ingredients and has a complex controlled-release action probably gets around this concern.
- Patients in Phase II had a relatively high baseline weight, potentially flattering the average weight loss seen.

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