

Obesity Revenue Projections

None Likely to be a Blockbuster

Companies:

Amylin Pharmaceuticals (AMLN)
Arena Pharmaceuticals (ARNA)
Athersys (ATHX)
Alizyme (London: AZM)
Merck (MRK)
Neurosearch (Copenhagen:NEUR)
Novo Nordisk (NVO)
Orexigen (OREX)
Roche (Swiss: ROG)
Sanofi Aventis (SNY)
Vivus (VVUS)

Products:

Xenical (Roche)
Meridia (Abbott)
Phentermine (generic)
Contrave (Orexigen)
Empatic (Orexigen)
Lorcaserin (Arena)
Qnexa (Vivus)
Liraglutide (Novo Nordisk)
Tesofensine (Neurosearch)
Cetilistat (Alizyme/Takeda)
Pramlintide + Leptin (Amylin)
Accomplia (Sanofi-Aventis)
ATHX-105 (Athersys)

- **inThought models the revenue potential of eight obesity drugs in clinical development** - Orexigen's Contrave and Empatic, Arena's lorcaserin, Vivus's Qnexa, Novo Nordisk's liraglutide, Neurosearch's tesofensine, Alizyme's Cetilistat, and Amylin's pramlintide/leptin combination.
- **None of the agents in late stage clinical development is likely provide an optimal anti-obesity solution** in terms of therapeutic effect magnitude, long-term safety, and reimbursement.
- **The highest revenue generator in our model is Arena's lorcaserin, with peak worldwide sales modeled at \$850 million if approved.**
- **In spite of our modest revenue projections, the potential market for obesity agents is huge. In this report, we discuss the factors that could lead to the "breakout" success of each of the obesity agents.** For example, lorcaserin could be a multi-billion dollar a year drug if it is safe and effective in combination with phentermine.
- **The challenges that each agent will face, especially CNS and cardiovascular adversities, as well as marginal weight loss profiles, are also discussed.**

Disease Overview

Obesity is a chronic condition in which excess body fat has accumulated to a degree associated with adverse effects on health. The U.S. National Institutes of Health (NIH) and the Centers for Disease Control and Prevention (CDC) have defined obesity as having a Body Mass Index (BMI) of 30 kg/m² and above. A BMI between 25 and 29.9 is considered overweight. The global cut-off points for overweight (BMI = 25.0 kg/m²) and obesity (BMI = 30.0 kg/m²) have been set by the World Health Organization (WHO). Much discussion surrounding the appropriateness of these cut-off points for the Asian and Pacific Island populations has resulted in lower cut-off points: BMI of 23 to 24.9 defined as overweight and at BMI of 25 and greater defined as obese in these populations.

Obesity is a multi-factorial condition with behavioral, environmental, and genetic components. The treatment of obesity requires dietary changes, exercise, and counseling in addition to any prescribed pharmacologic intervention. Bariatric surgery (e.g. gastric bypass or banding) is recommended for individuals classified as ‘morbidly obese,’ with a BMI of over 40.

Obesity is associated with increased risk for coronary heart disease, diabetes, cancer, hypertension, stroke, depression, sleep apnea, and overall mortality. Moderate weight loss (5%-10%) has been shown to significantly decrease many of these risks.

Epidemiology

According to the CDC, obesity affects approximately 34% of the U.S. population. Approximately another third meets the clinical definition for being overweight. Data from national population surveys (NHANES) have demonstrated that, since 1960, the prevalence of obesity has more than doubled, from 13% to 27% of the population.

The WHO estimates that the worldwide prevalence of obesity is over 300 million, forecasting that the prevalence will increase to over 700 million by 2015. Globally, there are more than 1 billion overweight adults.

In the top five European markets, there are an estimated 46 million obese individuals with close to 91 million meeting the clinical definition for being overweight. Studies suggest there are around 16

million overweight people in Japan. Of that number, roughly 80% are estimated to be obese. Data suggest the rate of obesity is growing at a faster rate in both Europe and Japan in comparison to other countries due to increasing consumption of fattier, “Westernized,” food.

With the CDC estimating that the total economic cost of obesity-associated diseases in the U.S. is over \$90 billion per year, there is a high unmet need for effective and safe anti-obesity agents.

Commercial Overview

The need for safe, tolerable, and efficacious anti-obesity drugs that can be used long-term fuels efforts in the search for better products. Current treatment options are modestly efficacious, poorly tolerated, and plagued by safety concerns. Of the prescription drugs that are available in the U.S. to treat obesity, only two – Abbott’s Meridia (sibutramine) and Roche’s Xenical (orlistat) – are approved for long-term use. In June 2008, Roche and its partner GlaxoSmithKline launched non-prescription orlistat 60mg under the brand name Alli.

While Meridia has the ability to control appetite, offering an average weight loss of 4.3% over one year, it can lead to hypertension and increased heart rate. Xenical leads to weight reduction through the inhibition of lipase-mediated breakdown of fat in the gastrointestinal tract. Despite leading to an average weight loss of 2.9% over one year, approximately 20-30% of patients taking the drug experience embarrassing and unpleasant gastrointestinal adversities, including fecal incontinence and urgency.

Phentermine, first introduced in the 1950s, is a generic appetite suppressant still in wide use today. It remains the most widely prescribed anti-obesity agent in the U.S., leading to an average placebo adjusted weight loss of 3.5% over 3 to 6 months. However, patients begin to regain weight quickly after stopping treatment. The drug, a schedule IV controlled substance, is indicated for treatment of less than 12 weeks.

Despite approximately 85 million individuals in the U.S. being classified as ‘obese,’ the patient population using pharmacologic therapy is very small. *inThought* expert consultants estimate that only 2% of eligible patients currently receive pharmacotherapy for weight loss. A company that

Current treatment options are modestly efficacious, poorly tolerated, and plagued by safety concerns.

develops a more efficacious drug therapy with proven longer-term safety stands to reap huge rewards.

While a minimal percentage of obese patients turn to pharmacological intervention, the percentage seeking some form of treatment for their obesity (e.g., behavior modification, dieting, exercise, OTC agents, and nutraceuticals) is significantly larger. Studies suggest that, at any one time, 35% to 80% of obese individuals are attempting to lose weight. Our model assumes that 55% of the obese individuals in the U.S. seek some form of treatment for their obesity.

In the European Union, both Xenical and Meridia are available. In October 2008, EMEA suspended the use of Sanofi-Aventis's Acomplia (rimonabant) due to the risk of developing serious psychiatric disorders and suicide, particularly in obese individuals. Phentermine was withdrawn in the E.U. in 2000. In January 2009, the E.U. approved Alli, the OTC version of orlistat. We estimate that 50% of obese individuals in the E.U. seek some form of treatment for their obesity. Similarly to the U.S. market, we estimate that the percentage of people currently using pharmacological therapy is quite low.

Despite a large proportion of the population being obese, the Japanese anti-obesity market is very small, dominated by mazindol. Mazindol is a sympathomimetic amine, similar to amphetamine. Mazindol increases heart rate and blood pressure, and decreases appetite. While neither Xenical (orlistat) nor Meridia (sibutramine) are currently available in Japan, the landscape is changing. In November 2007, Eisai submitted an application with the Ministry of Health, Labour and Welfare (MHLW) for approval of sibutramine (KES524) for obesity. We anticipate sibutramine to be on the market shortly. In January 2009, Taisho entered into an agreement with Glaxo Group Ltd, a subsidiary of GlaxoSmithKline, for development and marketing of orlistat (R212) in Japan.

We anticipate that approximately 50% of obese individuals in Japan seek some form of treatment for their obesity with a minimal percentage resorting to pharmacotherapy.

Drivers of Adoption

Three factors will drive the adoption of anti-obesity agents: efficacy, safety, and reimbursement. Should a drug prove safe, considerably more effective than available therapies, and achieve favorable reimbursement, the percentage of obese individuals seeking pharmacological treatment will increase dramatically.

Efficacy

The FDA has provided guidance on what constitutes the minimally acceptable degree of clinically relevant weight loss. A product can be considered efficacious in a weight management program if, after one year of treatment, either of the following occurs:

1. "The difference in mean weight loss between the active product and placebo treated groups is at least 5 percent and the difference is statistically significant." (The EMEA stipulates weight loss of more than 10%.)
2. "The proportion of subjects who lose \geq to 5 percent of baseline body weight in the active-product group is at least 35 percent, is approximately double the proportion in the placebo-treated group, and the difference between groups is statistically significant."

Measurement of other factors, such as effects on blood pressure, lipids, and glucose tolerance, is also encouraged by the FDA. Additionally, guidance focuses on safety, requiring long-term exposure data with a minimum of one year of placebo-controlled exposure in 1,500 patients treated with drug, followed by a second year of drug exposure in 200-500 patients.

While a 5% weight loss could technically satisfy FDA approval requirements, inThought experts agree that a more significant degree of weight loss, on the order of at least 15%, is needed for optimal reimbursement and commercial success.

On this front, no single agent qualifies. While NeuroSearch's tesofensine and Vivus' Qnexa have demonstrated the highest placebo-adjusted weight loss of the late stage agents - 8.6% and 10.6% respectively - neuropsychiatric side effects may limit adoption. Although Arena's lorcaserin has shown efficacy on par currently marketed agents, it is not known the degree to which phentermine co-administration may prove additive or synergistic.

Three factors will drive the use of anti-obesity agents: efficacy, safety, and reimbursement.

Safety

Regulators are increasingly cautious about long-term psychiatric safety of anti-obesity agents. The increased incidence of psychiatric side effects led to the discontinuation of two cannabinoid receptor antagonists: Sanofi Aventis's rimonabant and Merck's taranabant.

Treating obesity is a long-term endeavor. To be commercially successful, a compound must demonstrate a manageable long-term safety profile. Of the late stage agents, the neuropsychiatric concerns of Vivus' Qnexa and the cardiac valvulopathy risk associated with Arena's lorcaserin remain our biggest concerns.

Reimbursement

Cost and reimbursement remain critical to the ultimate adoption of any anti-obesity medication. Current anti-obesity drugs are not generally reimbursed by third party payors in the U.S. Many patients are unwilling to pay the estimated \$100 per month for disappointing efficacy.

While FDA obesity development guidelines do not specifically require diabetes-associated data points, treatment experience in diabetics is important. Developmental agents able to obtain labeling for use in diabetics will be more likely to obtain favorable reimbursement, resulting in faster rates of adoption and more significant revenue growth. Changes in the reimbursement status of the anti-obesity agents are unlikely in the near future, but two potential strategies for gaining reimbursement exist:

1. Demonstrating significant efficacy on the order of 15-20% weight loss, leading to increased public pressure that would arise from demand.
2. Obtaining labeling for an additional indication that is more easily reimbursable, such as type 2 diabetes.

inThought believes that none of the agents in late stage clinical development is likely provide an optimal anti-obesity solution in terms of therapeutic effect magnitude, long-term safety, and reimbursement. Consequently, we project conservative uptake of each of the agents.

With data from several phase III studies anticipated before the end of this year, and an additional one during 2010, a number of factors could change our

view. In this report, we assess each candidate across these three drivers and highlight what could propel each of them toward blockbuster status.

The Players

Four agents in late stage clinical development are featured in our revenue model:

- Arena Pharmaceutical's **lorcaserin**, currently being tested in phase III trials, is similar to the ill-fated Redux (dexfenfluramine) in its mechanism of action. With its higher selectivity the serotonin 2c (5HT2c) receptor than for the serotonin 2b (5HT2b), lorcaserin may present an acceptable cardiac valvulopathy risk profile.
- Orexigen's **Contrave** is a fixed-dose combination of sustained release naltrexone and bupropion in a single, trilayer tablet. Top-line results from four trials were reported this week, with an NDA with planned for the first half 2010.
- Vivus' **Qnexa**, a combination of low-dose phentermine and topiramate, is currently in three phase III studies for obesity and a phase II study for diabetes.
- Novo Nordisk's **liraglutide** is a long-acting, stable analogue of the natural hormone glucagon-like peptide-1 (glp-1), currently in phase III for obesity, and under regulatory review in the U.S., Europe, and Japan for diabetes.

inThought also models earlier stage agents, including Orexigen's **Empatic**, Amylin's **pramlintide / metreleptin** combination, NeuroSearch's **tesofensine**, and Alizyme's **Cetilistat**.

Developmental agents able to obtain labeling for use in diabetics will be more likely to obtain favorable reimbursement.

Combination approaches continue to be the most promising strategy in the pharmacologic management of obesity. Rather than one perfect drug, physicians and patients would benefit from multiple mechanisms of action, similar to the current treatment of cardiovascular disease and diabetes. Please see our April 13, 2009 report for more information: *Obesity Drug Development, Combination Approaches Most Promising*.

2009 will bring a great deal of trial data from novel therapies. Several agents in the current obesity pipeline are anticipated to be on the market in 2011, and may become attractive to large biotech or large pharma once additional phase

III data become available later this year (Table 1). We present the latest available clinical data and

highlight next catalysts for each developmental agent in Table 2.

Table 1: Promising Developmental Obesity Agents

Drug Name	Developer	Phase	WKHAI*	Estimated U.S. Approval	2016 U.S. Revenue (million)	2016 Worldwide Revenue (million)
Lorcaserin	Arena Pharmaceuticals	III	67% (B)	March 2011	\$713	\$849
Contrave	Orexigen Therapeutics	III	74% (A)	March 2011	\$546	\$673
Qnexa	Vivus	III	72% (B)	August 2011	\$437	\$521
Liraglutide	Novo Nordisk	III	na	March 2012	\$517	\$701
Empatic	Orexigen Therapeutics	II	na	March 2013	\$243	\$299
Tesofensine	NeuroSearch	II	na	March 2013	\$267	\$329
Pramlintide/ Metreleptin	Amylin	II	na	August 2013	\$291	\$359
Cetlistat	Takeda/Alizyme	II	na	March 2014	\$12	\$121

Source: Company reports, R&D Insight, Clinical Trials Insight, and inThought estimates.

* WKHAI = Wolters Kluwer Health Approvability Index (probability of approval); na=not available.

Table 2: Comparison of Developmental Obesity Agents

	Contrave	Lorcaserin	Qnexa	Liraglutide	Empatic	Pramlintide/ metreleptin	Tesofensine	Cetilistat
Study	NB-302 (phase III)	BLOOM (phase III)	EQUATE/OB-301 (phase III)	phase II	Z-201 (phase II)	phase IIa	TIPO-1 (phase IIb)	phase IIb (EU)
Duration	4+52 weeks ⁽¹⁾	104 weeks	4+24 weeks ⁽²⁾	52 weeks	24 weeks	4+20 weeks	2+24 weeks	12 weeks
N	793	3,182	756	564	623	139	203	
Placebo-adjusted weight loss	4.2% (previous 24-week phase IIb study of 4.3%)	3.6% (previous 12-week phase II of 2.9%)	7.5% for high-dose; 6.8% for the mid-dose (previous 24-week phase II, OB-201, of 8.7%)	Highest dose: loss of 5.5-6.0 kg. Xenical: loss 1.5-2.0kg from baseline; placebo - 2kg.	ITT: 7.5%; Completers 9.1%.	12.7% absolute weight loss versus pramlintide alone (8.4%); no evidence of plateau.	9.5-10% seen in both of the two highest dose groups	Cetilistat 360 mg/day lead to reductions in bodyweight of 3.5kg (p<0.05 vs baseline).
Dropout rate	Overall discontinuation rates: 42%. Overall discontinuation rate due to AEs was 25.9% for Contrave vs 13.0% for placebo.	52-week completion rate: lorcaserin (55.4%), placebo (45.1%). Year 2 completion rates similar: 74.3%, 72.7%, and 68.9% for patients continuing on lorcaserin both years.	29%	Overall withdrawal rate across the study was ~20%.	ZB-201: The discontinuation rate was 14%.	na	21%	Cetilistat 40, 80 and 120mg tid for 12 weeks: 15.7%, 14.9% and 11.7%, respectively, versus placebo (17.5%) and orlistat (18.5%)
Positive	Modest efficacy. No observed AEs on mood, outside of those that appear manageable, including suicidal ideation. Benefit across series of secondary efficacy endpoints (waist circumference, triglycerides, HDL, hs-CRP).	Modest efficacy but potential in combination with phentermine. Most extensive safety record of the late stage candidates - data from 7,000+ patients at filing. No increase in depression or suicidal ideation.	Good efficacy. Pursuing independent anti-diabetes indication. Significantly improved blood glucose control in non-diabetic patients. Data in over 4,500 patients at filing.	Proportion of patients achieving a weight loss ≥ 10% for highest dose greater than 35%, superior to Xenical (18%).	Strong efficacy, low discontinuation rate.	Theoretical safety advantage over centrally acting agents.	Highest observed absolute weight loss.	Fewer, less severe GI AEs than Xenical.
Negative	Efficacy may be confounded by behaviour modification component.	Cardiac valvulopathy risk contributes degree of uncertainty to program. No diabetes data included in NDA. Unknown effect from combination with phentermine.	Psychiatric adversities (cognitive impairment, depression, suicidality).	Concerns about thyroid tumors persist.	One SAE reported. Patient delivered an infant who required corrective surgery for a heart abnormality.	Daily injections likely required - could limit use to the most severe obesity cases.	Cardiovascular safety will be a key priority. Potential neuropsychiatric concerns.	Modest efficacy.
Next catalyst	Additional data from remaining three phase III trials, NB-301, -303 and -304, expected at NAASO 2009.	Phase III BLOSSOM data expected Sept 2009. BLOOM-DM expected mid-2010.	Results from three phase III - EQUATE (OB-301), EQUIP(OB-302) and CONQUER(OB-303) studies are expected in 3Q09.	Phase III program initiated Nov 2008. Completion expected Jan 2010 with one-year data expected early 2011.	Trial results from second phase IIb (ZB-202) expected 3Q09.	Phase IIb dose-ranging to complete mid-2009.	Phase III program to commence mid-2009.	Phase III in Japan - data expected late 2010/2011. Phase II in U.S.

Source: Company reports, R&D Insight, Clinical Trials Insight, and inThought estimates. na=not available.

(1) Drug dosages initially titrated over a four week period, and then administered over 52 weeks of therapy at full dose.

(2) Patients underwent 4-week titration period followed by treatment at the final dose level (7.5/46 mg/day) for 24 weeks.

(3) Data from subjects who crossed over into the open-label extension are not included in the 48 week analysis.

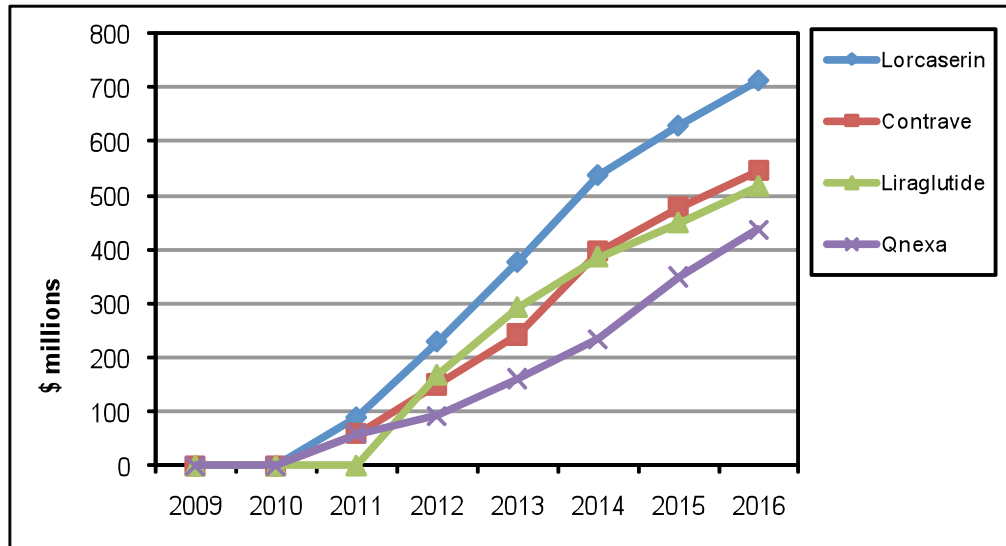
Revenue Projections for Late Stage Agents

Figures 1 and 2 show projected revenue for late stage obesity agents in development. We model revenue in U.S., Europe, and Japan. For developmental agents, the revenue forecast assumes the drug is approved. Risk adjusted

valuations can be developed by multiplying the revenue potential by the probability of approval as assessed by the WK Health Approvability Index.

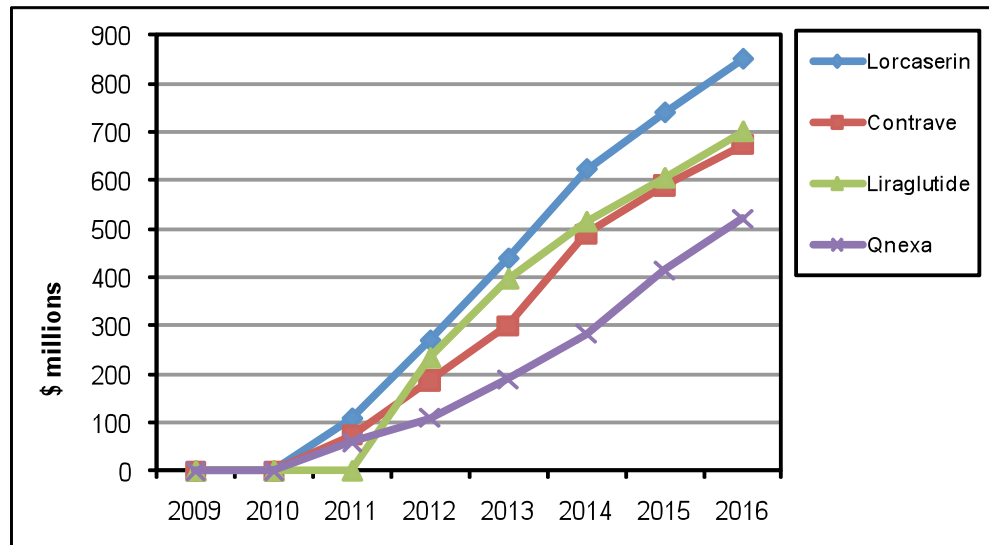
Of the late stage agents in development, *inThought* does not expect a clear winner to emerge, at least in the near term.

Figure 1: U.S. Revenue Projections for Late Stage Developmental Obesity Agents



Source: *inThought* estimates.

Figure 2: Worldwide Revenue Projections for Late Stage Developmental Obesity Agents



Source: *inThought* estimates.

Lorcaserin

We anticipate that lorcaserin will emerge as the highest revenue generator of the developmental drugs in our model, with \$849 million in worldwide sales by 2016. Our model assumes a 67% probability that lorcaserin will be on market by 2011, launching during the same timeframe as Contrave and Qnexa.

Lorcaserin is currently being tested in three phase III trials, BLOOM, BLOSSOM, and BLOSSOM-DM, in approximately 7,800 overweight and obese patients. Submission of an NDA based on data from BLOOM and BLOSSOM is expected by the end of 2009. Data from the BLOOM-DM in diabetics are not expected until mid-2010 and therefore will not be part of the NDA.

Efficacy

As a single agent, lorcaserin offers modest weight loss no better than currently marketed agents (3.6% placebo-adjusted weight loss). While this may be inferior to other late stage agents in development, the ultimate value of lorcaserin may be dependent on combination use with phentermine. Once commercialized, it is likely that lorcaserin would be paired with phentermine, creating a new "fen-phen" combination.

The lorcaserin / phentermine combo is a major wild card. Should it demonstrate weight loss on par with that seen with fen-phen in the context of good long-term safety, revenues would be significantly higher than we model.

inThought anticipates that broad acceptance of the lorcaserin / phentermine combination will take at least three years after lorcaserin's launch. Many doctors will need data in hand before feeling comfortable with prescribing lorcaserin in combination. Although our model does not anticipate widespread use of the combo, we do model increasing penetration of lorcaserin use starting in 2013.

Safety

Lorcaserin will be filed along with safety data from over 7,000 patients, the most experience of the late stage agents. Lorcaserin lacks the magnitude of neuropsychiatric concerns associated with Qnexa. However, cardiac valvulopathy remains a prime concern. While lorcaserin's theoretical risk of inducing valvulopathy is greatly reduced by its specificity for serotonin 5HT2c receptors over

5HT2b, experts stress that the risk is difficult to dismiss without clinical testing in humans in combination with phentermine.

Excess lorcaserin-associated valvulopathy has not been observed in trials to date. While the two-year echocardiographic data are reassuring, experts stress need for data from the full phase III cohort in order to be comfortable with valvulopathy risk and CNS adversity. Because Arena will pool all echocardiography data collected in BLOOM and BLOSSOM in order to compare valvulopathy rates in patients treated with lorcaserin vs. placebo, final valvulopathy analysis will not be available until late 2009.

Approval Timing and Use Considerations

While updated FDA obesity development guidelines do not require diabetes trials, treatment experience in this population is requested. The timing of the submission of diabetes safety data could potentially delay lorcaserin timelines as there is a risk that the FDA may ask for data in diabetics before approval. The company maintains that the BLOOM and BLOSSOM will provide enough safety information for adequate regulatory review of lorcaserin.

A label without data on diabetics could be inferior to competitors launching within a similar timeframe. Contrave and Qnexa will both file with data in diabetics.

If concerns about cardiac valvulopathy risk are adequately ruled out in the upcoming phase III data and the lorcaserin / phentermine combination demonstrates significant weight loss and safety, Lorcaserin could exceed our expectations and become a blockbuster obesity drug.

Contrave

Orexigen Therapeutics' Contrave is a proprietary fixed-dose combination of sustained release naltrexone and bupropion in a single trilayer tablet. Top-line results from four trials were reported this week, with an NDA with planned for the first half of 2010.

Experts with whom we have spoken remain enthusiastic regarding Contrave's potential, stressing that it is one of the few obesity drugs in development that is truly a "product of basic science" and "designed rationally rather than empirically." Because of its effects on the human

The ultimate value of lorcaserin will be dependent on combination use with phentermine.

reward system, Contrave is likely to be used to control cravings.

Efficacy

Top line data from NB-302, the first of four phase III trials, were reported January 2009. While both co-primary endpoints of change from baseline in percent of total body weight loss and proportion of subjects who lose at least 5% of their baseline body weight were met with statistical significance, the 4.2% placebo-adjusted weight loss was underwhelming. The trial incorporated an intensive behavior modification component which could have had a dilutive effect on the relative difference in absolute weight loss between the Contrave and placebo groups.

The percent of Contrave patients who lost at least 5%, 10%, or 15% of baseline body weight compared to placebo was notable. While a high percentage in both the Contrave and the placebo groups lost $\geq 5\%$ (66% for Contrave vs. 42% placebo), the observed difference was more robust for weight loss $\geq 10\%$, (42% vs. 20%), and weight loss $\geq 15\%$ (29% vs. 11%).

Data from the remaining three phase III trials, NB-301, NB-303 and NB-304, were released July 20, 2009. Unlikely NB-302, none had the intensive behavior modification component and all included smokers. All trials were double blind, placebo controlled 56 week trials with an initial 4 week titration period.

In all three studies, clinical effect of modest magnitude appeared consistent with previous trials.

In the two non-diabetic trials, placebo-adjusted weight loss on an intent to treat (ITT) basis was 4.5% (NB-310) and 5.2% (NB-303). NB-304, the study in obese diabetics, demonstrated a 3.2% placebo-adjusted weight loss, Contrave recipients showed a 0.6% reduction in HbA1c from baseline, compared to a 0.1% reduction for placebo (ITT, $p < 0.001$).

Although details of the three trials are sparse, Contrave appears to have demonstrated improvement in other markers of cardiometabolic risk including waist circumference, fasting HDL, LDL, triglycerides, insulin, and blood glucose. Contrave also showed improvement in patient-reported outcomes, namely improved ability to reduce cravings.

inThought believes that Contrave's small therapeutic effect magnitude will more likely affect usage than approval. Dropout accounting formats that tend to inflate apparent weight loss figures do no more than reinforce our effect magnitude conclusion.

Based on the top-line results of the three trials, we are increasing the probability of approval for Contrave in the Wolters Kluwer Health Approvability Index (WKHAI) from 73%(A) to 74%(A).

Safety

The safety profile of Contrave appears consistent with that of its individual components. Importantly, neuropsychiatric adversity appears limited and manageable to date.

This week's data offers little reassurance on the safety of Contrave. While the company stated patients generally tolerated Contrave well, investigators attributed seven serious adverse events as possibly related to drug treatment, including one case of gallbladder inflammation and two seizures. These events require further investigation. Favorably, Contrave was not associated with increases in symptoms of depression or suicidal ideation.

inThought will be attending the 27th Annual Scientific Meeting of The Obesity Society in Washington D.C., October 24 through October 28, 2009. We expect further details on Contrave's longer term safety to be disclosed.

Our model projects that there will be a high degree of switching between lorcaserin and Contrave in the first two years post launch.

Reimbursement

Presentations at the American Diabetes Association's (ADA) 69th Scientific Sessions shed light on Contrave's ability to improve predictive markers for heart disease, such as waist circumference, triglycerides, HDL-cholesterol, and hsCRP. Positive data from NB-304, a 56-week study designed to assess the safety and efficacy of Contrave in obese diabetics, could support reimbursement, which would increase adoption and use significantly.

Our model projects a high degree of switching between lorcaserin and Contrave in the first two years post launch. Should Contrave demonstrate a more significant weight loss in the upcoming phase III trials with observed neuropsychiatric concerns limited to highly manageable ones, it could capture

a greater share of the market than our current model predicts.

Qnexa

Vivus' Qnexa is a combination of low-dose phentermine and topiramate. Topiramate, marketed as Topamax for the treatment of seizure disorders and migraine, had been developed as a monotherapy treatment for obesity, but this clinical program was discontinued due to formulation and tolerability concerns.

Qnexa is currently in three phase III studies for obesity and a phase II study for diabetes. A phase II study showed improved cardiovascular outcomes, suggesting an ability to address co-morbidities including diabetes and cardiovascular risks.

Efficacy

Qnexa has demonstrated 8.6% placebo adjusted weight loss at 24 weeks. It has also shown a positive impact on secondary measures, including blood pressure and cholesterol.

Safety

Because of its efficacy, Qnexa may be appealing to the public, initially. However, concerns about psychiatric adverse effects, namely cognitive impairment and, to a lesser degree, depression and suicidality, could significantly limit use. *inThought* anticipates safety will be the most significant barrier to approval and adoption.

While wariness over Qnexa's tolerability remains high, some experts have suggested that the adversity profiles of phentermine and topiramate offset one another. While phentermine promotes anxiety and nervousness, topiramate causes sluggishness and drowsiness. At higher doses, topiramate also causes cognitive dulling, one reason for Johnson & Johnson's decision to discontinue development of the monotherapy for obesity. *inThought* expert consultants suggest that phentermine is able to temper cognitive slowing induced by topiramate, while topiramate decelerates the rate of dopamine increase to reduce abuse potential.

Reimbursement

Qnexa is pursuing an independent anti-diabetes indication. OB-202, a phase II trial of Qnexa in

obese patients with type 2 diabetes, and DM-230, the six-month extension study, have both reported positive data. 58 week data from DM-231, the second extension study evaluating long-term glycemic control, is expected to be completed by the end of 2009.

Additional analysis of the EQUATE (OB-301) study presented at ADA showed significantly improved blood glucose control in non-diabetic patients receiving Qnexa compared with those receiving placebo. Should Qnexa continue to demonstrate a benefit in the diabetic population, it would be more likely to gain favorable reimbursement status, leading to a greater and more rapid degree of uptake.

Qnexa may also have a reasonable price. Off label, the combination of phentermine and topiramate costs between \$400-\$500 per month. *inThought* estimates that Qnexa will cost less than its individual components, avoiding an issue that has brought down other combination drug products.

Our model assumes a 72% probability that Qnexa will launch in 2011, soon after lorcaserin and Contrave. We forecast worldwide Qnexa sales of \$521 million by 2016 (Tables 1 and 2, Figure 1 and 2). The outlook for Qnexa will depend on its evolving adversity profile.

Liraglutide

Novo Nordisk's liraglutide is a long-acting, stable analogue of the natural hormone glucagon-like peptide-1 (glp-1), currently in phase III development for obesity. One-year data from the ELIOT-Maintain study are expected in early 2011. Liraglutide is under regulatory review for Type 2 diabetes. Please see *inThought's* June 15 report, *DPP4s and glp-1s for Diabetes: Throwdown at the ADA Meeting in New Orleans*, for analysis of liraglutide for diabetes.

Efficacy

Liraglutide has demonstrated good weight loss and a beneficial effect on systolic blood pressure. In a phase II study versus orlistat, the mean reduction of body weight was between 4.8kg and 7.2kg across the four liraglutide dosages. Moreover, more than 75% of the patients treated at highest dose experienced weight loss greater than 5%, and over 25% experienced weight loss greater than 10% relative to their body weight at randomization.

Liraglutide's profile appears manageable, but the requirement for daily subcutaneous injection may hamper adoption.

Safety

In diabetes trials, liraglutide has drawn concern over its association with papillary thyroid cancer and C-cell tumors. In their commentary of the LEAD-6 data published in *The Lancet*, De Block and Van Gaal cited a rate of 1.8% per 1000 patient-years for liraglutide-associated papillary thyroid cancer as compared to a rate of 0.6% for Amylin and Lilly's Byetta (exenatide). We expect this safety issue to more so delay approval than to limit use of the agent. For obesity, liraglutide's profile appears manageable, but the requirement for daily subcutaneous injection may significantly hamper adoption.

Reimbursement

inThought anticipates that liraglutide will launch in diabetes in September 2010. This makes it the most likely of the late stage obesity agents to garner favorable reimbursement at launch.

Our model anticipates liraglutide will launch for obesity in 2012. It will compete in obesity with other glp-1 formulations, even if other drugs such as exenatide once weekly are not formally approved for obesity. If approved for obesity, we anticipate worldwide liraglutide sales of \$701 million in 2016

for use in non-diabetic obese patients. Please see our June 15 report for sales estimates for this agent in diabetes.

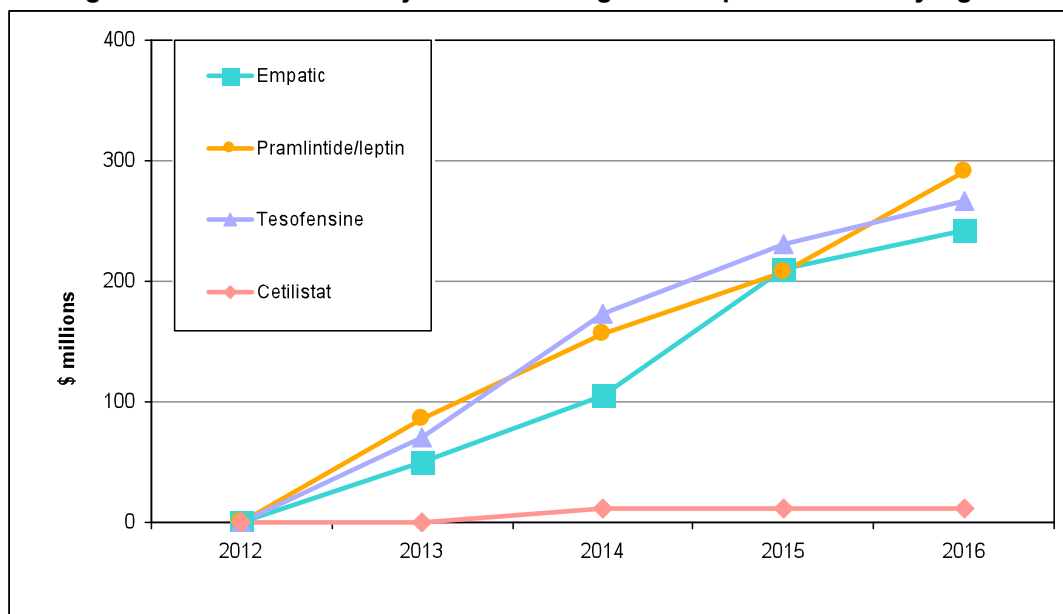
Revenue Projections for Earlier Stage Compounds

Our model forecasts sales of several promising obesity agents that could launch in 2013-2016 (Figures 3 and 4.) These compounds are generating interesting data and could become important treatment options.

Empatic

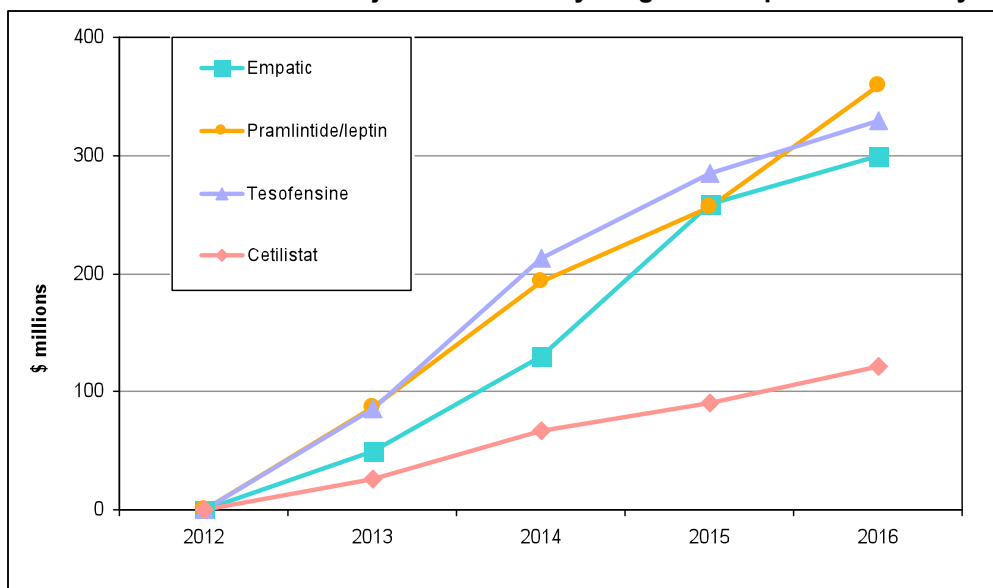
Orexigen is also developing Empatic, a fixed dose combination of a proprietary formulation of zonisamide sustained release (SR) and bupropion SR. Bupropion was approved for marketing in the United States in 1985 for depression, and in 1997 for smoking cessation. Zonisamide SR is a long acting version of the active anticonvulsant component of Eisai's Zonegran, long used for both seizure disorders and movement disorders such as Parkinson's disease. Duke University Medical Centre and Élan are developing zonisamide for obesity as well.

Figure 3: U.S. Revenue Projections for Stage Developmental Obesity Agents



Source: Company reports, R&D Insight, Clinical Trials Insight, and inThought estimates.

Figure 4: Worldwide Revenue Projections for Early Stage Developmental Obesity Agents



Source: Company reports, R&D Insight, Clinical Trials Insight, and inThought estimates.

In a phase IIb study (ZB-201), Empatic demonstrated promising 24-week data, with a placebo-adjusted weight loss in the intent-to-treat (ITT) group of up to 7.5%, and in completers of up to 9.1%. Top line data from a second phase IIb study (ZB-202), initiated in July 2008, are expected in 3Q09.

Our model assumes Empatic will be on the market in 2013. We forecast sales of \$299 million by 2016.

Tesofensine

Neurosearch's tesofensine is a triple monoamine reuptake inhibitor that blocks serotonin, dopamine, and norepinephrine, affecting weight loss both through the suppression of appetite and through increased energy expenditures.

The decision to develop the compound for obesity was based on the observations of a significant weight loss in phase II trials in patients with Alzheimer's and Parkinson's disease. Tesofensine has been discontinued in these indications, but is currently in phase II development for obesity.

Tesofensine has demonstrated a 10.6% placebo-adjusted weight loss, the best 'absolute' efficacy seen in phase II obesity trials for the compounds in this report. However, concerns about elevated blood pressure and increased heart rate remain. Cardiovascular safety will be a key issue in phase III studies. The risk of neuropsychiatric adverse events also cannot be ignored.

Although tesofensine works similarly to other agents designated as having mild abuse potential, results from a recent abuse liability study (TIPO-5) released May 2009 suggest minimal abuse potential.

Trial design for the phase III program has not been disclosed, although the program is expected to begin shortly. It is unclear whether a trial in diabetics will be conducted.

Our model assumes launch in 2013. If approved, we project worldwide sales of \$329 million by 2016.

Pramlintide / Metreleptin

Amylin's combination of pramlintide and metreleptin is currently in phase II. Hormonal approaches such as this may have a potential safety advantage over more classically centrally acting agents. Concerns over CNS side effects, such as depression, anxiety and cognitive dulling, may prove lower with this agent, although it must be remembered the significant role of hormone-associated neurohumoral molecular axes in craving, satiety, and energy metabolism.

Pramlintide is Amylin's approved diabetes medicine Symlin. Metreleptin is a form of a signaling molecule synthesized in white fat that is involved in satiety. The combination has demonstrated strong efficacy to date. In the phase IIa program. Patients treated with the combination lost an average of

12.7% body weight, versus 8.4% with pramlintide alone, an average of 25 lbs versus 17 lbs.

Importantly, the weight loss with the combination therapy continued throughout the study, with no evidence of plateau. However, the trial reported results for only those patients that responded to pramlintide alone in a four week lead-in period; 22% of patients did not meet this requirement. Therefore, weight loss on an intent-to-treat basis would be considerably lower, making direct comparisons with other agents difficult. We estimate that only 10-20% of obese patients will be good candidates for this injectable treatment.

Data from a second phase IIb study, announced in early July, demonstrated results consistent with previous trials. At 28 weeks, evaluable patients with a starting BMI less than 35 kg/m², and treated with the highest pramlintide/metreleptin doses, experienced significantly more weight loss on average (11%; 22 pounds, p<0.01) than those receiving placebo (1.8%; 4 pounds) or either agent alone (approximately 5%; 10 pounds). Patients may continue on the therapy for a total of 52 weeks as part of an extension. The combination was well tolerated with no cardiovascular or neuropsychiatric safety signals observed.

Our model assumes the combination will be on the market in 2013 if phase III trials are successful. We forecast sales of \$359 million by 2016. There is considerable upside to our estimates should the combination gain favorable reimbursement.

Cetilistat

Cetilistat is a lipase inhibitor, similar in action to Roche's Xenical but demonstrating fewer and less severe gastrointestinal adversities. As Cetilistat acts peripherally, CNS issues should be minimal.

Cetilistat has completed phase I and II development programs in the U.S. and Europe. Phase III in the U.S. should begin shortly, pending the conclusion of a commercial agreement. A Phase III trial was initiated December 2008 in Japan, with data expected late 2010 or early 2011. Our model

assumes a 2013 launch in Japan and a 2014 launch in the U.S. and Europe. *inThought* models a modest revenue potential for Cetilistat in comparison to other agents in development.

Conclusions

1. None of obesity agents in late stage clinical development is likely to be an optimal therapeutic solution in terms of effect magnitude, long-term safety, and reimbursement.
2. We anticipate that Arena Pharmaceutical's lorcaserin will emerge as the highest revenue generator of the developmental drugs in our model, with \$849 million in worldwide sales by 2016. Revenue could exceed our estimates if lorcaserin can demonstrate significant efficacy and safety when paired with phentermine.
3. The obesity market is large enough for several drugs to be successful. Success of one agent in this model would not significantly lower the revenue potential of any other agent.

inThought Revenue Forecasts

inThought revenue forecasts employ a proprietary model developed to assess both currently approved and developmental drugs as well as medical devices. Models are developed for a given therapeutic area using a "top-down" approach based on the addressable patient population, allowing for detailed assessment of a compound's real or potential competitive landscapes. Epidemiological considerations include estimates of disease incidence, prevalence, growth rates, and death rates. Models are developed separately for the U.S., Europe, and Japan. *inThought* drug revenue models look seven years into the future and three years into the past; device revenue models project three to five years forward and three years back. For developmental agents, the revenue forecast assumes the drug or device is approved. Risk adjusted valuations can be developed by multiplying the revenue potential, if approved, by the probability of approval as assessed by the WK Pharma Solutions Approvability Index.

Copyright © 2009 Wolters Kluwer Pharma Solutions. All rights reserved

Wolters Kluwer Pharma Solutions Research Reports provide unbiased analysis and ideas based on the needs and direction of clients. The material herein, while not guaranteed, is based upon information believed to be reliable and accurate. We do not: (a) give investment advice; or (b) advocate the sale or purchase of any security or investment. The material herein is not to be deemed an offer or solicitation on our part with respect to the sale or purchase of any securities. Any copying, redistribution or republication of the analyses provided by Wolters Kluwer Pharma Solutions, or the content thereof, for commercial gain is strictly prohibited.