Biotechnology

Obesity: Where are the deals?

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Obesity: Where are the deals?

Pivotal data have been now reported for all three of biotech's most advanced oral anti-obesity projects, something we had expected to serve as the trigger for licensing activity with big pharma. A licensing deal is a key event for each of the companies involved, but despite data now being out no such alliance has yet materialised. In this report we investigate the prospects for licensing and outline some alternative strategies being pursued while deal negotiation continues.

Three drugs about to be filed

The three most advanced oral anti-obesity projects have now completed Phase III trials, with Vivus's Qnexa clearly ahead in terms of efficacy and Arena's lorcaserin generally trailing in third place. Both of these are due to be filed by the end of 2009, while an NDA for Orexigen's Contrave is due in the first half of 2010.

Pharma yet to be convinced?

The product with the strongest efficacy/side-effect profile should command the best economic terms in a licensing deal. However, the absence of any alliances to date suggests that big pharma may still be undecided. The stage is set for a showdown as originators try to persuade pharma companies that, despite its history of setbacks, obesity is a therapy area that is still worth pursuing.

Economic potential

It is possible that big pharma is awaiting the FDA's response to upcoming filings. Vivus, Orexigen and Arena have all improved their cash runways through fund-raisings, which should improve their position in negotiations. Of the three products, lorcaserin has an advantage in terms of being the only new chemical entity (NCE), but given its relatively weaker efficacy there may be unrealistically high expectations of deal value.

A big enough market for several drugs

The obesity market should be big enough for several products to be successful. Orexigen is planning an in-house launch to specialist prescribers, and it could be that all three projects end up being launched initially by their originators, while prospective licensees wait until in-market trends confirm their potential.

November 2009

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COMPANIES FEATURED IN THIS REPORT

Arena Pharmaceuticals

NeuroSearch

Orexigen Therapeutics

Vivus

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Investment summary: Pivotal data now in

Three key players in the near term

Pivotal study data have now been reported for the three most advanced oral anti-obesity projects, Vivus's Qnexa (phentermine plus topiramate), Orexigen's Contrave (bupropion plus naltrexone) and Arena's lorcaserin. All three need big pharma licensing partners to be marketed to primary physicians and thus achieve their full potential, but despite the safety and efficacy data shown in Phase III none has yet been taken up in a licensing deal.

We reiterate our view of obesity as a potential multi-billion dollar pharmaceutical market, and expect a successful drug (one able to produce 5-10% placebo-adjusted weight loss over a year period, with a relatively clean side-effect profile) to seize significant market share. In a market this size there is room for more than one drug.

In terms of efficacy as measured by the ITT-LOCF analysis, Qnexa is the clear winner with up to 9.4% placebo-adjusted weight loss over 56 weeks, easily meeting both FDA benchmarks for approvability of a weight loss drug. Contrave's efficacy is less strong at 4.8%, but still has potential in our view, while lorcaserin's 3.6% figure risks making it only marginal clinically relevant. Qnexa and lorcaserin are due to be filed with the US FDA by the end of 2009, while Orexigen expects the Contrave filing to occur in the first half of 2010.

Is big pharma ready?

As no major company has yet decided to take up licensing rights to any of these projects, there are still many unknowns. It is not clear, for instance, how big pharma views patent coverage on fixed dose combinations of off-patent drugs, and whether it is ready to buy into such reformulations (historically it has proved reluctant to do so). Indeed, there has been evidence of some pharma companies giving up on the obesity sector altogether, in light of its disappointing history.

Nevertheless, Vivus, Arena and Orexigen have each raised money, and this should strengthen their bargaining positions with potential licensees. In addition, Orexigen is planning to launch Contrave unpartnered through a specialist sales force while simultaneously negotiating a licensing deal to target primary care prescribers. Vivus and Arena may also be considering a similar strategy.

Orexigen also has a follow-on project, Empatic (yet to enter Phase III), and this report additionally considers a fourth company, NeuroSearch, whose tesofensine is a highly efficacious potential drug although also at an earlier stage of development.

Exhibit 1: Companies profiled in this report

Note: *As of 4 November 2009; **estimated.

Company	Country of listing	Share price ($)*	Market cap ($)*	2008 revenues ($)	2009 YE net cash ($)**	Obesity project(s)
Arena Pharmaceuticals	US	3.52	326m	9.8m	32.5m	Lorcaserin
NeuroSearch	Denmark	19.10	312m	13.3m	136.4m	Tesofensine
Orexigen Therapeutics	US	7.02	326m	0.1m	92.9m	Bupropion + naltrexone (Contrave)/ bupropion + zonisamide (Empatic)
Vivus	US	8.05	553m	102.2m	192.9m	Phentermine + topiramate

Source: Edison Investment Research

FDA guidelines

FDA draft guidance on the development of weight loss drugs, published in February 2007, states that one of two efficacy benchmarks (but not necessarily both; Exhibit 2) must be met.

Exhibit 2: Summary of FDA recommendations for weight loss drugs

EITHER benchmark 1	OR benchmark 2
One year of treatment results in a difference in mean weight loss between active and placebo groups of ≥5%, with statistical significance.	One year of treatment results in at least 35% of active recipients losing ≥5% of baseline body weight, **and** this is ***approximately double*** the proportion in the placebo group, with statistical significance.

Source: FDA guidance for industry, developing products for weight management, February 2007

In pivotal trials only Vivus's Qnexa clearly met both benchmarks, while Orexigen's Contrave missed the first but appears to have met the second. Meanwhile, whether Arena's lorcaserin is approvable under these guidelines depends on the semantics of 'approximately double' (Exhibit 3).

Exhibit 3: Summary of pivotal trial results at highest dose tested (ITT population)

Note: *Meets tougher benchmark of patients losing ≥10% and ≥15% of body weight, both more that double the placebo effect.

Product	Study	Placebo-adjusted weight loss	FDA benchmark 1 met?	% losing ≥5% of baseline weight vs placebo	FDA benchmark 2 met?
Qnexa	EQUATE	7.5%	Yes	66% vs 15%	Yes
Qnexa	EQUIP	9.4%	Yes	67% vs 17%	Yes
Qnexa	CONQUER	8.6%	Yes	70% vs 21%	Yes
Contrave	NB-301	4.8%	No	48.0% vs 16.4%	Yes
Contrave	NB-302	4.2%	No	66.4% vs 42.5%*	No*
Contrave	NB-303	5.2%	Yes	56.3% vs 17.1%	Yes
Contrave	NB-304	3.2%	No	44.5% vs 18.9%	Yes
Lorcaserin	BLOOM	3.6%	No	47.5% vs 20.3%	Yes
Lorcaserin	BLOSSOM	3.1%	No	47.2% vs 25.0%	Debatable

Source: Edison Investment Research

Safety: A major consideration

Historically, development of anti-obesity agents has been beset with safety problems, and as such it will be vital for all developers of potential weight-loss products to show a clean profile. However, this is a difficult issue, and historically even very large pivotal programmes (such as that for Sanofi-Aventis's now withdrawn anti-obesity drug rimonabant) have failed to highlight safety issues that become evident in a real-world setting, when many thousands more patient exposures take place.

None of the three projects' pivotal programmes raised serious adverse event signals, although all had a relatively high all-cause dropout rate (this was highest in placebo groups, owing to lack of efficacy). The highest dropout rate was seen with Contrave, although dropouts tended to occur early (Exhibit 4). Importantly for Arena, extensive echocardiographic monitoring throughout the pivotal programme showed no valvulopathy risk with lorcaserin.

The Phase II projects appear to have more side-effect issues. Empatic contains zonisamide at its highest approved dose (possible CNS-related adverse events) and will have a strict pregnancy warning owing to zonisamide's teratogenicity. Tesofensine has shown statistically relevant elevation in blood pressure and heart rate at the 1mg dose, and this dose is not being taken into Phase III.

Qnexa is the only agent that has shown significant blood pressure benefits in the population studied in Phase III. Lorcaserin has shown a numerical, but statistically insignificant, improvement.

Exhibit 4: Summary of side-effect profiles

Note: *24-week study.

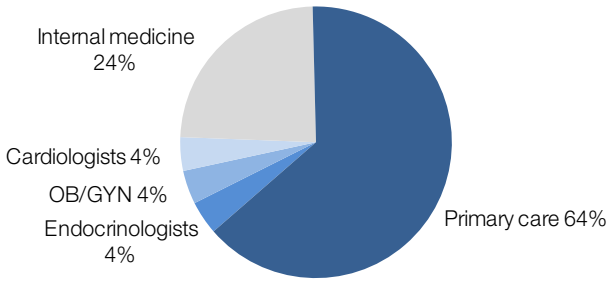
Product	Patients discontinuing in trial	Common adverse events (AEs)	Patients discontinuing owing to AEs	Other notes
Qnexa	31-43%	Dry mouth, tingling, altered taste, constipation	12-18%	Non-significant depression. No suicidal behaviour. No signal for QT prolongation, and no significant change in cognitive function.
Contrave	46-51%	Nausea, headache, constipation, vomiting	20-29%	Seven SAEs attributed to Contrave. One death on (but not attributed to) Contrave. Seizure rate lower than on Wellbutrin label. Non-significant cardiovascular SAEs.
Lorcaserin	41-45%	Headache, nausea, dizziness	6-7%	One death on placebo. Infrequent depression, anxiety and suicidal ideation. Non-significant neuropsychiatric SAEs. Echo data showed no signal for increased valvulopathy risk.
Tesofensine	22%*	Dry mouth, nausea, constipation, insomnia	not available	Significant blood pressure and heart rate increases with 1mg dose (no longer being pursued). Additional cardiovascular safety trial has been carried out.
Empatic	40-42%*	Headache, dry mouth, insomnia, constipation	23-25%	Non-significant neuropsychiatric differences. Full-strength zonisamide (label highlights CNS effects). Teratogenicity will necessitate strict pregnancy warning.

Source: Edison Investment Research

The need for a big pharma licensing partner

Exhibit 5 illustrates the current way in which drug treatments for obese people are prescribed in the US, with a clear majority of prescriptions being written by primary care physicians. The second most common prescribers are internal medicine physicians; internal medicine is a speciality concerned with the diagnosis, management and non-surgical treatment of unusual or serious diseases, and is a discipline particularly developed in the US (where these specialists are known as 'internists'). Much of the work of an internist tends to be hospital-based.

Exhibit 5: Physicians prescribing anti-obesity agents in the US



Source: Wolters Kluwer Health

Because of the nature of these leading prescribers it is widely accepted that a large, primary care-focused sales force is needed for an obesity drug to reach its peak potential sales; in 2008 it was estimated that there were around 40,000 internists in the US, so even a sales force targeting just these prescribers would be out of the reach of a biotech company on its own.

Orexigen, the only one of the four companies profiled that is planning an initial in-house launch, intends to set up a sales force numbering 50-75 reps, which it believes would be adequate to target specialist prescribers such as endocrinologists. However, this effort would be unlikely to generate significant sales relative to Contrave's blockbuster potential.

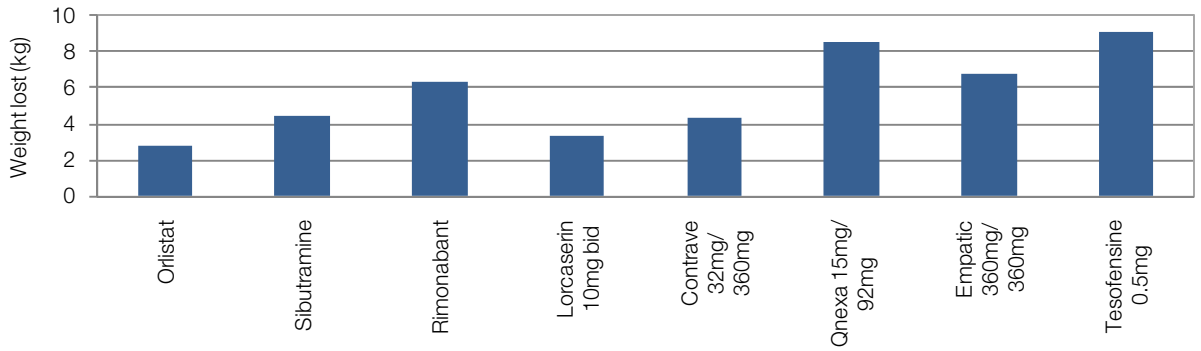
Historical comparison

Despite the amounts spent historically on oral anti-obesity agents, by far the most prescriptions (80%) are currently being written for phentermine, a drug approved for short-term use in 1959. Sibutramine (Abbott's Meridia) and orlistat (Roche's Xenical and OTC as Alli) are approved for long-term use, but have failed to make major inroads, with prescription shares of just 5% and 3% respectively. This is most likely due to side-effect problems and a general lack of efficacy.

Exhibit 6 shows the potential efficacy of projects currently under late-stage development relative to orlistat, sibutramine and rimonabant (withdrawn in 2008 owing to psychiatric adverse events).

Exhibit 6: Placebo-adjusted weight loss at one-year

Note: Data for Empatic and tesofensine are from 24-week studies.



Source: Edison Investment Research

Exhibit 7 summarises recent and potential near-term news flow triggers.

Exhibit 7: 2009/10 competitive timeline for anti-obesity projects

Date	Product	Company	Event
8 January 2009	Contrave	Orexigen	Data reported from first Phase III trial (NB-302); statistically significant but clinically ambiguous.
30 March 2009	Lorcaserin	Arena	3,182-patient Phase III BLOOM study shows 3.6% placebo-adjusted weight loss over one year. $100m Deerfield loan (17 June) and $52m fund-raising (8 July).
June 2009	Empatic	Orexigen	Completion of Phase II ZB-202 study.
20 July 2009	Contrave	Orexigen	Statistically significant data reported from Phase III NB-301, NB-303 and NB-304 studies. $86m fund-raising announced 23 July.
9 September 2009	Qnexa	Vivus	Highly positive data reported from Phase III EQUIP and CONQUER studies. $109m fund-raising announced 16 September.
18 September 2009	Lorcaserin	Arena	Data from 4,008-patient BLOSSOM study show 3.1% placebo-adjusted weight loss over a year at the high dose.
30 September 2009	Empatic	Orexigen	Data from Phase II ZN-202 study.
H209	Qnexa	Vivus	US NDA filing.
H209	Lorcaserin	Arena	US NDA filing.
H110	Tesofensine	NeuroSearch	Start of first Phase III study (funded in house).
H110	Contrave	Orexigen	US NDA filing.

Source: Edison Investment Research

Is pharma interested?

We have reviewed the landscape of orally available industry projects for obesity currently at Phase II and above, summarised in Exhibit 8, and this indicates the high attrition that has taken place since Edison's first sector report into obesity, published in May 2008. Since the withdrawal of Sanofi-Aventis's rimonabant in 2008 every other CB1 antagonist has been discontinued (including projects by Merck & Co, Pfizer and Bristol-Myers Squibb).

Among other discontinuations are Pfizer's CP-866087 (completed a 94-patient Phase II trial) and CE-3266597 (CCK receptor antagonist, now in development only for type 2 diabetes), and Merck & Co's neuropeptide Y5 antagonist MK0557 (failed in Phase II, now in development for schizophrenia). A number of other projects have completed Phase II trials but data have not been published and their active development appears to be on hold. Accordingly, it is not entirely clear whether the pharmaceutical industry still believes in obesity as a standalone therapy indication, and whether it is willing to re-enter this historically disappointing area of research.

Exhibit 8: Selected anti-obesity drugs in development at Phase II and above

Drug name	Company	Status	Mechanism of action	Notes
Qnexa (phentermine + topiramate)	Vivus	Phase III	Topiramate = GABA and other agonist properties	Pivotal programme (three studies, 4,500 pts) completed. Non-pivotal extension trial and diabetes studies underway. Filing due end 2009.
Lorcaserin	Arena	Phase III	Selective $5HT_{2C}$ receptor agonist	Pivotal programme (two studies in 7,000 pts) complete. Non-pivotal trial in obese diabetics underway. Filing due end 2009.
Contrave (naltrexone + bupropion)	Orexigen	Phase III	Bupropion = dopamine and noradrenaline reuptake inhibitor; naltrexone = opioid antagonist.	Pivotal programme (four Phase III studies in 4,500 pts) complete. Filing due in H110.
Victoza (liraglutide)	Novo Nordisk	Phase III	GLP-1 analogue.	420-pt Phase III trial (results: August 2010). Injectable. Approved (EU) for Type 2 diabetes.
Tesofensine	NeuroSearch	Phase IIb	Dopamine/noradrenalin/ 5HT reuptake inhibitor	Phase IIb study in 203 obese pts showed statistical significance after 24 weeks. Phase III trial to start in H110.
Empatic (zonisamide + bupropion)	Orexigen	Phase IIb	Bupropion = dopamine and noradrenaline reuptake inhibitor; zonisamide = GABA agonist	Positive data reported in Phase IIb study in over 600 patients. End of Phase II meeting with FDA due shortly.
R256918	Johnson & Johnson	Phase II	Gut-selective MTP inhibitor	12-week study in 320 pts testing 5mg, 10mg and 15mg doses completed in June 2008. No data.
SCH-497079	Merck & Co	Phase II	Histamine H3 receptor antagonist	12-week study in 300 pts completed in January 2009. No data.
Cetilistat	Norgine/ Takeda	Phase II	Lipase inhibitor	Takeda is conducting a Phase III trial in Japan.
Canagliflozin (JNJ28431754)	Johnson & Johnson	Phase II	Sodium/glucose cotransporter 2 inhibitor	12-week study in 376 pts testing 50mg, 100mg and 300mg doses completed in Sep 2008. No data.
Pramlintide/ metreleptin	Amylin/Takeda	Phase II	Amylin analogue in combination with metreleptin.	400-pt Phase II study completed, results pending. Injectable.
Davalintide	Amylin/Takeda	Phase II	Amylinomimetic	240-pt Phase II results completed, results pending. Injectable.
THR-4109	Theracos	Phase II	venlafaxine = norepinephrine/5HT uptake inhibitor; rivastigmine = cholinesterase inhibitor	24-week, 220-pt study completed. No data.
N-5984	Nisshin Kyorin	Phase II	Selective β3 antagonist	May have less cardiac effect than previous compounds.
Velneperit	Shionogi	Phase IIb	Neuropeptide Y5 receptor antagonist	12-week Phase IIa study gave mixed results. Possible candidate for combination.
Histalean (betahistine)	Obecure	Phase II	Histamine receptor activation	Phase II study in 281 pts failed. Phase II trial in 180 pre-menopausal women complete. No data.

Source: Edison Investment Research

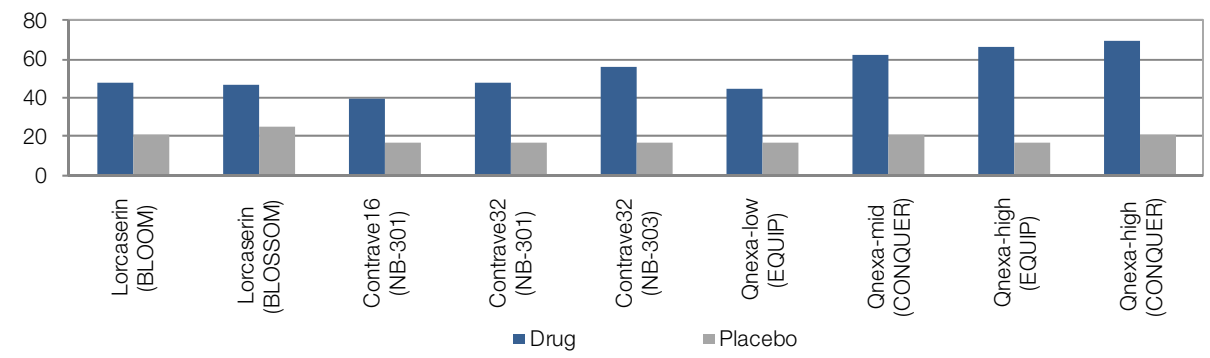
Comparison of Phase III clinical trial data

The most scientifically robust analysis (and hence the regulatory examination) of trial data will focus on placebo-adjusted weight loss on an ITT-LOCF basis (intention to treat, last observation carried forward). The ITT dataset includes all trial participants who received the study drug for whom there is one post baseline data point. If a patient drops out of the study, eg after experiencing undesirable side-effects, their last observation is carried forward to completion.

The analysis of data for completers and the categorical data, that is the proportion of patients who achieve a given level of weight loss, is likely to be crucially important for differentiation of the products in the market. Comparison of these data still show Qnexa as providing the best efficacy, but the differentiation between Contrave and lorcaserin becomes less clear. It is also important to note that cross-study comparisons should be treated with caution, because of protocol differences in the studies (including differing patient groups etc). Data are shown in Exhibits 9 to 13.

Exhibit 9: Categorical data: % patients achieving ≥ 5% weight loss at one year (ITT-LOCF)

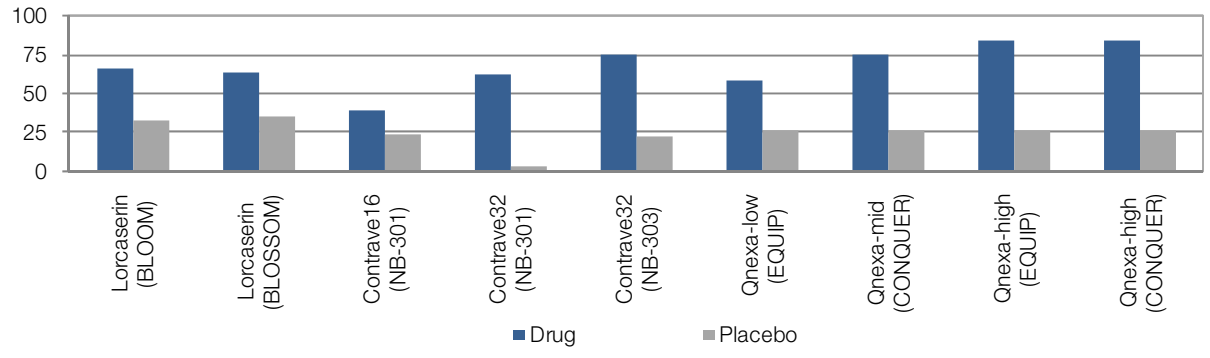
Note: Lorcaserin (52 weeks); Qnexa (56 weeks).



Source: Edison Investment Research

Exhibit 10: Percentage of patients achieving ≥ 5% weight loss at one year, completer data

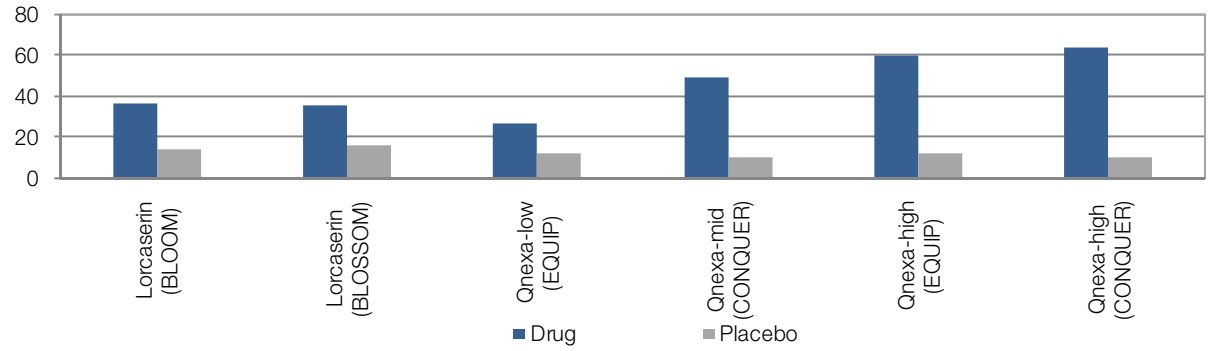
Note: Lorcaserin (52 weeks); Qnexa (56 weeks); Lorcaserin per protocol data; Qnexa and Contrave completer data.



Source: Edison Investment Research

Exhibit 11: Percentage of patients achieving ≥ 10% weight loss at one year, completer data

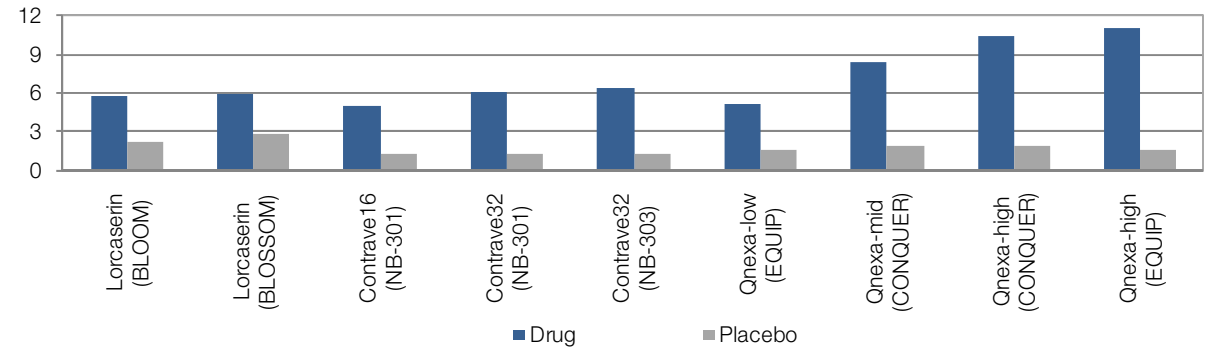
Note: Lorcaserin (52 weeks); Qnexa (56 weeks); Lorcaserin data per protocol; Qnexa data completers. Corresponding Contrave data not yet disclosed.



Source: Edison Investment Research

Exhibit 12: Mean % weight loss at one year (ITT-LOCF)

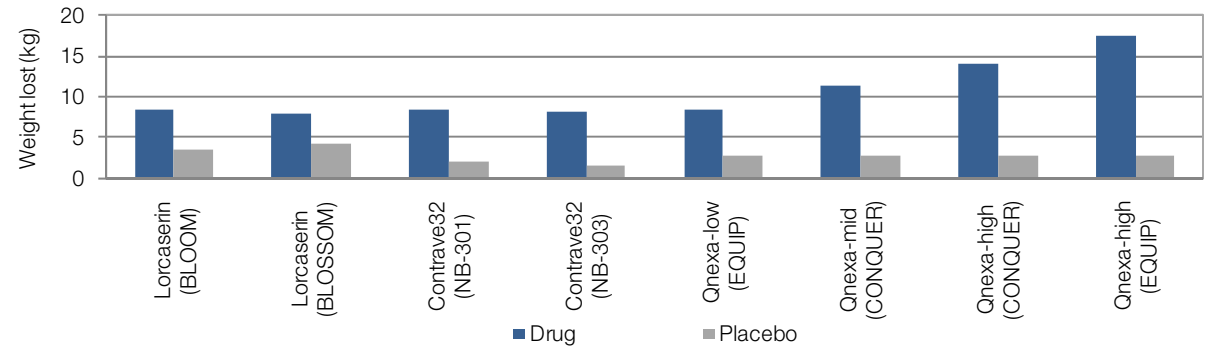
Note: Lorcaserin (52 weeks) or Contrave/Qnexa (56 weeks)



Source: Edison Investment Research

Exhibit 13: Actual weight loss (kg) (completers/per protocol)

Note: Lorcaserin (52 weeks) or Contrave/Qnexa (56 weeks)



Source: Edison Investment Research

Company profiles

Arena Pharmaceuticals

Year end	Revenue ($m)	PBT* (£m)	EPS* ($)	DPS ($)	P/E (x)	Yield (%)
12/07	19.3	(132.8)	(2.2)	0.0	N/A	N/A
12/08	9.8	(226.8)	(3.1)	0.0	N/A	N/A
12/09e	10.9	(143.0)	(1.7)	0.0	N/A	N/A
12/10e	13.3	(96.8)	(1.1)	0.0	N/A	N/A

Note: *PBT and EPS exclude one-off and non-cash items.

Investment summary: Safety first

Lorcaserin, the only new molecular entity among the industry's three obesity projects that have completed pivotal trials, has shown a relatively clean safety profile, with no cardiovascular side-effects in large scale clinical studies. However, the efficacy has disappointed and, in our view, the project could be marginal as a single agent. In addition, management appears to be setting extremely high expectations on the value of a licensing deal, and has ruled out use in combination with phentermine, which we believe would be a way of boosting efficacy.

Valvulopathy all clear

A key question mark over lorcaserin has been the risk that it might be associated with valvulopathy, a cardiovascular side-effect that had led to the withdrawal in 1997 of two anti-obesity products. However, safety reviews and echocardiography monitoring throughout its pivotal studies showed no statistical association between lorcaserin and risk of valvulopathy.

Efficacy just 3.1-3.6% over one year

In a pivotal programme of around 7,200 patients, lorcaserin has demonstrated placebo-adjusted weight loss of just 3.1-3.6% of baseline body weight after one year, the lowest of the three agents that have completed Phase III studies. This is barely adequate in our view, and risks making locaserin marginal as a single agent.

A semantic subtlety

Although lorcaserin missed the FDA's 5% placebo-adjusted weight loss criterion, Arena argues it has met a second benchmark – that at least 35% of patients on active drug lose ≥5% of baseline weight, which should be approximately double the placebo rate. We argue that this depends on the semantics of 'approximately double'.

Much at stake

Arena's management has publicly stated that it expects to sign a licensing deal whose value would be several times the $500m to $1bn that it has sunk into developing lorcaserin so far. In our view this seems highly optimistic, and suggests that the company might turn down more realistic proposals. Furthermore, loan liabilities and a manufacturing agreement represent significant risks to the business.

Price	$3.52*
Market cap	$326m

** Priced as at 4 November 2009.*

Share price graph

Share details

Code	ARNA
Listing	NASDAQ
Shares in issue	92.6m

Price

52-week	High	Low
	$7.42	$2.26

Business

Arena is a NASDAQ-listed biotechnology company whose lead project, lorcaserin, has completed Phase III trials for obesity. R&D also includes joint development projects with Merck & Co and Ortho-McNeil-Janssen (Johnson & Johnson).

Recent news flow

Sep 2009 – Results of BLOSSOM Phase III trial presented

Jul 2009 – $52m fund-raising closes

Jun 2009 – $100m loan from Deerfield

Mar 2009 – Positive data from BLOOM study

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Efficacy disappointment, but safety confirmed

Arena's lorcaserin is the only new chemical entity among the three oral anti-obesity projects that have completed pivotal studies, and accordingly its intellectual property position is likely to be seen by potential licensees as more robust than its competitors. As such, the investment case is free from sensitivities around whether big pharma views fixed dose combinations of established drugs as viable. However, weighing against this are lingering, if possibly unfounded, concerns on side-effects and efficacy that is barely adequate in terms of placebo-adjusted weight loss on an ITT-LOCF basis. In our view, there is a risk that lorcaserin could be marginal as a standalone drug.

Lorcaserin's Phase III programme consists of three trials, BLOOM, BLOSSOM and BLOOM-DM, but only the first two are pivotal; BLOOM data were reported in March, while BLOSSOM results were published six months later. BLOOM-DM, in obese and overweight patients with type 2 diabetes, should complete in mid-2010 and is intended to supplement the lorcaserin NDA. A key strength, however, is the size of this Phase III programme, which at 7,800 patients, was one of the largest conducted to date in this therapy area.

Heart valve scrutiny

A key question over the development of lorcaserin was its cardiovascular safety profile. Lorcaserin exerts its action at the $5HT_2$ receptor. This was also the target for fenfluramine and dexfenfluramine, which were withdrawn in 1997 after reports of heart valve disease and pulmonary hypertension associated with their use. Both agents were part of the so-called Fen-Phen anti-obesity combination (with phentermine).

However, 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. Thus lorcaserin has been developed specifically to circumvent the cardiovascular side-effects that led to fenfluramine/dexfenfluramine's withdrawal.

Lorcaserin's pivotal programme included multiple reviews by safety monitoring boards specifically looking at potential signs of valvulopathy, and none were seen; this is an important factor in allowing lorcaserin to have a broad anti-obesity label. But despite the relatively clean side-effect profile (outlined below), lorcaserin has shown very poor efficacy relative to its two competitors, and furthermore Arena seems to have ruled out seeking approval of a combination of the product with phentermine, which would likely prove far more active.

BLOOM

Phase III data from the 3,182-patient BLOOM study showed lorcaserin to have a weight loss effect of 5.8% of body weight compared with 2.2% for placebo, with 47.5% of patients (cf 20.3% for placebo) losing at least 5% of their body weight and 22.6% (cf 7.7% for placebo) losing at least 10% of their body weight (all these efficacy endpoints were statistically significant; $p<0.0001$).

These data were negatively received by the markets because of the relatively low level of placebo-adjusted efficacy (3.6% of body weight). Although clearly showing insufficient efficacy in terms of the absolute weight loss parameter, the trial did meet the second of the FDA's possible two benchmarks for approvability – that one year of treatment results in at least 35% of active recipients

losing ≥5% of baseline body weight, and this should be approximately double the proportion in the placebo group, with statistical significance.

BLOSSOM

BLOSSOM was a one-year study, during which patients took lorcaserin at two doses (10mg once daily or 10mg twice daily). Data from this trial proved were also disappointing and showed an even lower level of placebo-adjusted weight loss at 56 weeks than had been seen in BLOOM. Efficacy data are summarised in Exhibit 14.

Exhibit 14: Summary of lorcaserin 56-week efficacy seen in BLOOM and BLOSSOM

Endpoint	BLOOM		BLOSSOM		
	10mg bid	Placebo	10mg bid	10mg qd	Placebo
Mean weight loss (ITT-LOCF)	5.8%	2.2%	5.9%	4.8%	2.8%
Mean weight loss (completers)	8.2%	3.4%	7.9%	6.5%	3.9%
Patients losing ≥5% of baseline weight (ITT)	47.5%	20.3%	47.2%	40.2%	25.0%
Patients losing ≥5% of baseline weight (completers)	66.4%	32.1%	63.2%	53.1%	34.9%
Patients losing ≥10% of baseline weight (ITT)	22.6%	7.7%	22.6%	17.4%	9.7%
Patients losing ≥10% of baseline weight (completers)	36.2%	13.6%	35.1%	26.3%	16.1%

Source: Arena presentation

The absolute weight loss efficacy benchmark was not met in the BLOSSOM trial and is unclear whether lorcaserin met the second benchmark (in the ITT population), since the proportion of patients losing ≥5% of body weight was less than double the rate seen on placebo. Arena argues that the FDA benchmark states only that this rate should be 'approximately double' that of placebo. However, it is concerning that the approvability of lorcaserin may hinge on a semantic subtlety.

Arena also argues that physicians will focus on the completer and categorical data, while the ITT-LOCF data is a regulatory requirement only. It also claims lorcaserin has an advantage in terms of speed of onset of weight loss.

Safety profile

Arena said that lorcaserin had been very well tolerated in the BLOSSOM study, with headache being the only adverse event whose incidence in the active groups exceeded that in placebo by five percentage points or more. Adverse events of depression, anxiety and suicidal ideation in active groups were infrequent, and similar to that in placebo (Exhibit 15). Serious adverse events were infrequent and as expected for middle-aged, overweight people.

Exhibit 15: Adverse events reported in BLOSSOM by ≥5% in any group

Adverse event	Lorcaserin 10mg bid	Lorcaserin 10mg qd	Placebo
Headache	15.6%	15.6%	9.2%
Upper respiratory infection	12.7%	14.6%	12.6%
Nasopharyngitis	12.5%	11.9%	12.0%
Nausea	9.1%	7.6%	5.3%
Dizziness	8.7%	6.2%	3.9%
Fatigue	8.4%	6.6%	4.1%
Sinusitis	7.6%	8.4%	7.3%
Urinary tract infection	6.7%	7.6%	4.8%
Back pain	6.3%	6.9%	5.7%
Diarrhoea	6.1%	6.6%	5.9%
Dry mouth	5.4%	3.4%	2.3%
Constipation	5.0%	5.1%	3.8%

Source: Arena presentation

In BLOOM the 52-week completion rate was higher for patients on lorcaserin (55.4%) than for those on placebo (45.1%). Arena said this was primarily attributed to higher discontinuation rates for 'Subject Decision' (19.2% lorcaserin vs 27.7% placebo), which includes 'Lack of Efficacy' (1.7%

lorcaserin vs 5.5% placebo). Discontinuations due to adverse events (7.1% lorcaserin vs 6.7% placebo) and other reasons were similar. Two-year completion rates were similar across the treatment groups: 74.3%, 72.7%, and 68.9% for patients continuing on lorcaserin for both years, patients taking placebo both years, and patients switching from lorcaserin to placebo in year two respectively. Discontinuations due to adverse events were also similar across the treatment groups, Arena said.

In BLOSSOM the 52-week completion rate was higher for patients on lorcaserin 10mg twice daily (57.2%) and 10mg once daily (59.0%) than for placebo (52.0%). Discontinuations due to adverse events were as follows: lorcaserin 10mg twice daily (7.2%), 10mg once daily (6.2%) and placebo (4.6%), with the most common adverse events being depression, anxiety and suicidal ideation. Serious adverse events occurred infrequently, and included one death in the placebo group. No serious adverse events of seizure were reported and the number of neuropsychiatric serious adverse events in lorcaserin patients did not exceed the number in the placebo group.

Valvulopathy all clear

Arena was required to show that lorcaserin was not associated with the cardiovascular side-effects that had led to the withdrawal of fenfluramine/dexfenfluramine, and this was done through periodic echocardiography screening at various points during the BLOOM and BLOSSOM studies (summarised in Exhibit 16).

Exhibit 16: Summary of lorcaserin Phase III programme, including safety monitoring

	BLOOM	BLOSSOM	BLOOM-DM
Start	Sep 2006	Dec 2007	Dec 2007
Number of patients	3,182	4,008	604
Treatment duration	Two years	One year	One year
Daily lorcaserin dose	20mg	10mg and 20mg	10mg and 20mg
Echo monitoring	At screening and at six, 12, 18 and 24 months	At entry and at six and 12 months	At entry and at six and 12 months
ESMB review	At month six and 12	None	None

Source: Arena presentation

The combined echocardiography dataset (Exhibit 17) from BLOOM and BLOSSOM ruled out a risk of valvulopathy in lorcaserin patients according to the criteria that had been requested by the FDA.

Exhibit 17: Combined echocardiographic dataset

	BLOOM		BLOSSOM		
	10mg bid	Placebo	10mg bid	10mg qd	Placebo
Valvulopathy rates at week 52	2.7%	2.3%	2.0%	1.4%	2.0%
Valvulopathy rates at week 104	2.6%	2.7%	N/A	N/A	N/A

Source: Arena presentation

Echocardiographic evaluations showed no association between lorcaserin and the development of heart valve insufficiency, Arena maintains, and in the individual and combined BLOOM and BLOSSOM datasets there was no evidence of a difference in the development of valve disease in lorcaserin patients versus control for up to two years of continuous use. Arena believes that no prospective echocardiographic programme had ever studied so many patients for such a long period of time.

Exhibit 18 summarises improvements seen in secondary endpoints in BLOSSOM. Data on glycaemic parameters were positive, but have yet to be reported. Inflammatory parameters were not measured in BLOSSOM, but were significantly reduced in BLOOM. Systolic and diastolic blood pressure did not increase in any group, and showed a significant reduction based on completer data.

Exhibit 18: Secondary endpoints seen to improve in BLOSSOM study

Risk factor	Improved?	p value (ITT)	p value (completers)
HDL cholesterol	Yes	0.0001	0.0004
Triglycerides	Yes	0.0172	0.0011
LDL cholesterol	Yes	0.0676	0.0727
Systolic blood pressure	Yes	0.0689	0.0003
Diastolic blood pressure	Yes	0.0804	0.0006

Source: Arena presentation

Financials

Our financial model for Arena is presented in Exhibit 19. The cash flow statement for 2009 includes a $52.1m (gross) fund-raising at $4.17 per share, completed in July.

In June Arena struck a financing deal with Deerfield Management, under which Deerfield provided it with a $100m credit facility, comprising a 2.25% transaction fee and 7.75% annual interest rate. The principal is repayable as follows: $10m by the end of the first year (this in fact became repayable immediately on Arena completing its July fund-raising), $20m at the end of the second year (ie, June 2011), $30m at the end of the third year and the remainder at the end of the fourth year (June 2013). Interest accrues on the amount outstanding until maturity in 2013. Arena has the option to redeem part or all of the debt at par at any time.

Deerfield has also been issued warrants for 28m Arena shares with an exercise price of $5.42 per share. Over the next two years, Deerfield may elect to provide Arena with up to an additional $20m loan on the same terms, with the additional funding also maturing in June 2013. For each additional $1m in funding, Arena will issue Deerfield additional warrants for 280,000 shares. All of the warrants issued expire on the loan facility's maturity date.

Manufacturing deal

Arena's revenue line represents accounting recognition of up-front payments received under previous alliances, as well as contract research revenue received under a deal with the Swiss manufacturer Siegfried. This relates to a deal that closed in January 2008, under which Siegfried agreed to supply Arena with lorcaserin API at 'competitive rates' for 15 years after FDA approval.

Around 70 Siegfried employees (and certain other assets) were transferred to Arena under the deal, and it was agreed that these would manufacture/finish certain current Siegfried APIs for Siegfried's customers for at least three years. This part of the deal included commitments on Arena's part to sell a minimum of CHF7.0m of finished product to Siegfried in 2009 and CHF6.6m in 2010. We recognise these amounts as forecast revenue, and assume that manufacturing continues to run at a loss in these years, the revenue amount being offset against a (greater) cost of sales item.

Arena purchased the Siegfried assets for an initial CHF22m in cash and 1.5m shares, in addition to CHF10m in cash payable in three equal instalments in January 2011, 2012 and 2013.

Arena said it expected most of the purchase price paid to Siegfried to be recouped through reduced manufacturing costs within one year of US launch of lorcaserin.

Significant risks

In light of the disappointing efficacy data that lorcaserin has shown, we consider the product to have at best a marginal economic viability. Accordingly, we view the liabilities associated with the Deerfield loan and with the manufacturing agreement with Siegfried to represent significant risks to equity investors in the business.

Exhibit 19: Arena financial forecast

Note: Figures exclude payments under potential licensing deal(s) that have not yet been signed.

$'000s	2007	2008	2009e	2010e
Year end 31 December				
PROFIT & LOSS				
Revenue	**19,332**	**9,809**	**10,920**	**13,349**
Cost of sales	0	(8,515)	(7,560)	(7,216)
Gross profit	19,332	1,294	3,360	6,133
EBITDA	**(140,099)**	**(213,458)**	**(126,817)**	**(81,814)**
Operating profit (before GW and except.)	**(147,947)**	**(225,123)**	**(137,983)**	**(92,814)**
Goodwill amortisation	(1,537)	(2,314)	(2,278)	(2,500)
Exceptionals	0	0	0	0
Share-based payment	(8,816)	(8,492)	(7,480)	(8,000)
Operating profit	**(158,300)**	**(235,929)**	**(147,741)**	**(103,314)**
Net interest	15,134	(1,644)	(5,000)	(4,000)
Profit before tax (norm)	**(132,813)**	**(226,767)**	**(142,983)**	**(96,814)**
Profit before tax (US GAAP)	**(143,166)**	**(237,573)**	**(152,741)**	**(107,314)**
Tax	0	0	0	0
Beneficial conversion for Series C preferred stock and other	(2,114)	(1,912)	0	0
Profit after tax (norm)	**(134,927)**	**(228,679)**	**(142,983)**	**(96,814)**
Profit after tax (US GAAP)	**(145,280)**	**(239,485)**	**(152,741)**	**(107,314)**
Average number of shares outstanding (m)	62.8	73.8	83.4	92.6
EPS - normalised ($)	(2.15)	(3.10)	(1.72)	(1.05)
EPS - US GAAP ($)	(2.31)	(3.24)	(1.83)	(1.16)
Gross margin (%)	100.0%	13.2%	30.8%	45.9%
EBITDA margin (%)	N/A	N/A	N/A	N/A
Operating margin (before GW and except.) (%)	N/A	N/A	N/A	N/A
BALANCE SHEET				
Fixed assets	**78,258**	**124,348**	**116,630**	**113,130**
Intangible assets	4,875	16,262	13,984	11,484
Tangible assets	65,940	102,740	96,646	95,646
Investment in associates	0	0	0	0
Restricted cash and other	7,443	5,346	6,000	6,000
Current assets	**409,248**	**116,983**	**137,740**	**37,876**
Stocks	0	0	0	2,000
Debtors	1,901	1,823	1,600	2,000
Cash and available-for-sale securities	398,185	110,129	131,140	28,876
Other	9,162	5,031	5,000	5,000
Current liabilities	**(30,289)**	**(47,199)**	**(39,049)**	**(57,861)**
Creditors	(30,289)	(47,199)	(35,000)	(35,000)
Other creditors	0	0	0	0
Short-term borrowings	0	0	0	(22,861)
Deferred income	0	0	(4,049)	0
Long-term liabilities	**(120,840)**	**(76,500)**	**(162,476)**	**(139,615)**
Long-term borrowings	(53,922)	(8,567)	(98,592)	(75,731)
Deferred income	(4,049)	(4,049)	0	0
Provisions and other long-term liabilities	(62,869)	(63,884)	(63,884)	(63,884)
Associated with assets held for sale	0	0	0	0
Net assets	**336,377**	**117,632**	**52,845**	**(46,470)**
CASH FLOW				
Operating cash flow	**(128,148)**	**(191,439)**	**(138,793)**	**(88,263)**
Net interest	(4,295)	(5,851)	(5,000)	(4,000)
Tax	0	0	0	0
Capex	(17,402)	(42,752)	(5,072)	(10,000)
Purchase of intangibles	0	0	0	0
Acquisitions/disposals	0	0	0	0
Financing	155,191	2,733	79,851	0
Dividends	0	0	0	0
Other	(198)	(1,967)	0	0
Net cash flow	5,148	(239,276)	(69,014)	(102,263)
Opening net debt/(cash)	**(337,017)**	**(344,263)**	**(101,562)**	**(32,548)**
HP finance leases initiated	0	0	0	0
Other	2,098	(3,425)	0	0
Closing net debt/(cash)	**(344,263)**	**(101,562)**	**(32,548)**	**69,716**

Source: Edison Investment Research/company accounts

NeuroSearch

Year end	Revenue (DKKm)	PBT (DKKm)	EPS (DKK)	DPS (DKK)	P/E (x)	Yield (%)
12/07	115.2	(294.7)	(21.2)	0.0	N/A	N/A
12/08	66.8	(415.9)	(24.5)	0.0	N/A	N/A
12/09e*	60.9	(356.7)	(15.6)	0.0	N/A	N/A
12/10e*	22.1	(334.5)	(12.4)	0.0	N/A	N/A

Note: *PBT and EPS exclude one-off and non-cash items. €1 = DKK7.45.

Investment summary: Cash to start Phase III

Although further behind in development than Qnexa, Contrave and lorcaserin, NeuroSearch's tesofensine has shown more impressive weight loss efficacy than any of these three projects. Nevertheless, there has been a cardiovascular safety signal at the highest dose, as a result of which NeuroSearch is planning to take two lower doses into Phase III. A recently announced rights issue will bolster the company's cash position and should help fund the first Phase III trial in house.

Phase III plan for tesofensine

At an end of Phase II meeting, the US FDA endorsed the potential filing of an NDA for tesofensine based on four 12-month studies in 5,700 patients with and without co-morbidities. Rather than risk having the project stall while seeking a licensing partner, NeuroSearch has decided to start the first Phase III study itself, and this will include a comparison against sibutramine.

Discounted fund-raising

NeuroSearch recently launched a deeply discounted rights issue, aiming to raise DKK416m (net) at DKK60 per share. This has put significant pressure on the stock, but should give the company sufficient funds to run the first Phase III study of tesofensine and strengthen its hand in negotiations with potential partners.

Triple mechanism

Tesofensine's mechanism of action as a triple monoamine reuptake inhibitor has been put forward as a key feature in the relatively high level of efficacy it has shown, but it has been suggested that activity at a number of targets might increase side-effects in larger studies. The project is a new molecular entity, and thus does not carry the IP risks associated with Qnexa, Contrave and Empatic.

Cardiovascular safety?

Tesofensine has shown a promising side-effect profile in around 1,000 patient exposures so far – an unusually large number for a project still at Phase II. However, significant increases in blood pressure and heart rate were seen with the 1mg dose, which will not be taken into Phase III.

Price	DKK90.5*
Market cap	DKK1,560m

** Priced as at 4 November 2009.*

Share price graph

Share details

Code	NEUR
Listing	NASDAQ OMX Nordic
Shares in issue	17.2m

Price

52-week	High	Low
	DKK155.44	DKK53.51

Business

NeuroSearch is a Danish biopharmaceutical company with a focus on central nervous system diseases. It has eight projects in clinical studies, including Huntexil for Huntington's disease (Phase III), and expects its obesity project, tesofensine, to start Phase III in 2010.

Recent news flow

Oct 2009 – Proposed DKK416m rights issue at DKK60 per share.

Aug 2009 – Discovery alliance signed with Janssen (Johnson & Johnson).

Jun 2009 – Successful completion of end of Phase II FDA meeting for tesofensine.

May 2009 – Supportive clinical data for tesofensine published.

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Investment summary: Efficacious NCE, Phase III ready

NeuroSearch's tesofensine is one of two oral anti-obesity projects that have successfully completed Phase II studies and are ready to enter Phase III. In Phase II studies it has been shown to be highly efficacious – demonstrating a weight loss effect over 24 weeks that was in excess of that shown in 56-week Phase III studies by Vivus's Qnexa (phentermine plus topiramate), the most efficacious of the three projects whose pivotal development has been completed. Tesofensine is a triple monoamine (dopamine, noradrenaline and 5HT) reuptake inhibitor, which was previously in a large Phase IIb programme for treating Alzheimer's and Parkinson's diseases, although development for these indications was discontinued owing to poor efficacy.

Of the five anti-obesity projects considered in this report, two are new chemical entities (NCEs): tesofensine and Arena's lorcaserin. Accordingly, IP issues (and the question of a big pharma licensee buying into the concept of reformulations of existing, off-patent drugs) do not feature as a significant sensitivity in NeuroSearch's investment case. Furthermore, tesofensine appears to be several-fold more efficacious than lorcaserin.

However, these positive factors are tempered with the fact that tesofensine has yet to undergo pivotal studies, and as such has to be considered to be at least two years behind the most advanced three projects (although clearly in a blockbuster market such as obesity there is likely to be space for multiple competitors). Additionally, an evaluation of its side-effect profile has shown an increase in adverse events (including those on the cardiovascular system) at the highest dose, and this has prompted NeuroSearch to put only the two lower doses of tesofensine forward to be studied in Phase III.

In contrast to many of its competitors, NeuroSearch has a broad pipeline of projects targeting CNS disorders, and has licensing deals in place with GlaxoSmithKline, Lilly, Johnson & Johnson and Abbott Laboratories. Its lead project, Huntexil (pridopidine), is completing pivotal studies for treating Huntington's disease.

TIPO-1

In September 2007 NeuroSearch reported data from TIPO-1, a Phase IIb proof-of-concept and dose-finding study. Data from 203 patients (BMI 30-40kg/m^2) showed that 24 weeks' treatment with tesofensine resulted in a dose-dependent average weight loss of 6.7-12.8kg against a weight loss of 2.2kg in the placebo group (Exhibit 20). In all treatment groups, the primary endpoints were met with high statistical significance ($p<0.0001$).

Exhibit 20: Summary of TIPO-1, a 24-week Phase IIb study of tesofensine (intent-to-treat population)

	Placebo	Tesofensine 0.25mg	Tesofensine 0.50mg	Tesofensine 1.00mg
Number of patients	52	52	50	49
Baseline body weight lost	2.2kg	6.5kg	11.2kg	12.6kg
% losing ≥5% of baseline weight	29%	59%	87%	91%
% losing ≥10% of baseline weight	7%	35%	53%	74%

Source: NeuroSearch

NeuroSearch subsequently decided that the lower doses (0.25mg and 0.5mg) and not the highest dose would be taken into Phase III, on the basis that the weight loss produced by 0.5mg was not significantly below that of the 1mg dose, but there were fewer side-effects.

TIPO-2

This was a 14-day study evaluating tesofensine's direct effect on metabolic parameters in 32 overweight patients (BMI 28-35kg/m^2). Detailed evaluation of this trial was published in August 2008: the tesofensine-treated group had an increased feeling of satiety with less desire to eat than placebo ($p<0.05$); tesofensine increased 24-hour fat oxidation by 15% ($p<0.05$), reduced 24-hour protein oxidation ($p<0.05$) and increased loss of fat tissue ($p<0.01$); tesofensine increased blood levels of adiponectin (a peptide hormone secreted exclusively by adipocytes) and improved insulin sensitivity; and tesofensine increased night-time energy expenditure by 6% ($p<0.05$). TIPO-2 showed that tesofensine exerted its effect on energy metabolism via loss of fat and not by increased muscle degradation or other catabolic effects.

TIPO-4

This is a completed open-label Phase II 48-week extension study, which offered all patients who concluded 24 weeks' treatment in TIPO-1 another year of treatment (140 of the 203 TIPO-1 patients were enrolled into TIPO-4). Patients continued treatment with the 0.5mg dose only (following a two-month washout period), as well as being encouraged to follow the same diet and exercise programme as in TIPO-1.

24-week interim analysis of TIPO-4 showed that patients previously treated with placebo in TIPO-1 achieved an average weight loss of 9kg in TIPO-4 (in addition to the 2kg they had already lost during TIPO-1). Patients previously treated in TIPO-1 with 0.5mg tesofensine lost almost 4kg in the subsequent treatment on 0.5mg in TIPO-4. Including the weight gained during washout, the combined effect of TIPO-1 and TIPO-4 results in an average weight loss of 13-14kg. Data from the entire 48-week extension period (ie, 72 weeks of total treatment) showed a levelling off of the weight loss effect at the above seen 13-14kg.

Consistent with earlier results, tesofensine was well tolerated over the 72 weeks, and dry mouth, insomnia and gastrointestinal disorders were the most frequently reported adverse events.

Pivotal study plan in place

NeuroSearch has recently decided on the next stage of development for tesofensine. Rather than risk having the project stall while a licensing partner is sought, it has decided to start the first of four planned Phase III studies itself, at an expected cost of DKK100m (€13m).

This follows a successful end of Phase II meeting with the US FDA in June 2009, at which the agency endorsed the potential filing of an NDA based on 12 months of safety and efficacy data, comprising four placebo-controlled Phase III trials in a total of around 5,700 obese patients with and without co-morbidities, such as type 2 diabetes, hypertension and dislipidaemia.

This appears to be broadly in line with the pivotal programme of other anti-obesity agents, and the proposed tesofensine doses that will be tested will be 0.25mg and 0.5mg.

Two of the four trials are to be powered to show that tesofensine has a better efficacy and safety profile than the marketed anti-obesity drug sibutramine (Abbott's Reductil/Meridia). The pivotal programme is summarised in Exhibit 21.

Exhibit 21: Summary of tesofensine pivotal study programme

Study name	Patient population	Partner needed?	Duration	Notes
TIPO-H	Overweight and obese with hypertension	No	One year	One of two trials that will include sibutramine as an active comparator. Could start in Q1 2010.
TIPO-O	Normotensive obese	Yes	One year	
TIPO-M	Overweight with co-morbidity or obese	Yes	One year	To be followed by a non-pivotal one-year extension trial.
TIPO-D	Overweight with type 2 diabetes	Yes	One year	

Source: NeuroSearch presentation

Safety

The combined clinical safety data base from five individual studies with tesofensine now counts approximately 1,000 patients exposed to relevant therapeutic doses (this includes studies that had been conducted on the product as a potential Alzheimer's/Parkinson's disease treatment). Consistent with earlier clinical results, the 24-week safety data from TIPO-4 showed that tesofensine was well tolerated also over extended periods of administration.

The results from the TIPO-1 study showed a good safety profile and good tolerability. There were no severe adverse events related to treatment with tesofensine. The most common adverse events caused by tesofensine were mild to moderate, and included dry mouth, nausea, constipation, hard stools, diarrhoea and sleep disturbances/insomnia. There was a tendency towards an increased number of adverse event observations in the highest dose groups (0.5mg and 1mg), and these also included increased anger and hostility, and gastrointestinal problems.

Based on the adverse event profile seen in the highest dose against the relatively small increase in efficacy seen in Phase II, NeuroSearch decided not to take the 1mg tesofensine dose into Phase III.

A summary of cardiovascular effects after 24 weeks is shown in Exhibit 22. Increases in systolic and diastolic blood pressure for the 0.25mg and 0.5mg groups were not significant compared with placebo. The heart rate increase seen in the 0.5mg group was statistically significant (p=0.0001).

Exhibit 22: Summary of cardiovascular effects seen with tesofensine (TIPO-1, 24 weeks)

	Placebo	Tesofensine 0.25mg	Tesofensine 0.50mg	Tesofensine 1.00mg
Increase in systolic blood pressure	0.7mmHg	0.7mmHg	1.6mmHg	7.0mmHg
Increase in diastolic blood pressure	0.4mmHg	1.7mmHg	2.5mmHg	5.7mmHg
Change in heart rate	–0.8bpm	+3.9bpm	+7.7bpm	+8.4bpm

Source: NeuroSearch

To supplement the safety profile demonstrated in Phase II, NeuroSearch conducted a small study in healthy volunteers to evaluate the tolerability and safety of tesofensine (at doses up to 4mg), particularly in situations that are stressful to the cardiovascular system.

Compared with placebo, tesofensine-treated volunteers showed: no deregulation of the cardiovascular response after getting up abruptly; no change in the ECG apart from changes relating to the increase in heart rate during exercise; no increase in blood pressure; and a lower systolic blood pressure under dynamic exercise, which tended to be more pronounced at higher plasma levels of tesofensine. NeuroSearch suggested that these observations might be attributable to tesofensine's activity on the presynaptic noradrenergic receptors in the brain stem, leading to a lowering of sympatholytic effects and eventually lower blood pressure. These are also known as 'clonidine-like' effects (clonidine belongs to a class of anti-hypertensive drugs) and have been described in other clinical studies involving hypertensive obese patients.

Results from an abuse liability trial in 44 recreational stimulant users were presented at ECO 2009, and showed no significant positive effects (eg, euphoria) at up to 9mg, with minimal or no abuse potential. Previous studies at up to a 9mg dose showed a significant level of side-effects (hence this dose is well outside the therapeutic window), and NeuroSearch believes that excessive tesofensine doses do not cause more weight loss, and the drug probably will not work in lean individuals – important considerations in assessing the drug's liability to be abused.

Financials

Our financial model for NeuroSearch is presented in Exhibit 23. We expect R&D expenditure of DKK390m in 2009 and DKK290m in 2010, including the expected start of the first Phase III trial of tesofensine without a partner.

Our revenue forecast for 2009 and 2010 comprises a DKK29.2m up-front payment received from Lilly, a €5m cash up-front from Janssen (both of these are being recognised in the income statement over several years), a €4m cash milestone from GSK (on entry of NSD-721 into Phase I in August 2009) plus a nominal amount for a small up-front received from GSK under the companies' new alliance.

The 2009 cash flow statement shows DKK619m in financing, comprising a recently announced DKK416m (net) rights issue, and equity purchases by Lilly (DKK99.2m), GSK (€5m) and Janssen (€10m). Further revenue is likely under NeuroSearch's alliances with big pharma, but we are not factoring this into our model at present (a milestone payment, not shown in the model, is due from Abbott once ABT-894 enters Phase III for ADHD, possibly in 2010).

Potential sales of Huntexil are not illustrated in our model, as we expect these to be realised beyond 2010. On the spending side, we expect 30 sales reps to be in place by 2012, and forecast an initial 10-strong sales force in 2010 at a total cost of DKK12.8m (€1.7m). We expect R&D expenditure of DKK390m in 2009 and DKK290m in 2010 (an increase from our previous forecast owing to the expected start of the first Phase III trial of tesofensine without a partner).

NeuroSearch is liable to pay a further DKK200m earnout to the vendors of Carlsson Research, which it acquired in 2006, comprising DKK100m on first commercial sales of Huntexil and DKK100m on entry of ACR325 into Phase II studies. If NeuroSearch ends up offering Huntexil to patients outside the Phase II/III programme for a fee, the first of these could be triggered. NeuroSearch earlier instituted a share purchase programme, taking advantage of its depressed share price earlier this year, and will likely effect much of the payments to Carlsson in stock.

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.

Exhibit 23: NeuroSearch financial forecasts

Note: Figures exclude payments under potential licensing deal(s) yet to be signed as well as a potential Phase III milestone from Abbott.

DKK'000s	2006	2007	2008	2009e	2010e
Year end 31 December					
PROFIT & LOSS					
Revenue	**66,341**	**115,206**	**66,766**	**60,900**	**22,067**
Cost of sales	0	0	0	0	0
Gross profit	66,341	115,206	66,766	60,900	22,067
EBITDA	**(165,770)**	**(216,086)**	**(324,728)**	**(330,700)**	**(287,502)**
Operating profit (before GW and except.)	**(179,629)**	**(230,917)**	**(340,884)**	**(345,700)**	**(302,502)**
Goodwill amortisation	(1,999)	(1,971)	(1,962)	(2,000)	(2,000)
Exceptionals	0	0	0	0	0
Share-based payment	(5,078)	(20,567)	(23,154)	(20,000)	(20,000)
Operating profit	**(186,706)**	**(253,455)**	**(366,000)**	**(367,700)**	**(324,502)**
Net interest	(4,787)	(20,783)	(31,312)	24,200	(10,000)
Share of profit/(loss) of associates	(20,673)	(20,487)	(18,607)	(13,200)	0
Profit before tax (norm)	**(205,089)**	**(272,187)**	**(390,803)**	**(334,700)**	**(312,502)**
Profit before tax (IFRS)	**(212,166)**	**(294,725)**	**(415,919)**	**(356,700)**	**(334,502)**
Tax	0	26,295	33,928	41,200	30,000
Profit after tax (norm)	**(205,089)**	**(245,892)**	**(356,875)**	**(293,500)**	**(282,502)**
Profit after tax (IFRS)	**(212,166)**	**(268,430)**	**(381,991)**	**(315,500)**	**(304,502)**
Average number of shares outstanding (m)	8.8	12.7	15.6	20.2	24.6
EPS - normalised (DKK)	(23.36)	(19.39)	(22.86)	(14.54)	(11.47)
EPS - IFRS (DKK)	(24.17)	(21.17)	(24.47)	(15.63)	(12.36)
Gross margin (%)	100.0%	100.0%	100.0%	100.0%	100.0%
EBITDA margin (%)	N/A	N/A	N/A	N/A	N/A
Operating margin (before GW and except.) (%)	N/A	N/A	N/A	N/A	N/A
BALANCE SHEET					
Fixed assets	**857,208**	**917,167**	**773,018**	**823,212**	**823,212**
Intangible assets	657,825	727,705	559,806	600,000	600,000
Tangible assets	169,715	170,479	202,498	212,498	212,498
Investment in associates	7,023	9,018	8,175	8,175	8,175
Available-for-sale financial assets	22,645	9,965	2,539	2,539	2,539
Current assets	**410,267**	**863,451**	**472,727**	**840,885**	**531,316**
Stocks	0	0	0	0	0
Debtors	23,272	18,178	19,351	20,000	20,000
Cash	386,995	845,273	453,376	820,885	511,316
Other	0	0	0	0	0
Current liabilities	**(174,133)**	**(348,548)**	**(125,530)**	**(153,266)**	**(153,266)**
Creditors	(60,410)	(73,780)	(70,399)	(65,000)	(65,000)
Other creditors	0	0	0	0	(22,067)
Short-term borrowings	(21,704)	(5,285)	(5,643)	(5,000)	(5,000)
Deferred income	(26,841)	(13,422)	0	(22,067)	(22,067)
Contingent consideration	(65,178)	(256,061)	(49,488)	(61,199)	(61,199)
Long-term liabilities	**(435,673)**	**(310,666)**	**(276,184)**	**(299,417)**	**(266,184)**
Long-term borrowings	(111,006)	(105,721)	(138,110)	(133,110)	(128,110)
Deferred income	0	0	0	(28,233)	0
Provisions and other long-term liabilities	(324,667)	(204,945)	(138,074)	(138,074)	(138,074)
Associated with assets held for sale	0	0	0	0	0
Net assets	**657,669**	**1,121,404**	**844,031**	**1,211,414**	**935,078**
CASH FLOW					
Operating cash flow	**(166,399)**	**(218,822)**	**(339,906)**	**(286,448)**	**(309,569)**
Net interest	(3,616)	(1,524)	6,843	24,200	(10,000)
Tax	0	0	0	41,200	30,000
Capex	(12,881)	(15,716)	(50,172)	(25,000)	(15,000)
Purchase of intangibles	0	0	0	0	0
Acquisitions/disposals	(208,284)	(8,164)	(13,145)	0	0
Financing	372,647	754,736	4,411	619,200	0
Dividends	0	0	0	0	0
Other	(11,797)	(4,999)	(24,012)	0	0
Net cash flow	(30,330)	505,511	(415,981)	373,152	(304,569)
Opening net debt/(cash)	**(274,823)**	**(254,285)**	**(734,267)**	**(309,623)**	**(682,775)**
HP finance leases initiated	0	0	0	0	0
Other	9,792	(25,529)	(8,663)	0	0
Closing net debt/(cash)	**(254,285)**	**(734,267)**	**(309,623)**	**(682,775)**	**(378,206)**

Source: Edison Investment Research/company accounts

Orexigen Therapeutics

Year end	Revenue ($m)	PBT ($m)	EPS ($)	DPS ($)	P/E (x)	Yield (%)
12/07	0.1	(55.6)	(3.0)	0.0	N/A	N/A
12/08	0.1	(87.5)	(2.6)	0.0	N/A	N/A
12/09e*	0.1	(55.1)	(1.4)	0.0	N/A	N/A
12/10e*	0.1	(43.4)	(0.9)	0.0	N/A	N/A

Note: *PBT and EPS exclude one-off and non-cash items.

Investment summary: Two-stroke engine

Data from the three remaining Phase III studies of Contrave have been reported, all three meeting an FDA weight loss benchmark that the first trial missed. Orexigen is likely to argue that the first study met two more stringent criteria, and on this basis we believe that Contrave is approvable. Orexigen is a pure-play anti-obesity company, and Empatic, its second project, has completed Phase II. This appears to be more efficacious than Contrave but if approved is likely to have a stricter label.

Unpartnered launch strategy

Although the pivotal dataset is positive, an expected licensing deal (or indeed an outright acquisition) has not materialised. Instead, the company is positioning itself to be able to launch Contrave itself, while seeking a big pharma licensee, and has managed to raise $81.6m primarily to establish an in-house, speciality sales force. US filing of Contrave remains on track for the first half of 2010.

Good efficacy at Phase III

Two large pivotal trials have shown more impressive average placebo-adjusted weight loss results than the first Contrave Phase III study, which included intensive diet and exercise. All three meet a key FDA benchmark that, taking a literal interpretation, was missed by the first Phase III trial.

FDA view?

The key issue will be whether the FDA accepts the four Phase III studies as sufficient for approval, and Orexigen is likely to argue that the 'failed' study does demonstrate clinical relevance because it meets two tougher benchmarks and answers a different question. The company is also likely to point to the fact that analyses of the total completer population yield more impressive absolute results.

Efficacious follow-on project

Orexigen is unique among the companies analysed in that its pipeline contains a second promising anti-obesity project, Empatic (also a reformulation of two known off-patent molecules), which has completed Phase II trials. Although more efficacious than Contrave, Empatic contains zonisamide at its highest approved dose, highlighting possible CNS side-effects, and teratogenicity will necessitate a strict pregnancy warning.

Price	$7.02*
Market cap	$326m

** Priced as at 4 November 2009.*

Share price graph

Share details

Code	OREX
Listing	NASDAQ
Shares in issue	46.4m

Price

	High	Low
52-week	$10.83	$1.55

Business

Orexigen is a US biopharmaceutical company focused on developing two treatments for 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 news flow

Sep 2009 – Positive Phase IIb data reported for Empatic

July 2009 – $86m fund-raising closes

July 2009 – Positive data reported from final three Phase III trials of Contrave

March 2009 – Michael Narachi named CEO

Jan 2009 – First Phase III trial of Contrave yield mixed results

Dec 2008 – Decision to terminate all non-obesity R&D work

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Investment summary: Pure-play anti-obesity business

Orexigen offers a pure-play investment geared to the success of its two late-stage projects, Contrave (naltrexone plus bupropion; all Phase III data recently reported) and Empatic (zonisamide plus bupropion; Phase II). It initially conducted R&D into antipsychotic-associated weight gain and obsessive-compulsive disorder as well as obesity, but decided to terminate all projects except Contrave and Empatic in December 2008 in an effort to conserve cash.

Data from the first Phase III trial of Contrave, which included intensive diet and behaviour modification, were announced in January 2009 and were generally seen as disappointing. However, subsequently released results from all three remaining Phase III studies were received more positively. With all pivotal trials of Contrave now complete, the product remains on track to be filed for US approval in the first half of 2010.

A key strength, in our view, of Contrave and Empatic is the fact that buproprion, the common constituent in both combinations, is widely used for treating depression (typically at 400mg/day), particularly in overweight people (because it is not associated with weight gain common with SSRIs).

Study NB-302 (COR-BMOD)

Study NB-302 was a relatively small study (793 patients enrolled) that was the first Phase III trial to report data, in early January 2008. In contrast to the three studies whose results were reported subsequently, NB-302 included an unusually stringent diet, exercise and behaviour-modification programme, and this was clearly the reason behind the unusually high response seen in the placebo group. Results were discussed in detail in our initiation note in March 2009, and are summarised in Exhibit 24.

Exhibit 24: Summary of study NB-302 (56 weeks, intent-to-treat population)

	Contrave (32mg naltrexone SR + 360mg bupropion SR)	Placebo	p value
Weight loss (kg)	9.2kg	5.0kg	<0.001
Weight loss (% body weight)	9.3%	5.1%	<0.001
% achieving 5% weight loss or more	66.4%	42.5%	<0.001
% achieving 10% weight loss or more	41.5%	20.2%	<0.001
% achieving 15% weight loss or more	29.1%	10.9%	<0.001

Source: Orexigen

Although the study showed Contrave to exert significant effects on weight loss vs placebo, on a literal interpretation the data missed both FDA benchmarks (the second on account of the very high placebo response) and were poorly received at the time.

However, the data did meet two stricter benchmarks, proportion of patients losing at least 10% and at least 15% of body weight, these responses being roughly twice and three times the placebo effect, respectively. Orexigen will therefore argue that this trial demonstrates clinical relevance because it was designed to answer a different question – whether Contrave can exert an effect when taken in addition to significant behaviour modification – and given that two tougher benchmarks have been met the company believes that the answer to this question is affirmative.

Study NB-301 (COR-I)

NB-301 was one of two large Phase III studies of Contrave, and enrolled 1,742 obese patients with a BMI of 27-45. The trial took place at 34 US centres, started in October 2007, and completed patient enrolment in April 2008. As well as testing what Orexigen considers to be the optimal dose of Contrave (32mg naltrexone plus 360mg bupropion), this trial also included a patient arm

randomised to a lower dose (16mg naltrexone plus 360mg bupropion), which might later be used to provide flexibility in certain clinical situations.

The co-primary endpoint was mean placebo-adjusted weight loss at 56 weeks and percentage of patients losing at least 5% of body weight, and both the 16mg and 32mg groups showed strong statistical significance, with the higher dose showing a better response. Interim analysis at 28 weeks suggested that most of the weight loss effect was seen in these first six months, with a plateau thereafter.

1,453 patients were eligible for evaluation on an intent-to-treat basis (ITT; at least one post-baseline observation while on study drug), and 870 of these completed the study. We have summarised the results at 56 weeks (including a secondary endpoint) with both the 16mg and 32mg dose (ITT population) in Exhibit 25.

Exhibit 25: Summary of study NB-301 (56 weeks, intent-to-treat population)

	Contrave (16mg naltrexone SR + 360mg bupropion SR)	Contrave (32mg naltrexone SR + 360mg bupropion SR)	Placebo	p value
Weight loss (kg)	Not available	6.0kg	1.4kg	<0.001
Weight loss (% body weight)	5.0%	6.1%	1.3%	<0.001
% achieving 5% weight loss or more	39.5%	48.0%	16.4%	<0.001
% achieving 10% weight loss or more	Not available	24.6%	7.4%	<0.05
% achieving 15% weight loss or more	Not available	11.9%	2.0%	<0.05

Source: Orexigen

Study NB-303 (COR-II)

This was the second of two large Phase III studies, and enrolled 1,496 obese patients with a BMI of 27-45. It took place at 36 US centres, started in December 2007, and completed patient enrolment in May 2008. This study also had as its co-primary endpoints placebo-adjusted weight loss and the percentage of patients losing at least 5% of their body weight, but incorporated a somewhat complex design: non-responders to Contrave 32 (ie, 32mg naltrexone plus 360mg bupropion) – classified as those who did not experience a 5% or greater weight reduction – were identified at a 28-week interim analysis and re-randomised in a blinded fashion to either the standard 32mg dose or a higher dose, containing 48mg of naltrexone.

The aim of this was to identify whether their lack of response was due to an insufficiently high dose and whether increasing the dose would result in additional weight loss, but in the event it turned out that raising the dose had no statistical effect. In the final analysis at 56 weeks, in order to eliminate any positive effect the 48mg dose might have had, the subgroup re-randomised to the 48mg dose was eliminated, while the one re-randomised to 32mg (but no other group in the study) was double counted. This design was based on discussions with the US FDA.

This trial showed highly statistically significant weight loss at 28 weeks (the primary endpoint; Exhibit 26), and similarly to NB-301 it was suggestive of a plateau effect after six months of treatment. The ITT population was 1,281 patients, of whom 701 completed the trial.

Exhibit 26: Summary of study NB-303 (intent-to-treat population)

	Contrave 32 (week 28)	Placebo (week 28)	Contrave 32 (week 56)	Placebo (week 56)	p value
Weight loss (kg)	6.4kg	2.0kg	6.3kg	1.3kg	<0.001
Weight loss (% body weight)	6.5%	1.9%	6.4%	1.2%	<0.001
% achieving >5% weight loss	55.6%	17.5%	56.3%	17.1%	<0.001
% achieving >10% weight loss e	Not available	Not available	32.9%	5.7%	<0.05
% achieving >15% weight loss	Not available	Not available	15.7%	2.4%	<0.05

Source: Orexigen

Study NB-304 (COR-Diabetes)

This was a smaller trial, looking specifically at the weight loss effects of Contrave on diabetics. It enrolled 505 patients with obesity (BMI of 27-45) and type 2 diabetes, 424 of whom comprised the ITT population, and 275 of these completed the trial. The trial took place at 52 US centres, began in May 2007 and completed patient enrolment in May 2008. Efficacy in terms of weight loss (percentage body weight and percentage of patients losing at least 5%) were the co-primary endpoints (Exhibit 27).

Exhibit 27: Summary of study NB-304 (56 weeks, intent-to-treat population)

	Contrave (32mg naltrexone SR + 360mg bupropion SR)	Placebo	p value
Weight loss (kg)	5.3kg	1.9kg	<0.001
Weight loss (% body weight)	5.0%	1.8%	<0.001
% achieving 5% weight loss or more	44.5%	18.9%	<0.001

Source: Orexigen

Although the placebo-adjusted weight loss in this trial was relatively very small (despite being statistically significant), this can be attributed to diabetics being a more challenging patient population in which to demonstrate a weight loss effect.

Secondary endpoints included proportion of subjects who lost at least 10% of baseline body weight and achieved an HbA1c value of <7% (diabetics in general exhibit higher levels of HbA1c); change in HbA1c; and effects on selected obesity-associated risk factors. Average placebo-adjusted HbA1c reduction of 0.5 points was seen within 14 weeks of treatment and the effect persisted throughout the trial, and fasting HDL and fasting triglyceride levels also improved vs placebo ($p \leq 0.05$). There was statistical significance in percentage of subjects with HbA1c <7% and percentage requiring rescue medication, but only vs baseline ($p \leq 0.05$), not vs placebo.

Safety

Contrave's Phase III dataset of over 4,500 patients has not raised any significant safety issues. Treatment-emergent adverse events across the three last reported Phase III trials are summarised in Exhibit 28.

Exhibit 28: Most common treatment-emergent adverse events in NB-301, NB-303 and NB-304

Adverse event	Placebo	NB-301 and NB-303		NB-304
		Contrave 16	Contrave 32	Contrave 32
Overall treatment-emergent adverse events	68-85%	80%	83-86%	90%
Nausea	5-7%	27%	29-30%	42%
Constipation	6-7%	16%	16-19%	18%
Headache	9%	16%	14-18%	14%
Vomiting	2-4%	6%	9-10%	18%
Upper respiratory infection	10-11%	9%	9-10%	8%
Insomnia	5-7%	6%	8-10%	11%
Dizziness	3-5%	8%	7-9%	12%
Dry mouth	2-3%	7%	8-9%	6%
Nasopharyngitis	5-14%	6%	5-8%	8%
Diarrhoea	4-10%	5%	5-6%	16%

Source: Orexigen presentation

There were a relatively high number of discontinuations in the active arm, and as previously the vast majority of these occurred early on in the study (within the first few weeks). Most discontinuations were due to adverse events, most commonly nausea. Significant numbers of discontinuations due to lack of efficacy were seen only in the placebo arm. Discontinuation rates are summarised in Exhibit 29.

Exhibit 29: Selected treatment discontinuations due to adverse events in NB-301, NB-303 and NB-304

Adverse event	Placebo	NB-301 & NB-303		NB-304
		Contrave 16	Contrave 32	Contrave 32
Overall discontinuation rate	41-50%	51%	46-49%	48%
Discontinuation rate due to AEs	10-15%	22%	20-24%	29%
Nausea	≤1%	5%	6%	10%
Headache	≤1%	2%	1-3%	2%
Dizziness	≤1%	2%	≤1%	≤1%
Vomiting	≤1%	≤1%	≤1%	3%
Depression	0-2%	≤1%	≤1%	≤1%
Insomnia	≤1%	≤1%	≤1%	≤1%
Anxiety	≤1%	≤1%	≤1%	≤1%
Diabetes mellitus (worsening)	≤1%	≤1%	≤1%	≤1%

Source: Orexigen presentation

There were only seven serious adverse events (SAEs) attributed to Contrave: two cases of cholecystitis (gallbladder inflammation, common in middle-aged obese people), two seizures (a lower rate compared with the four in 1,000 estimated in the current Wellbutrin [bupropion] label), and one case each of palpitations, paresthesia and vertigo. Cardiovascular serious adverse events were similar between Contrave and placebo, and there was one death on study drug (due to myocardial infraction), although this was not attributed to Contrave (Exhibit 30).

Exhibit 30: Serious adverse and cardiovascular events in NB-301, NB-303 and NB-304

Risk factor	Phase III programme summary
SAE attributed to Contrave	Cholecystitis (two events), seizure (two), palpitation (one), paresthesia (one) and vertigo (one).
Cardiovascular SAE	Similar rates between Contrave and placebo. One death on Contrave.
Depression and suicidal ideation	No treatment effects. Placebo (three events of suicidal ideation), Contrave (one).
Blood pressure	Contrave patients @56wk: mean BP unchanged vs baseline. Placebo patients @56wk: mean BP slightly decreased (~2mm) vs baseline. Patients losing ≥5% weight on Contrave had small BP decreases at endpoint. Contrave treatment did not appear to disrupt normal circadian BP pattern. Elevated BP as an adverse event was higher in diabetics (10%) cf placebo (4%). Discontinuations due to elevated BP on Contrave (<1%).
Pulse	Slight increase in mean pulse on Contrave (~1BPM) cf placebo (negligible).
Labs, ECGs, LFTs	No meaningful treatment effects on ECGs or lab measures including liver function tests.

Source: Orexigen presentation

Plans to launch unpartnered if necessary

With the completion of its pivotal programme, Orexigen plans to file Contrave in the first half of 2010. It has also announced plans to proceed with a launch on its own, if no partnering deal is secured by this time. While it still wants to sign a broad licensing deal, this is could occur later, possibly after launch, with Orexigen aiming to set up its own small speciality sales force. Typically, this would be expected to number 50 to 75 reps. In order to support this effort, Orexigen recently raised $81.6m (net).

Although all four pivotal studies have shown a high degree of statistical significance, it remains to be seen how they are viewed by the US FDA in terms of their clinical relevance. On a literal interpretation, only three of Contrave's four pivotal studies have met one or other of the US FDA's two benchmarks. However, NB-302 did meet two more stringent criteria (regarding ≥10% and ≥15% weight loss), consistent with its design, which included intensive diet and behaviour modification. Orexigen is likely to argue that NB-302 demonstrates clinical relevance because it was designed to find out whether Contrave could exert an effect when taken in addition to significant behaviour modification.

Empatic: A second shot at goal

Empatic, Contrave's other anti-obesity project, is a proprietary formulation of bupropion SR and zonisamide SR. The project appears to exert a greater weight loss effect than Contrave, but is at least two years behind in development. It also contains zonisamide at its highest approved dose, and it has been suggested that this might give rise to safety concerns.

An earlier Phase II trial of Empatic showed impressive weight loss data at 24 weeks, and this reached 12.9% of baseline body weight (placebo-adjusted, intent-to-treat basis) in the highest-strength group (zonisamide 360mg plus bupropion 360mg). 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 part of the study.

In September Orexigen announced topline results from a 24-week US Phase IIb trial (ZB-202) that enrolled 729 patients with BMIs of 30-45, or as low as 27 in the presence of hypertension or dislipidaemia. This study compared two doses of Empatic against placebo as well as the two standalone active ingredients, and statistically significant efficacy of both doses against each comparator arm was seen with $p<0.001$. Topline data are summarised in Exhibit 31.

Exhibit 31: Summary of 24-week Phase IIb study of Empatic (intent-to-treat population)

	Placebo	Bupropion 360mg	Zonisamide 120mg	Zonisamide 360mg	Empatic 360+120mg	Empatic 360+360mg
Number of patients	75	81	77	158	81	164
Baseline body weight lost	1.4%	2.3%	3.2%	5.3%	6.1%	7.5%
% losing ≥5% of baseline weight	14.7%	Not available	Not available	Not available	46.9%	60.4%

Source: Orexigen

The next stage in Empatic's development will be an end-of-Phase-II meeting with the US FDA that Orexigen plans to hold shortly, with the goal of developing a Phase III plan for the project.

Safety and likely contraindication

Orexigen said that adverse events and laboratory findings seen with Empatic appeared to be consistent with those seen with its individual components (summarised in Exhibit 32).

Exhibit 32: Most common treatment-emergent adverse events in Phase IIb trial of Empatic

Adverse event	Placebo	Empatic 360+120mg	Empatic 360+360mg
Overall treatment-emergent adverse events	Not available	Not available	Not available
Headache	3.4%	12.9%	14.8%
Insomnia	4.5%	15.1%	12.1%
Nausea	5.6%	7.5%	12.1%
Constipation	0.0%	6.5%	12.1%
Dry mouth	1.1%	7.5%	10.4%
Nasopharyngitis	5.6%	6.5%	8.2%
Upper respiratory infection	5.6%	5.4%	7.7%
Fatigue	1.1%	4.3%	7.1%
Diarrhoea	3.4%	5.4%	4.4%
Irritability	1.1%	2.2%	7.1%

Source: Orexigen presentation

There were no serious adverse events attributed by the investigators to Empatic in the Phase IIb study, and differences between Empatic and placebo in neuropsychiatric scales (depression scale PHQ-9, anxiety scale GAD-7, mini mental status exam MMSE, cognitive function Cog State Battery and Columbia Suicide Severity Rating) were not statistically or clinically significant. Study discontinuations due to treatment-related adverse events are shown in Exhibit 33.

Exhibit 33: Selected treatment discontinuations due to adverse events in Phase IIb Empatic trial

Adverse event	Placebo	Empatic 360+120mg	Empatic 360+360mg
Overall discontinuation rate	40%	42%	40%
Discontinuation rate due to adverse events	13.5%	24.7%	23.1%
Insomnia	1.1%	2.2%	1.6%
Headache	0.0%	2.2%	1.1%
Urticaria (hives)	0.0%	2.2%	0.5%
Nausea	0.0%	0.0%	2.2%
Disturbance in attention	0.0%	1.1%	1.1%

Source: Orexigen presentation

The current label for zonisamide (the product is sold as Zonegran for treating epilepsy) states that it is teratogenic, saying that animal studies had shown a variety of fetal abnormalities, including cardiovascular defects, and embryo-fetal deaths occurred at maternal plasma levels similar to or lower than therapeutic levels in humans. As such, women of childbearing potential who are prescribed zonisamide are advised to use effective contraception, and zonisamide should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

It is reasonable to assume, therefore, that Empatic's label will recommend birth control for women of childbearing age, and the product is likely to be contraindicated in women who are pregnant or breastfeeding. As a result, Empatic's market is likely to be constrained, the product being reserved for overweight men and post-menopausal women.

The tolerability of Empatic has yet to be determined in a large Phase III study, and the presence of zonisamide at its highest approved dose has caused some concern in light of CNS-related adverse events associated with Zonegran (and also stated on its label). The most significant of these are psychiatric symptoms, including depression and psychosis; psychomotor slowing, difficulty with concentration, and speech or language problems, in particular word-finding difficulties; and somnolence or fatigue.

As with Vivus's Qnexa, the key sensitivity for Contrave and Empatic is the extent to which big pharma embraces fixed-dose combinations, given the relative strength of IP versus NCEs and/or fears over off-label generic substitution. Orexigen has a composition patent on Contrave running until 2025 and methods of use patent running until 2024. It also believes off-label generic threat is minimal, because of the pharmacokinetic profile of the SR formulations used in Contrave and Empatic. Furthermore, the exact doses used are not commercially available and the generic constituents are in any case expensive, so that it would cost around $10 per day to try to recreate the products with generics. Orexigen would therefore have flexibility to price below this, at say $5-7 per day. Off-label use of generics is a potential risk, although physicians might feel uncomfortable prescribing these types of drugs without an FDA label.

Financials

Our financial model for Orexigen is presented in Exhibit 34, and has been updated to include the $81.6m (including costs) that the company raised in July. The funding is expected to be used largely to help set up a small, specialist sales force (probably in the region of 50-75 reps) to support the initial launch of Contrave by Orexigen, before a deal is struck with a company that has a large, primary sales force. Typically, Orexigen would be expected to have a specialist sales force in place six months before launch, and as an NDA for Contrave is expected to be filed in the first half of 2010 our forecast operating costs in that year account for this.

Exhibit 34: Orexigen financial forecast

Note: Figures exclude payments under potential licensing deal(s) that have not yet been signed.

$'000s	2006	2007	2008	2009e	2010e
Year end 31 December					
PROFIT & LOSS					
Revenue	**88**	**88**	**88**	**88**	**88**
Cost of sales	0	0	0	0	0
Gross profit	88	88	88	88	88
EBITDA	**(27,127)**	**(58,534)**	**(88,592)**	**(53,802)**	**(42,296)**
Operating profit (before GW and except.)	**(27,171)**	**(58,672)**	**(89,039)**	**(54,202)**	**(42,696)**
Goodwill amortisation	(82)	2,273	1,338	1,500	1,500
Exceptionals	0	0	0	0	0
Share-based payment	(1,115)	(4,423)	(7,123)	(5,000)	(5,000)
Operating profit	**(28,368)**	**(60,822)**	**(94,824)**	**(57,702)**	**(46,196)**
Net interest	864	3,055	1,584	(900)	(700)
Profit before tax (norm)	**(26,307)**	**(55,617)**	**(87,455)**	**(55,102)**	**(43,396)**
Profit before tax (US GAAP)	**(27,504)**	**(57,767)**	**(93,240)**	**(58,602)**	**(46,896)**
Tax	0	0	0	0	0
Beneficial conversion for Series C preferred stock and other	(13,891)	(10)	0	0	0
Profit after tax (norm)	**(40,198)**	**(55,627)**	**(87,455)**	**(55,102)**	**(43,396)**
Profit after tax (US GAAP)	**(41,395)**	**(57,777)**	**(93,240)**	**(58,602)**	**(46,896)**
Average number of shares outstanding (m)	2.2	18.8	33.8	39.2	45.9
EPS - normalised ($)	(18.33)	(2.97)	(2.59)	(1.40)	(0.94)
EPS - US GAAP ($)	(18.88)	(3.08)	(2.76)	(1.49)	(1.02)
Gross margin (%)	100.0%	100.0%	100.0%	100.0%	100.0%
EBITDA margin (%)	N/A	N/A	N/A	N/A	N/A
Operating margin (before GW and except.) (%)	N/A	N/A	N/A	N/A	N/A
BALANCE SHEET					
Fixed assets	**2,175**	**3,395**	**4,557**	**5,159**	**5,259**
Intangible assets	0	0	0	0	0
Tangible assets	528	924	2,059	2,659	2,759
Investment in associates	0	0	0	0	0
Restricted cash and other	1,647	2,471	2,498	2,500	2,500
Current assets	**34,635**	**87,925**	**87,351**	**102,928**	**53,202**
Stocks	0	0	0	0	0
Debtors	0	0	0	0	0
Cash and available-for-sale securities	34,413	85,454	86,167	101,718	51,992
Other	222	2,471	1,184	1,210	1,210
Current liabilities	**(4,991)**	**(13,277)**	**(26,489)**	**(21,230)**	**(15,088)**
Creditors	(4,903)	(8,454)	(18,810)	(16,142)	(15,000)
Other creditors	0	0	0	0	0
Short-term borrowings	0	(4,735)	(7,591)	(5,000)	0
Deferred income	(88)	(88)	(88)	(88)	(88)
Long-term liabilities	**(1,769)**	**(13,160)**	**(11,625)**	**(6,537)**	**(5,567)**
Long-term borrowings	0	(11,072)	(8,800)	(3,800)	(3,800)
Deferred income	(1,235)	(1,147)	(1,058)	(970)	0
Provisions and other long-term liabilities	(534)	(941)	(1,767)	(1,767)	(1,767)
Associated with assets held for sale	0	0	0	0	0
Net assets	**30,050**	**64,883**	**53,794**	**80,320**	**37,806**
CASH FLOW					
Operating cash flow	**(21,808)**	**(54,388)**	**(74,696)**	**(56,558)**	**(43,526)**
Net interest	0	(581)	1,323	(900)	(700)
Tax	0	0	0	0	0
Capex	(427)	(534)	(1,647)	(1,000)	(500)
Purchase of intangibles	0	0	0	0	0
Acquisitions/disposals	0	0	0	0	0
Financing	29,141	88,441	75,202	81,600	0
Dividends	0	0	0	0	0
Other	89	219	(67)	0	0
Net cash flow	6,995	33,157	115	23,142	(44,726)
Opening net debt/(cash)	**(27,418)**	**(34,413)**	**(69,647)**	**(69,776)**	**(92,918)**
HP finance leases initiated	0	0	0	0	0
Other	0	2,077	14	0	0
Closing net debt/(cash)	**(34,413)**	**(69,647)**	**(69,776)**	**(92,918)**	**(48,192)**

Source: Edison Investment Research/company accounts

Vivus

Year end	Revenue ($m)	PBT ($m)*	EPS ($)*	DPS ($)	P/E (x)	Yield (%)
12/07	54.7	6.6	0.02	0.00	N/A	N/A
12/08	102.2	(5.2)	(0.08)	0.00	N/A	N/A
12/09e*	45.4	(53.6)	(0.72)	0.00	N/A	N/A
12/10e*	11.4	(60.4)	(0.75)	0.00	N/A	N/A

Note: *PBT and EPS exclude one-off and non-cash items.

Investment summary: Phase III efficacy leader

Vivus's potential main value driver, Qnexa, has proved to be the most efficacious of the three anti-obesity projects that have completed pivotal development. A US filing, most likely for full, mid and low doses of Qnexa, is expected by the end of 2009, and at the current price the market seems to be pricing in a large part of a potential big pharma licensing deal. A recent $109m fund-raising should strengthen Vivus's hand in negotiations with potential licensees.

Comfortably meets FDA benchmarks

In its last two remaining pivotal studies, Qnexa showed placebo-adjusted weight loss of up to 9.4% of baseline body weight over 56 weeks, comfortably meeting both US FDA efficacy benchmarks and putting it well ahead of the other two late-stage anti-obesity projects (Contrave and lorcaserin) in terms of efficacy. A 650-patient extension study is proceeding, comprising active and placebo groups, but is not required for US approval.

Bargaining position stronger

Vivus recently completed a $109m (gross) fund-raising, and this should strengthen the company's hand as it seeks to attract a licensing deal with a big pharma partner with a strong primary sales force to maximise Qnexa's potential. Although it has not disclosed specifically how the funds could be used, we expect that an initial in-house launch (before signing a deal) is a possibility.

Questions surround reformulation concept

Qnexa's side-effect profile has been shown to be relatively clean, and the project has demonstrated important cardiovascular benefits. However, it has yet to be seen whether big pharma sees the IP position as being strong enough, and whether it will buy into what is effectively a reformulation of two established, off-patent drugs.

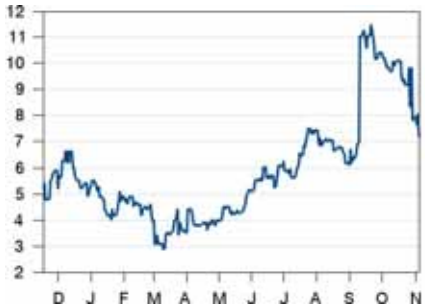
Priced in?

We view Qnexa as the most promising late-stage anti-obesity project, and expect it to seize the greatest share of the initial market, and Vivus's market price rose strongly on publication of the Phase III data. Therefore it seems that much of the value of a big pharma licensing deal might already be priced in at this level.

Price	$8.05*
Market cap	$553m

** Priced as at 4 November 2009.*

Share price graph



Share details

Code	VVUS
Listing	NASDAQ
Shares in issue	80.5m

Price

52-week	High	Low
	$12.88	$2.72

Business

Vivus is a NASDAQ-listed biotechnology company developing therapeutics for treating obesity and sexual health. It markets an erectile dysfunction treatment, and in 2007 licensed rights to Evamist, a transdermal estradiol spray for menopause symptoms, to KV Pharmaceutical.

Recent news flow

Sep 2009 – $109m fund-raising closes

Sep 2009 – Positive data from final two Phase III studies of Qnexa

Mar 2009 – Full-year 2008 financial results

Dec 2008 – Positive data from first Phase III trial of Qnexa

Aug 2008 – $65m fund-raising closes

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Investment summary: Qnexa key in the near term

Although Vivus's R&D pipeline comprises a number of projects in sexual health in addition to Qnexa (phentermine plus topiramate), the company's near-term investment case is centred on obesity. Qnexa has shown highly positive data in its Phase III trials, making it the most efficacious anti-obesity project of the three that have completed pivotal development. However, a key big pharma licensing deal has yet to be signed.

Vivus recently raised $109m (gross) and says a filing for Qnexa with the US FDA should be made by the end of 2009. The company has repeatedly stated that it is not dependent on a licensee to bring Qnexa to the market, although one is clearly needed to target primary care prescribers and enable the product to seize maximum sales. Vivus has made no public statements regarding the possibility of launching Qnexa itself. It generates relatively modest revenue on sales of its erectile dysfunction drug Muse (alprostadil).

In September Vivus announced highly positive data from all three pivotal trials of Qnexa; 56-week data from the EQUIP and CONQUER trials exceeded the already promising levels of weight loss seen in EQUATE, an earlier six-month trial. We believe that the strength of these data should put Vivus in pole position regarding the signing of a licensing deal, although key uncertainties remain as far as whether big pharma believes in the strength of the IP and the economic potential of a product comprising a formulation of two marketed, off-patent drugs.

Qnexa is a fixed-dose combination of phentermine and topiramate, designed to complement the former's appetite-reducing 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 the agent's therapeutic window. The Phase III development programme for Qnexa comprises four studies in a total of almost 4,500 patients, although only three of these (EQUATE, EQUIP and CONQUER) are pivotal.

EQUATE data

This was a six-month study that looked at mid and full doses of Qnexa; it was the only Phase III trial also to include active comparator groups (ie, phentermine and topiramate monotherapy). 756 obese patients were recruited with average weight of 101.2kg and baseline BMI of 36.3kg/m^2 at 32 US sites. Results are summarised in Exhibit 35.

Exhibit 35: Phase III EQUATE data (intent-to-treat basis, with last observation carried forward)

	Placebo	Phentermine 7.5mg	Topiramate 46mg	Qnexa 7.5/46
Weight loss	1.71%	5.45%	5.13%	8.46%
Completion	68%	72%	73%	73%
5%+ weight loss	15%	43%	39%	62%
10%+ weight loss	7%	12%	19%	39%
Placebo-adjusted weight loss	N/A	3.74%	3.42%	6.75%

	Placebo	Phentermine 15mg	Topiramate 92mg	Qnexa 15/92
Weight loss	1.71%	6.06%	6.44%	9.21%
Completion	68%	74%	72%	69%
5%+ weight loss	15%	46%	49%	66%
10%+ weight loss	7%	21%	24%	41%
Placebo-adjusted weight loss	N/A	4.35%	4.73%	7.50%

Source: Edison Investment Research

All the data above were statistically significant, percentage weight loss for mid and full-dose Qnexa (vs placebo and standalone actives) with $p<0.001$, and the remaining parameters with $p<0.0001$.

EQUIP (OB-302)

This was a 56-week trial in 1,267 morbidly obese patients (1,050 females and 217 males) without metabolic co-morbidities, across 93 US centres. The average BMI was 42.1kg/m^2, and the average weight at baseline was 116kg. All the data summarised in Exhibit 36 were statistically significant ($p<0.0001$), and full-dose Qnexa-treated patients additionally showed significant improvements in blood pressure, triglycerides and cholesterol.

Exhibit 36: Phase III EQUIP data (intent-to-treat basis, with last observation carried forward)

	Placebo	Qnexa 3.75/23	Qnexa 15/92
Weight loss	1.6%	5.1%	11.0%
Completion	47%	57%	59%
5%+ weight loss	17%	45%	67%
Placebo-adjusted weight loss	N/A	3.5%	9.4%

Source: Edison Investment Research

For the completer population, 60% of the full-dose Qnexa patients lost at least 10% of their baseline weight, and 43% of the full-dose Qnexa patients lost at least 15% of their baseline weight.

EQUIP was the only Phase III trial to investigate a low dose of Qnexa (3.75mg phentermine plus 23mg topiramate), and this had not been expected to show efficacy. The fact that efficacy has been seen even at this dose (with statistical significance) came as a surprise, and accordingly the US regulatory filing is now likely to include an application to approve all three doses. Vivus has yet to decide its strategy on dosing, but one obvious option would be to use the low dose to start certain patients before titrating up. Alternatively, patients could initially take the high dose, and after seeing a significant amount of weight loss they could be switched to the low dose for future maintenance of their body weight.

CONQUER (OB-303)

This was a 56-week study in 2,487 overweight and obese patients (1,737 females and 750 males) with metabolic co-morbidities (high blood pressure, high cholesterol or type 2 diabetes); average body weight was 103kg, and BMI 36.6kg/m^2 at baseline. All the data summarised in Exhibit 37 were statistically significant ($p<0.0001$).

Exhibit 37: Phase III CONQUER data (intent-to-treat basis, with last observation carried forward)

	Placebo	Qnexa 7.5/46	Qnexa 15/92
Weight loss	1.8%	8.4%	10.4%
Completion	57%	69%	64%
5%+ weight loss	21%	62%	70%
Placebo-adjusted weight loss	N/A	6.6%	8.6%

Source: Edison Investment Research

A predefined subset analysis of higher-risk patients, defined as those in the upper 25th percentile of a specific co-morbidity, who were treated with full-dose Qnexa for 56 weeks, showed changes in several cardiovascular risk factors. Systolic blood pressure was reduced from 147mmHg at baseline by 20mmHg, compared with a 14mmHg reduction in the placebo group ($p<0.0001$), and Qnexa-treated patients also took significantly fewer blood pressure medications vs placebo.

Triglyceride levels were reduced from 268mg/dl at baseline by 98mg/dl, compared with a 42mg/dl decrease from 262mg/dl at baseline in the placebo group ($p<0.0001$). Haemoglobin A1c levels were reduced by 0.6 points from 7.3% at baseline, compared with a 0.1-point reduction from 7.4% at baseline for placebo recipients ($p<0.0001$), in the presence of a significant reduction in antidiabetic medications in Qnexa-treated patients.

Around 650 patients from the CONQUER study are continuing in OB-305, a one-year extension trial. This comprises active and placebo groups, as appropriate. It is not required for US NDA filing.

Qnexa is separately in a late-stage programme in type 2 diabetes patients, the aim of which is to generate data for an additional indication. Two completed Phase II studies, OB-202 (200 patients treated for six months) and DM-230 (130 patients treated for 12 months), generated positive results in a number of measures. Phase III diabetes studies are in the planning stage.

Safety

Topline pivotal data for Qnexa have not shown any unexpected events, with the most commonly reported side-effects being dry mouth (seen in 17-21% of full-dose Qnexa patients), tingling (19-21%), constipation (14-17%), upper respiratory infection (12-13%), altered taste (8-10%) and insomnia (8-10%) across the 3,749 patients participating in the two 56-week studies, EQUIP and CONQUER (Exhibit 38).

Exhibit 38: Adverse events reported in EQUIP and CONQUER by ≥5% in any group

Adverse event	EQUIP (n=1,264)			CONQUER (n=2,485)		
	Placebo	Qnexa low	Qnexa full	Placebo	Qnexa mid	Qnexa full
Dry mouth	3.7%	6.7%	17.0%	2.4%	13.5%	20.8%
Tingling	1.9%	4.2%	18.8%	2.0%	13.7%	20.5%
Constipation	6.8%	7.9%	14.1%	5.9%	15.1%	17.4%
Upper respiratory infection	10.9%	15.8%	12.3%	12.9%	12.2%	13.4%
Altered taste	1.0%	1.3%	8.4%	1.1%	7.4%	10.4%
Insomnia	4.9%	5.0%	7.8%	4.7%	5.8%	10.3%
Headache	10.1%	10.4%	11.9%	9.1%	7.0%	10.2%
Dizziness	4.1%	2.9%	5.7%	3.1%	7.2%	10.0%
Common cold	7.2%	12.5%	9.0%	8.7%	10.6%	9.9%
Sinus infection	5.5%	7.5%	7.2%	6.7%	6.8%	8.6%
Back pain	5.1%	5.4%	5.5%	4.9%	5.6%	7.2%
Nausea	4.7%	5.8%	7.2%	4.2%	3.6%	6.8%
Blurred vision	3.1%	6.3%	4.5%	3.6%	4.0%	6.0%
Bronchitis	4.3%	6.7%	5.5%	4.3%	4.4%	5.2%
Diarrhoea	4.5%	5.0%	4.7%	4.8%	6.4%	5.8%
Urinary tract infection	3.5%	3.3%	4.7%	3.7%	5.2%	5.4%
Cough	3.5%	3.3%	5.1%	3.0%	3.8%	4.8%
Influenza	4.7%	7.5%	5.1%	4.3%	4.6%	3.5%

Source: Vivus presentation

18% of full-dose Qnexa patients discontinued because of adverse events (most commonly insomnia, depression, tingling and irritability), vs 12% of low and mid-dose Qnexa and 9% of placebo recipients (Exhibit 39).

Exhibit 39: EQUIP and CONQUER completion rates and discontinuations due to adverse events

	Placebo	Qnexa low	Qnexa mid	Qnexa full
Number of subjects	1,508	241	498	1,507
Completers	53%	57%	69%	62%
Discontinuations due to AEs	9%	12%	12%	18%
Blurred vision	0.5%	2.1%	0.8%	0.7%
Headache	0.7%	1.7%	0.2%	0.9%
Insomnia	0.4%	0.0%	0.4%	1.7%
Depression	0.2%	0.0%	0.8%	1.4%
Tingling	0.0%	0.4%	1.0%	1.2%
Irritability	0.1%	0.8%	0.8%	1.2%
Anxiety	0.3%	0.0%	0.2%	1.1%
Dizziness	0.2%	0.4%	1.2%	0.8%

Source: Vivus presentation

Monthly assessments using prospective psychometric instruments (according to FDA guidance) showed no signal for risk of suicidality. There were no suicide attempts or suicidal behaviour in the 56-week studies, and there was no signal for suicidal ideation across all treatment groups including placebo. Moderate to severe depression or depressed mood were less than 2% and were similar among patients in the Qnexa and placebo groups.

Vivus also completed a QT study evaluating Qnexa subjects, and this showed no signal for QT prolongation. Subjects taking Qnexa also underwent cognitive and psychomotor testing using

validated, FDA-accepted methodologies, showing no clinically significant change in overall cognitive function or effect on psychomotor skills.

Several important secondary endpoints, including blood pressure benefits, have also shown positive results (Exhibit 40).

Exhibit 40: Improvements in cardiovascular and diabetes risk factors

Risk factor	p values in EQUIP (ITT)		p values in CONQUER (ITT)	
	Qnexa low	Qnexa full	Qnexa mid	Qnexa full
Waist circumference	<0.0001	<0.0001	<0.0001	<0.0001
Systolic blood pressure	0.002	<0.0001	<0.0001	<0.0001
Diastolic blood pressure	Not significant	0.0002	Not significant	0.0031
Triglycerides	Not significant	<0.0001	<0.0001	<0.0001
Total cholesterol/HDL ratio	0.0148	<0.0001	<0.0001	<0.0001
Total cholesterol	0.05	0.0014	0.0345	<0.0001
LDL	Not significant	0.0157	Not significant	0.0069
HDL	Not significant	0.0005	<0.0001	<0.0001
Haemoglobin A1c	NA	NA	<0.0001	<0.0001
Fasting blood glucose	NA	NA	0.0047	<0.0001
OGTT insulin	NA	NA	<0.0001	<0.0001
Insulin resistance (HOMA)	NA	NA	0.0007	<0.0001

Source: Vivus presentation

In terms of the IP position, Vivus owns patents protecting the Qnexa formulation, and while competitors could in theory attempt to mimic Qnexa's action by using generic topiramate (which comes off patent this year) and phentermine (an established, off-patent drug), dosing appears to be too complex to make this realistic. Nevertheless, big pharma clearly has yet to buy into the concept of established drugs reformulated for new uses.

Financials

In September, Vivus raised $109m (gross) in an equity offering priced at $10.5 per share, although it has made no indication as to the specific use of the proceeds; it is possible that Vivus might be considering a Qnexa launch with its own sales force, targeting specialist physicians (eg, endocrinologists), as Orexigen is doing with Contrave. The extra cash should also strengthen the company's hand in negotiations with potential licensees.

Vivus's revenue line comprises US and international in-market sales of Muse, as well as up-front and milestone payments received from licensees. Much of the 2007, 2008 and 2009 revenue is a result of the $140m milestone received from KV Pharmaceutical under the Evamist deal (received in August 2007), which has been booked in full as a deferred revenue item on the balance sheet, and is being recognised in the income statement over around two years.

Our financial model for Vivus is presented in Exhibit 41, and this assumes R&D spending of around $70m in 2009 and $40m in 2010 as late-stage Qnexa spending winds down. We show the recently announced fund-raising as a cash financing inflow of $103.2m (net) in 2009.

Exhibit 41: Vivus financial forecast

Note: Excludes potential up-front fees under deal(s) yet to be signed.

$'000s	2006	2007	2008	2009e	2010e
Year ending 31 December					
PROFIT & LOSS					
Revenue	**17,245**	**54,698**	**102,233**	**45,396**	**11,413**
Cost of sales	(11,933)	(12,097)	(11,956)	(11,600)	(12,000)
Gross profit	5,312	42,601	90,277	33,796	(587)
EBITDA	**(19,444)**	**3,529**	**236**	**(49,937)**	**(55,714)**
Operating profit (before GW and except.)	**(20,518)**	**2,449**	**(905)**	**(51,137)**	**(56,914)**
Goodwill amortisation	0	0	0	0	0
Exceptionals	0	0	0	0	0
Share-based payment	(2,065)	(3,903)	(4,718)	(5,000)	(5,000)
Operating profit	**(22,583)**	**(1,454)**	**(5,623)**	**(56,137)**	**(61,914)**
Net interest	979	4,165	(4,314)	(2,500)	(3,500)
Profit before tax (norm)	**(19,539)**	**6,614**	**(5,219)**	**(53,637)**	**(60,414)**
Profit before tax (US GAAP)	**(21,604)**	**2,711**	**(9,937)**	**(58,637)**	**(65,414)**
Tax	(20)	(5,095)	(3)	(12)	0
Profit after tax (norm)	**(19,559)**	**1,519**	**(5,222)**	**(53,649)**	**(60,414)**
Net unrealised gain/(loss) on securities	19	(57)	0	0	0
Profit after tax (US GAAP)	**(21,605)**	**(2,441)**	**(9,940)**	**(58,649)**	**(65,414)**
Average number of shares outstanding (m)	48.1	58.5	63.7	75.0	80.3
EPS - normalised ($)	(0.41)	0.02	(0.08)	(0.72)	(0.75)
EPS - US GAAP ($)	(0.45)	(0.04)	(0.16)	(0.78)	(0.81)
Gross margin (%)	30.8%	77.9%	88.3%	74.4%	(5.1%)
EBITDA margin (%)	NA	6.5%	0.2%	N/A	N/A
Operating margin (before GW and except.) (%)	NA	4.5%	(0.9%)	N/A	N/A
BALANCE SHEET					
Fixed assets	**9,249**	**8,117**	**8,770**	**7,307**	**6,557**
Intangible assets	0	0	0	0	0
Tangible assets	8,549	7,417	6,726	5,976	5,226
Investment in associates	0	0	0	0	0
Restricted cash and others	700	700	2,044	1,331	1,331
Current assets	**68,965**	**191,172**	**198,852**	**221,111**	**160,187**
Stocks	3,327	2,567	3,041	3,200	3,300
Debtors	4,359	4,202	4,157	4,200	4,300
Cash and available-for-sale securities	58,871	179,510	187,910	209,711	148,587
Other	2,408	4,893	3,744	4,000	4,000
Current liabilities	**(11,401)**	**(101,362)**	**(63,972)**	**(31,260)**	**(30,000)**
Creditors	(9,562)	(17,179)	(32,114)	(30,000)	(30,000)
Other creditors	(1,245)	0	0	0	0
Short-term borrowings	0	0	0	0	0
Deferred income	(594)	(84,183)	(31,858)	(1,260)	0
Long-term liabilities	**(13,673)**	**(38,180)**	**(12,437)**	**(16,809)**	**(16,809)**
Long-term borrowings	(11,488)	(5,062)	(11,177)	(16,809)	(16,809)
Deferred income	(2,185)	(33,118)	(1,260)	0	0
Provisions and other long-term liabilities	0	0	0	0	0
Associated with assets held for sale	0	0	0	0	0
Net assets	**53,140**	**59,747**	**131,213**	**180,349**	**119,935**
CASH FLOW					
Operating cash flow	**(19,509)**	**124,082**	**(63,554)**	**(84,111)**	**(57,174)**
Net interest	(518)	(518)	(831)	(2,500)	(3,500)
Tax	(13)	(4,414)	(64)	(12)	0
Capex	(465)	(282)	(450)	(450)	(450)
Purchase of intangibles	0	0	0	0	0
Acquisitions/disposals	0	0	0	0	0
Financing	46,079	2,710	75,846	103,241	0
Dividends	0	0	0	0	0
Other	19	(57)	422	0	0
Net cash flow	25,593	121,521	11,369	16,169	(61,124)
Opening net debt/(cash)	**(21,790)**	**(47,383)**	**(174,448)**	**(176,733)**	**(192,902)**
HP finance leases initiated	0	0	0	0	0
Other	0	5,544	(9,084)	0	0
Closing net debt/(cash)	**(47,383)**	**(174,448)**	**(176,733)**	**(192,902)**	**(131,778)**

Source: Edison Investment Research/company accounts

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