



## Obesity Drugs Ripe For the Picking

### Partnerships Expected Prior to FDA Approval

Companies:

**Arena Pharmaceuticals (ARNA)**  
**Orexigen Therapeutics (OREX)**  
**Vivus (VVUS)**

Products:

**Qnexa** (NDA submitted, Vivus)  
**Lorcaserin** (NDA submitted, Arena Pharmaceuticals)  
**Contrave** (phase III, Orexigen Therapeutics)

- The FDA has accepted the New Drug Applications (NDA) for Vivus's (VVUS) Qnexa and Arena's (ARNA) lorcaserin, which are vying to become the first new prescription obesity drug in the U.S. in more than a decade.
- But it is Orexigen's (OREX) Contrave that may be the first of the late-stage obesity drugs to attract a large pharmaceutical partner.
- All three obesity drugs have at least a 70% *inThought* Approvability Index score, although we continue to project modest delays for lorcaserin approval and significant delays for Qnexa approval.
- Although Contrave may be the first to be licensed, *inThought* believes that partnerships for Qnexa and lorcaserin are also likely in the next several weeks.
- Many large pharmaceutical companies have stated goals of marketing an obesity agent. Coupled with attractive valuations, especially for Orexigen and Arena, partner candidates are unlikely to wait for FDA approval when competition for licensing would become intense.

The FDA has accepted the New Drug Applications (NDA) for Vivus's Qnexa and Arena's lorcaserin. Orexigen plans to file for Contrave approval in the next few months. Securing a partner is the next major catalyst for all three obesity drugs. Last year we concluded that potential partners would wait for these drugs to get closer to approval before pulling the trigger on a licensing deal or an acquisition. We now believe that, with the goal line in sight, partners will emerge over the next several weeks.

### Qnexa

Vivus' Qnexa is a combination of low-dose phentermine and topiramate. Its PDUFA date for an FDA decision on approval is October 28, 2010. Qnexa's approval package, designed under a Special Protocol Assessment (SPA), consists of three phase III trials in over 4,500 patients: EQUATE (OB-301), EQUIP (OB-302) and CONQUER (OB-303).

The EQUATE study was a 28-week randomized, double-blind, placebo-controlled, 7-arm, prospective trial with patients randomized to receive once-a-day treatment with mid- or full-dose Qnexa, the respective phentermine and topiramate constituents, or placebo. The EQUIP and CONQUER studies were 56-week, randomized, double-blind, placebo-controlled, 3-arm, prospective trials with patients randomized to receive once daily treatment with low-, mid-, or full-dose Qnexa, or placebo.

### Probability of Approval and Revenue Potential

Qnexa's efficacy is undisputed, but its safety is suspect. Following discussions with our expert consultants, we believe the FDA will request additional data to support Qnexa's safety prior to approval, particularly in individuals with depression. We continue to model an August 2011 approval. The *inThought* Approvability Index (IAI) for Qnexa is 74%(C). In spite of a later approval estimate, Qnexa has a slightly higher IAI score than lorcaserin because of superior clinical experience with its individual components.

If approved, Qnexa will likely be used sparingly. We model worldwide revenue of \$1,019 million in 2017. Adversities such as cognitive impairment, depression, and liver concerns, are likely to limit use of Qnexa to severely obese patients without psychiatric illness, liver issues, and other risk factors.

Although we do not assume a pristine safety profile, our model assumes that disastrous adversities, such as those seen with rimonabant and phen-fen, do not occur. Confidence in Qnexa's real world profile is bolstered by the fact that its components are already extensively prescribed.

**Table 1: Unpartnered Obesity Agents**

Drug Name	Developer	Phase	IAI*	Estimated US Approval	2017 U.S. Revenue (million)	2017 Worldwide Revenue (million)
<b>Qnexa</b> (phentermine/ topiramate)	Vivus	NDA submitted	74%(C)	August 2011	\$770	\$1,019
<b>Lorcaserin</b>	Arena Pharmaceuticals	NDA submitted	70%(C)	March 2011	\$757	\$968
<b>Contrave</b> (naltrexone/ bupropion)	Orexigen Therapeutics	III	74%(A)	March 2011	\$575	\$722

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

\* IAI = *inThought* Approvability Index (probability of approval)

## Securing a Partner

We previously stated that potential partners for Qnexa would wait for data from EQUIP and CONQUER, and possibly also for results from DM-231, a second extension study in diabetes. Potential bidders have now had sufficient time to examine those data. Compared to lorcaserin and Contrave, a partner for Qnexa would have to be willing to take on some phen-fen-like safety risk - Qnexa has the best weight loss of the three drugs, but also the highest likelihood that safety issues will delay approval or, worse, lead to market withdrawal. Still, the drug is likely to be a hot ticket following its FDA approval, and *inThought* believes it likely that at least one company will want to step in front of that event.

## Lorcaserin

Arena Pharmaceutical's lorcaserin is similar to the ill-fated Redux (dexfenfluramine) in its mechanism of action. But with its higher selectivity for the serotonin 2c (5HT2c) receptor than for the serotonin 2b (5HT2b) receptor, lorcaserin appears to have an acceptable cardiac valvulopathy risk profile. The FDA has assigned a PDUFA date of October 22, 2010 for the review of lorcaserin for obesity.

Lorcaserin's approval package includes the most extensive safety record of the late stage candidates. The NDA includes data from 18 clinical trials totaling 8,576 patients. Together, the BLOOM and BLOSSOM trials have evaluated about 7,200 patients for up to two years.

Overall, safety appears manageable. Importantly, lorcaserin lacks the neuropsychiatric concerns that may be associated with Qnexa. Its weakness, however, is efficacy, with placebo adjusted weight loss under 5% in some studies.

## Probability of Approval and Revenue Potential

The IAI score for lorcaserin is 70%(C). Cognizant of the possibility that physicians will prescribe lorcaserin with phentermine, the FDA could ask for a combination trial prior to approval, or at the least include strong labeling against the combination. Without phentermine, lorcaserin offers efficacy no better than marketed weight loss drugs.

We project a March 2011 approval, a five month delay from the PDUFA date. In our model lorcaserin slightly underperforms Qnexa, generating \$993 million in worldwide sales by 2017.

## Securing a Partner

Lorcaserin may be the most challenging of the three phase III agents to partner. To date, no controlled studies evaluating lorcaserin and phentermine in combination have been conducted, meaning any future partner must be willing take on the possibility that the combination could be highly efficacious and / or highly toxic. Arena has little incentive or resources to develop lorcaserin with phentermine. A partner on the other hand may be unimpressed by half a billion in annual revenue potential, but interested in conducting the phentermine combo trials to unlock the multi-billion dollar potential of lorcaserin.

## Contrave

Contrave is a fixed-dose combination of sustained release naltrexone and bupropion. In combination, the two agents are thought to stimulate proopiomelanocortin (POMC) neuronal firing and modulate food cravings through an effect on the reward pathways. Three

phase III trials of Contrave (NB-301, NB-303 and NB-304) have met their endpoints. Orexigen plans to submit an NDA for the combination agent in the first half of 2010.

## Probability of Approval and Revenue Potential

Experts with whom we have spoken remain enthusiastic regarding Contrave's potential, stressing that it is one of the few obesity drugs in development that is truly a product of basic science, designed rationally rather than empirically. Additional details of the drug's improvements in markers of cardiometabolic risk, particularly hsCRP, waist circumference, fasting HDL, and fasting triglycerides presented at last year's Obesity Society meeting were favorably received.

The IAI score for Contrave is 74%(A), largely driven by the relatively benign safety profile and the extensive clinical experience with the active ingredients of Contrave. We continue to estimate U.S. approval in March 2011. 2017 revenue, if

Contrave's association with improvements in markers of cardio-metabolic risk was favorably received at last year's Obesity Society meeting.

approved, reaches \$722 million worldwide in our model.

### **Securing a Partner**

Orexigen's Contrave has been overshadowed by the attention showered on Qnexa and lorcaserin. Given the issues around Qnexa safety and the combination of lorcaserin with phentermine, it is likely that Contrave will be the first obesity drug to find a partner, perhaps even before its NDA is submitted.

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