EDISON

Orexigen Therapeutics

Outlook

Contrave continues rebound

Pharma & biotech

Orexigen's consumer-focused re-launch of Contrave continues to be successful with a 39% increase in prescriptions in the United States in Q117 compared to Q416. Outside of the US, progress continues as the product has launched in 14 countries, with another seven expected by the end of the year, including the Nordic countries, where Orexigen has just signed a local commercial and distribution partner.

Year end	Revenue ($m)	PBT* ($m)	EPS* ($)	DPS ($)	P/E (x)	Yield (%)
12/15	24.5	(67.3)	(5.24)	0.0	N/A	N/A
12/16	33.7	(138.1)	(9.73)	0.0	N/A	N/A
12/17e	87.3	(139.2)	(8.23)	0.0	N/A	N/A
12/18e	160.3	(75.5)	(4.86)	0.0	N/A	N/A

Note: *PBT and EPS are normalised, excluding amortisation of acquired intangibles, exceptional items and share-based payments.

Successful patient-centric campaign

A shift from previous partner Takeda's healthcare provider-focused marketing to a campaign focused on consumers (but with continued detailing of high prescribing physicians) has yielded a dramatic increase in prescriptions. Prescriptions increased 39% in Q117 versus Q416 and they now have approximately 50% of the branded obesity market (~8% of the total) according to Symphony Health.

Telemedicine strategy has potential

Orexigen is currently engaged in a telemedicine pilot program and will be in 47 states as by the end of May. Telemedicine has two main benefits, time (as patients do not have to travel to/from a doctor and wait to be seen) and a more comfortable, less intimidating experience for those wishing assistance with weight loss. While early, this strategy has the potential to reach a significant number of patients who are currently not being treated.

Continued progress in international launches

Contrave (Mysimba outside the US), has now launched in 14 countries, including South Korea, Spain and Poland. Launches in the UK and Ireland are expected in Q217. Also, due to a recently signed commercial and distribution agreement with Navamedic ASA, a launch in four Nordic countries (Denmark, Finland, Norway and Sweden) is expected in Q417 (as well as another three launches through other partners). Orexigen is partnered in a total of 44 countries outside of the US.

Valuation: $194m or $12.76 per share

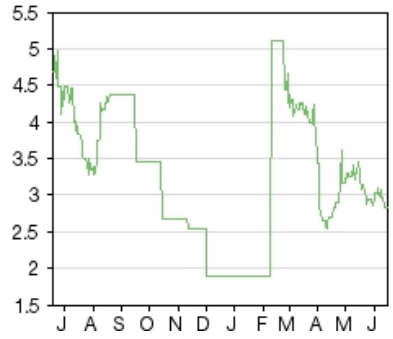
We are adjusting our valuation from $193m ($12.70/share) to $194m ($12.76/share). We increased our US Orexigen sales estimates, altered the launch trajectory for product sales outside of the US (though we left peak sales largely the same) and increased our SG&A spending estimates. Orexigen's financing requirement is now $90m through to 2020, although this does not include the $245m in convertible debt due in that year. Also, our per-share valuation does not include any potential equity dilution to cover the financing requirement.

16 June 2017

Price	**US$2.84**
Market cap	**US$43m**

Net debt ($m), including restricted, at 31 March 2017	51
Shares in issue	15.2m
Free float	64.8%
Code	OREX
Primary exchange	NASDAQ
Secondary exchange	N/A

Share price performance



%	1m	3m	12m
Abs	(17.7)	(31.7)	(37.9)
Rel (local)	(18.7)	(33.1)	(47.1)

52-week high/low	US$5.4	US$1.7

Business description

Orexigen Therapeutics is a biopharmaceutical company focusing on obesity treatments. It recently reacquired the rights to sell its sole product, weight management treatment Contrave, in the US from its previous partner, Takeda. Contrave was launched in the US in October 2014 and approved in the EU in March 2015 under the trade name Mysimba.

Next events

Launches in nine additional countries	2017

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Investment summary

Company description: Pure play in obesity

Headquartered in La Jolla, California, Orexigen is a biopharmaceutical company focused on the treatment of obesity. In October 2014 it launched Contrave in the US as an addition to a reduced-calorie diet and increased exercise in overweight (with comorbidity factors) and obese adults. Orexigen owns the commercialization rights to Contrave in the US and is currently marketing it with a 160-person salesforce. Known as Mysimba in international markets, the product is partnered in 44 countries outside the US and has launched in 14 of them. NASDAQ-listed, Orexigen was founded in 2002 and went public in April 2007. An additional $510m in capital has been raised since then. Orexigen currently employs 132 people full-time and employs a contract sales force.

Valuation: Highly dependent on sales trajectory

We are adjusting our valuation from $193m ($12.70/share) to $194m ($12.76/share). This change is due to an increase in our US Orexigen sales estimates and is mitigated by a more conservative launch trajectory for product sales outside of the US (though peak sales are largely the same) and higher SG&A spending estimates. Our fair value is based on an NPV analysis of the FCF from Contrave/Mysimba and the company's ongoing costs for R&D and SG&A, to which we apply a 10% discount rate, appropriate for a biotechnology company with an approved and marketed product. Our analysis is highly sensitive to Orexigen's ability to penetrate the vast obesity market, with a large swing factor in fair value on small changes in penetration.

Financials: Heavy marketing spend expected to pay dividends

Sales of Contrave in the US were $14.8m in Q117, up 12% compared to Q116. They also booked $4.3m in sales of Contrave to international partners. Due to an aggressive consumer-focused campaign (which helped increase Contrave prescriptions by 39% in Q117 compared to Q416), operating expenses were $66.8m in the quarter, including $55.2m in SG&A. These expenses are expected to decline over the course of the year. The company is currently guiding for $180-200m in cash operating expenses for 2017. It is important to note that in 2016, the company had guided for $160-180m in cash operating expenses but spent $146m, 9-19% lower than guidance. The company had $126.6m in cash, restricted cash and marketable securities at the end of Q117 and is guiding for a cash balance of $40-50m at the end of 2017. Our estimated financing requirement is now $90m through 2020 (not including the $245m in convertible debt due in that year) and we continue to expect profitability in 2021. Also, our per share valuation does not include any potential equity dilution.

Sensitivities: Commercialization risk dominates

Orexigen is subject to the execution risks associated with a pharmaceutical company in the midst of a commercial launch. Additionally, due to under-reimbursement for medical therapies for obesity, out-of-pocket costs for Contrave are relatively high ($90 per month for those without insurance coverage for Contrave if they have a savings card) making it a tougher sell. Their main competitor, which holds over 80% on the market, is phentermine, part of the amphetamine class and currently generic. While it does have serious side effects normally associated with amphetamines, euphoria and other "feel good" effects of the drug makes it unlikely that it will lose its market leading position without regulatory action. There are also intellectual property concerns as Contrave is a combination of two generic substances, naltrexone and bupropion though it does have 11 FDA orange book listed patents that expire between 2024 and 2032. Orexigen is currently involved in Paragraph IV litigation with Actavis over their filing for approval of a generic version of Contrave. While we expect the patents to hold up, the bench trial is scheduled to begin in June 2017 and if Actavis emerges victorious, a generic Contrave could be available after Contrave's exclusivity period expires in September 2017.

Orexigen: Taking on a big market

Orexigen offers a pure-play investment in the treatment of obesity, a rapidly growing yet relatively underserved market. It had initially been partnered in the US with Takeda who had ~900 reps detailing Contrave. Although it became the #1 branded obesity treatment thanks to its efficacy and clean safety profile, prescriptions plateaued and Orexigen announced it was re-acquiring Contrave rights in the US in March of 2016 (the acquisition was completed in August 2016). Since launching a patient-focused campaign at the beginning of 2017, prescriptions for Contrave quickly rebounded and surpassed the levels attained by Takeda, which was strictly focused on marketing to physicians. Contrave, which is known as Mysimba in most international markets, has now launched in 14 countries, including South Korea, Spain and Poland and is partnered in an additional 30.

Contrave

Contrave aims to target the behavioral mechanisms of craving and reward that can lead to overeating. The extended-release (ER) tablets combine bupropion HCl ER and naltrexone HCl ER, regulating appetite and energy expenditure through central nervous system (CNS) activity. The individual compounds work on two separate, complementary areas of the brain: the hypothalamus and the dopamine reward system (the fact that it works on two areas of the brain is at the center of their patient-focused campaign). The hypothalamus plays an important role in the regulation of the body's appetite, satiety and metabolism (energy expenditure) receiving various chemical and hormonal stimuli including glucose, insulin, leptin and peptides secreted by the gut processing food. The dopamine reward system regulates control eating behavior and cravings.

First approved in 1985, bupropion has been widely used for treating depression under the brand Wellbutrin (typically at 400mg/day), particularly in overweight people. Although efficacy in depression looks to be comparable to the commonly prescribed SSRIs, the drug has not been associated with their weight gain (or lack of sex drive) and in fact one of the side effects of bupropion reported in clinical trials in depression was modest weight loss. Bupropion was also FDA approved for smoking cessation in 1997 under the brand Zyban. A norepinephrine dopamine reuptake inhibitor (NDRI), the compound has been shown in studies to activate the pro-opiomelanocortin (POMC) area in the hypothalamus, which looks to cause a reduction in appetite and increase in energy expenditure. The firing of POMC neurons (brought on by bupropion) appears to lead to the production of a natural opioid, beta-endorphin that can slow the POMC system equally, moderating potential weight loss. Naltrexone counters this impact by blocking opioid receptors in the brain and limiting the impact of beta-endorphin on the POMC system. Thus, when administered together in a single pill, the increase in activity of the POMC neurons is sustained over an extended period. In a separate mechanism, both bupropion and naltrexone are approved for addiction disorders through the regulation of dopamine and naturally occurring opioids and therefore, when taken together, it is expected they may also impair food craving. Naltrexone is marketed in generic fast-release form as its hydrochloride salt, naltrexone hydrochloride, under the brands ReVia and Depade and Vivitrol (1x monthly ER injectable). In the US, naltrexone was approved for opioid addiction in 1984 and in 1994 for alcoholism. Orexigen's proprietary ER oral formulation of naltrexone alleviates the common side effect of nausea in its original immediate release form.

Contrave clinical data in obesity

Contrave was approved in September 2014 in the US and in March 2015 in the EU on the back of a large Phase III pivotal trial program, COR, evaluating the drug in 4,536 patients in four studies across three doses of naltrexone ER (16mg, 32mg and 48mg) with bupropion ER (360mg). All studies were 56-week, randomized double-blind and placebo controlled, with one focusing on the evaluation of patients with type 2 diabetes (COR-Diabetes) and another on intensive behavior

modification (COR-BMOD). Co-primary endpoints for all trials were those typically used in anti-obesity studies: the proportion of patients achieving at least 5% weight loss and percentage change in body weight vs placebo. Endpoints were analyzed using a modified intent-to-treat (ITT), last observation carried forward (LOCF) on treatment. All trials met their endpoints with efficacy broadly in line with the other currently marketed anti-obesity treatments, although data suggest that Vivus's Qsymia (phentermine/topiramate) has an edge on efficacy.

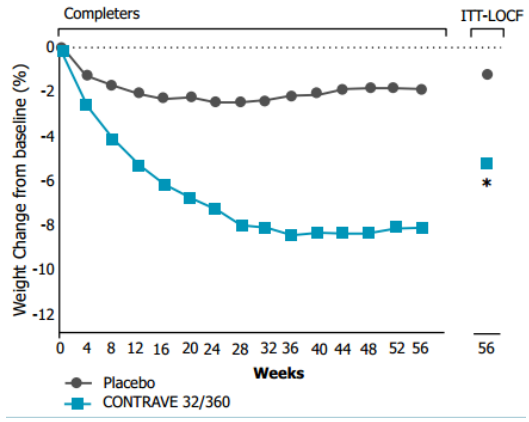
Overall, the program discontinuation rates of 42-51% for those on Contrave were similar to placebo (41-50%) with 19-29% due to adverse events (mainly moderate and transient nausea, headache, dizziness and vomiting) vs 10-15% on placebo.

Exhibit 1: Results of the COR-program

	Modified intent to treat		Completers	
	Contrave	Placebo	Contrave	Placebo
COR-I*				
56 weeks				
*diff from placebo, p<0.001	n=471	n=511	n=296	n=290
Mean weight loss (%)	6.1%	1.3%	8.1%	1.8%
Mean weight loss (lbs)	13.3	3.0	17.5	4.1
≥ to 5% weight loss (%)	48%	16.4%	61.8%	23.1%
≥ to 10% weight loss (%)	24.60%	7.40%	34.5%	10.70%
COR-II**				
56 weeks				
**diff from placebo, p<0.001	n=702	n=456	n=434	n=267
Mean weight loss (%)	6.4%	1.2%	8.2%	1.4%
Mean weight loss (lbs)	13.8	2.9	17.5	3.4
≥ to 5% weight loss (%)	50.5%	17.1%	64.9%	21.7%
≥ to 10% weight loss (%)	28.3%	5.7%	39.4%	7.9%
COR-BEMOD***				
56 weeks				
***diff from placebo, p<0.001	n=482	n=193	n=301	n=106
Mean weight loss (%)	9.3%	5.1%	11.5%	7.3%
Mean weight loss (lbs)	20.3	11.0	25	16.0
≥ to 5% weight loss (%)	66.4%	42.5%	80.4%	60.4%
≥ to 10% weight loss (%)	41.5%	20.2%	55.2%	30.2%
COR-diabetes***				
56 weeks				
****diff from placebo, p<0.001	n=265	n=159	n=175	n=100
Mean weight loss (%)	5.0%	1.8%	5.9%	2.2%
Mean weight loss (lbs)	11.6	4.2	13.5	5.1
≥ to 5% weight loss (%)	45%	18.9%	53.1%	24.0%
≥ to 10% weight loss (%)	18.5%	5.7%	26.3%	8.0%

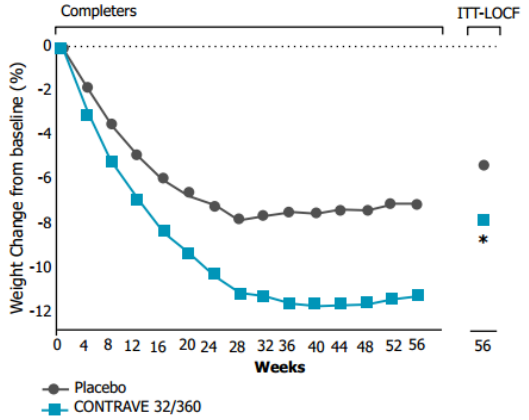
Source: Orexigen

Exhibit 2: Weight loss over time in the completer population – COR-I Trial



Source: Orexigen

Exhibit 3: Contrave with intensive BMOD (behavior modification – COR-BMOD completer analysis



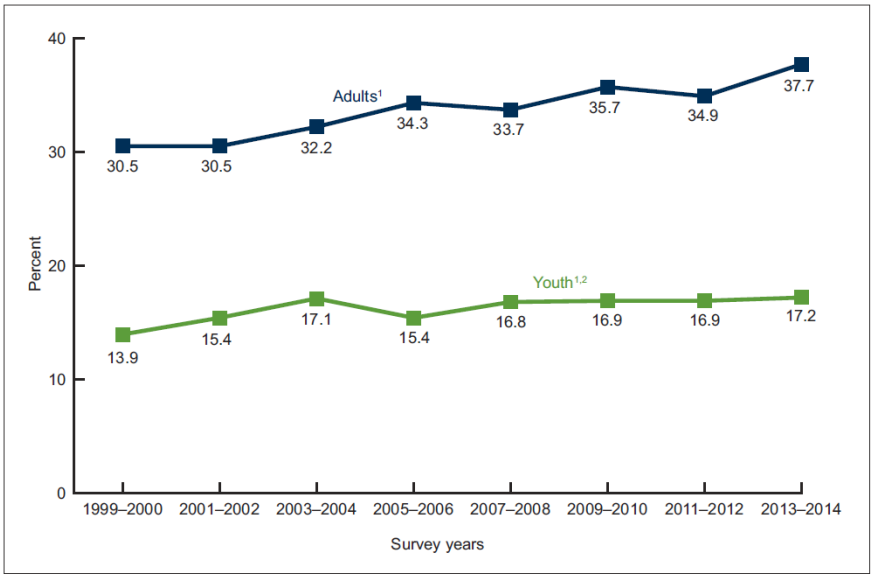
Source: Orexigen

Obesity, an attractive but difficult market

Obesity is currently recognized by the larger medical community worldwide as a serious health condition, growing in prevalence globally with decreased life expectancy and related comorbidities including type 2 diabetes, heart disease, obstructive sleep apnoea (OSA), liver and pulmonary disease and certain types of cancer. Additional comorbidities include anxiety, depression, chronic pain and substance abuse. According to the Centers for Disease Control (CDC), in the US 37.7% of adults and 17.2% of youth (~100m people) are considered obese (body mass index or BMI ≥30) and these percentages continue to grow (see Exhibit 4). If you include the overweight (body mass index or BMI ≥25), between 60-70% of US adults are in need of losing weight.[1]

Exhibit 4: Obesity rates in the US

Figure 5. Trends in obesity prevalence among adults aged 20 and over (age-adjusted) and youth aged 2–19 years: United States, 1999–2000 through 2013–2014



Source: CDC. National Center for Health Statistics, National Health and Nutrition Examination Survey

This comes at an enormous cost to the US healthcare system, with obesity and related comorbidity expenses in the US estimated at over $147bn.[2] Worldwide, 2.1bn people are considered overweight or obese[3] with a global economic impact of $2trn annually according to the McKinsey Global Institute.

Due to the sheer size of the potential multi-billion dollar market for obesity, there is capacity for multiple market contenders. Although a large and growing market, the development of anti-obesity agents has been fraught with safety issues historically (see Exhibit 5).

[1] Ng M et al., *Lancet* 2014 Aug 30;384(9945):766-81
[2] Finklestein E et al., *Health Affairs* 28, No.5 (2009):w 822-w 831

[3] Ng M et al., *Lancet* 2014 Aug 30;384(9945):766-81

Exhibit 5: Select drugs historically used for the treatment of obesity

Drug	Mechanism	Dates used	Issues	FDA approved?
Thyroid extract	Increase metabolic rate	1893-	Cardiotoxicity	No
Dinitrophenol	Increase metabolic rate	1918-	Cardiotoxicity, death	No
"rainbow pills"	Mainly increase metabolism	1940s-1960s	Many (including death) as rainbow pills often included amphetamines, thyroid hormones, barbiturates, diuretics and laxatives	No
Fenfluramine	Reduces appetite by increasing serotonin	1973-1997	Cardiotoxicity	Yes, withdrawn in 1997
Dexfenfluramine	Reduces appetite by increasing serotonin	1996-1997	Cardiotoxicity	Yes, withdrawn in 1997
Sibutramine	Reduces appetite by increasing serotonin and norepinephrine	1997-2010	Cardiotoxicity	Yes, withdrawn in 2010

Source: *Pharmacotherapy of Obesity* by John Wilding, Grundlingh J et al., *Journal of Medical Toxicology* 2011 Sep; 7(3): 205-212, Cohen P et al., *American Journal of Public Health*. 2012 September; 102(9): 1676-1686, FDA.

Despite numerous scandals and disappointments in the segment, the landscape for obesity compounds has changed with some relatively recent approvals by the FDA. This newer generation of drugs looks to be comparatively safe based on data from their respective large Phase III clinical programs.

The competitive landscape in obesity

The cause of obesity is considered to be a combination of genetic, behavioral and environmental influences and it is therefore not surprising that multi-faceted weight management programs, which consist of medication, together with diet, exercise and behavior modification, have been shown to work best – not only in weight loss but, importantly, in the ability to keep weight off. The human body uses many chemicals and hormones to protect its stores of fat – a defense mechanism likely useful to our ancestors when food was scarce – and a complete circumvention of this natural protection of stored fat must therefore be multi-faceted and complex. Hence, new solutions in the treatment of obesity rely more and more on combination drugs targeting multiple pathways. As such, current obesity drugs on the market take differing approaches to enhance behavior modification through various mechanisms, some with combination-complementary approaches, and are showing reasonably good success.

The brain acts as a regulator to functions controlling weight including decisions about how much, when and what we eat. In the obese, the brain becomes desensitized to signals to stop eating. However, the brain is sensitive to any losses in weight, at which time metabolism slows and hunger signals are communicated. Weight loss treatments therefore need to target the propensity for the body to crave food and gain weight once pounds are shed. Current and potential anti-obesity drugs may operate through various mechanisms, including appetite suppression (such as phentermine and other amphetamine-based drugs and anti-depressants), the increase of metabolism or the interference in the body's ability to absorb certain components of food (such as orlistat or OTC fiber supplements like glucomannan and guar gum). It is generally thought that the non-CNS approach, which can initially induce weight loss, is susceptible to a weight loss plateau after several months or a year of therapy, in the absence of treating the underlying behavioral mechanisms in the body.

The main obesity treatments currently marketed in order of launch are as follows:

- **Phentermine (generic):** FDA approved in 1959 it continues to be the most widely prescribed anti-obesity medication. Part of the amphetamine class and a controlled substance. It is only approved for short-term use (a few weeks) but it is likely that many doctors are ignoring that on the label and prescribing for longer periods, though some states like Ohio are attempting to crack down on that practice. Acts as an appetite suppressant and stimulant. One advantage of phentermine over Contrave is its price. For cash-pay patients, it is less than half the cost of Contrave for a 30-day prescription (around $35 on average according to GoodRx).

- **Orlistat (Xenical/Alli, Roche/GSK):** FDA-approved in 1999, Orlistat acts as a lipase inhibitor, preventing the absorption of fats from the diet. Approved for long-term use, Xenical (as prescription originally sold by Roche but currently generic) and Alli (as OTC sold by GSK) have failed to make major inroads, with negligible prescription share more than likely due to infamous side effects including oily stools, fecal incontinence, stomach pain and flatulence. Orlistat has been found to modestly reduce blood pressure and in a large randomized trial reduce the incidence of diabetes by nearly 40% in the obese. All Alli products were voluntarily recalled in March 2014 due to package tampering concerns and the product didn't return to the market until February 2015; since then sales figures have not been reported. However, in 2014 sales of Xenical and Alli were $17m and $107m respectively.
- **Phentermine/Topiramate ER (Qsymia, Vivus):** Phentermine, as mentioned above, is a sympathomimetic amine that acts as an appetite suppressant and stimulant as well as a controlled substance. Topiramate is an anticonvulsant with weight loss properties (although the exact mechanism is unknown). Launched in September 2012, Qsymia is the only recently approved obesity treatment to show significant blood pressure benefits in Phase III trials but, conversely, was denied approval in Europe in 2013 on cardiovascular and psychiatric side effects. Net Qsymia sales were $48.5m in 2016.
- **Lorcaserin (Belviq/Belviq XR, Arena/Eisai):** lorcaserin, an oral pill, is the only new chemical entity (NCE) of the newer oral obesity drugs. It works by promoting satiety through selective activation of 5-HT2C receptors on anorexigenic pro-opiomelanocortin neurons located in the hypothalamus. The compound was approved in June 2012 and launched in June 2013 following the completion of additional studies after an FDA advisory panel recommended against approval in 2010 on cancer-causing concerns (in rats) and marginal efficacy. Lorcaserin has shown a numeric but statistically insignificant benefit on blood pressure. In July 2016, an extended release version, Belviq XR, was approved by the FDA but according to Symphony Health prescription data has thus far mainly cannibalized their Belviq franchise. Arena sold its remaining commercialization rights to Eisai in January 2017 as it exited the obesity market. Lorcaserin is a controlled substance due to its hallucinogenic properties at higher than approved doses. Sales of Belviq/Belviq XR were $34m in 2016.
- **Bupropion/Naltrexone (Contrave, Orexigen):** launched in the US in October 2014 and approved in Europe in March 2015, Contrave is a new formulation of two active ingredients. Bupropion, approved as Wellbutrin since 1985, increases dopamine activity thereby reducing appetite. Naltrexone, first approved in its injectable form in 1984 for addiction, inhibits addictive behavior by blocking opioid receptors. In Q117 sales of Contrave were $14.8m in the US and Orexigen is guiding towards $75-85m for the year.
- **Liraglutide (Saxenda, Novo Nordisk):** a double-dose version of Novo's blockbuster type 2 diabetes treatment Victoza, Saxenda was launched in April (approval in December 2014) for chronic weight management. The GLP-1 receptor agonist was evaluated in more than 4,800 patients with and without weight-related conditions. We expect Saxenda to be positioned as a niche product (there is considerable overlap between type 2 diabetes and obesity populations) given the drug's high pricing (~$1,200 per month), as well subcutaneous injections.

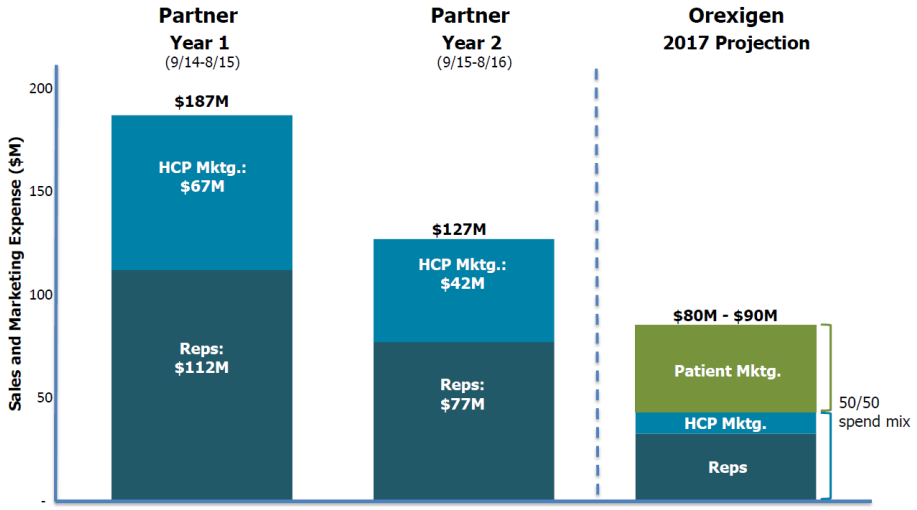
We do not expect the competitive landscape to change markedly in the next few years as there appears to be only one active Phase III program in obesity following the discontinuation of Zafgen's novel MetAP2 inhibitor, beloranib, due to an increased risk of thromboembolic events. The program belongs to a private company called Gelesis (it attempted to IPO in 2015 but withdrew the S-1, likely due to lack of investor interest). Its product, Gelesis100, consists of an oral capsule that contains thousands of hydrogel particles that expand to 100 times their usual size once in the stomach. When taken with food the idea is that this will give patients the feeling of fullness (by physically filling the stomach) so that people eat less. Data so far has been relatively lackluster. In its three-month FLOW study of 128 patients, the 2.25g dose achieved 2% placebo-adjusted weight

loss and the 3.75g dose achieved only 0.4% placebo-adjusted weight loss. The company is currently running the six-month 460-patient GLOW study which has co-primary endpoints of 3% placebo-adjusted weight loss as well as 5% weight loss in at least 35% of patients (43% lost 5% of their weight in the 2.25g arm in the FLOW study). We view this study as high risk as success requires a higher placebo-adjusted weight loss than seen previously.

Contrave marketing

Contrave was approved in the US on 9 September and launched in October 2014 as an adjunct to a reduced-calorie diet and increased physical activity in adults with a BMI of 30kg/m^2 or greater (obese) or 27kg/m^2 or greater (overweight), with one weight-related comorbid condition. As of June 2015, Contrave became the most widely prescribed weight loss treatment in the US. Unlike lorcaserin, Contrave is not a controlled substance, although packaging does include a black box warning owing to the class-wide risk of anti-depressants increasing risk of suicidal thoughts and behaviors in adolescents, as well as bupropion's association with serious neuropsychiatric events when used for smoking cessation. In the US, Orexigen is commercializing Contrave on its own after re-acquiring the rights from Takeda and re-launched with its own sales force in August 2016. Since, re-launching, Orexigen has changed the marketing strategy from one exclusively focused on physician-focused marketing and detailing to one with a significant consumer component (especially since the beginning of 2017), although with continued detailing of high prescribing physicians (see Exhibit 6).

Exhibit 6: The evolving Contrave marketing strategy



Source: Orexigen

The thinking behind the change in strategy is that with physicians typically not spending that much time with patients (see Exhibit 7), they are likely to note the patient's weight and potentially mention they should lose some, but not spend the time discussing obesity medication.

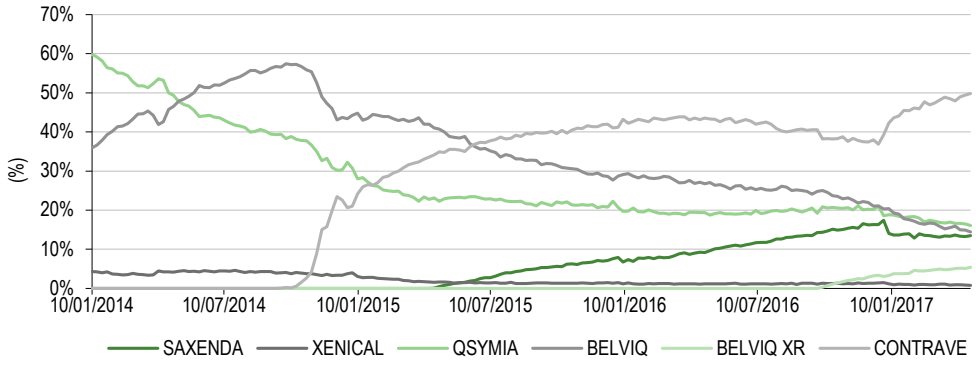
Exhibit 7: Time spent with physicians per office visit by patient

Time	Number of visits ('000s)	Percent (%)
1-5 minutes	9,880	1.1%
6-10 minutes	68,761	7.6%
11-15 minutes	297,967	32.9%
16-30 minutes	382,885	42.3%
31-60 minutes	134,857	14.9%
61+ minutes	11,455	1.3%
Total	905,805	100%

Source: National Ambulatory Medical Care Survey 2013, CDC

However, if the patient comes in asking about Contrave, the physician is more likely to spend the time to discuss the patient's obesity and potentially prescribe medication. In a survey of physicians sponsored by Orexigen, physicians said that when a patient asks for a prescription for Contrave, they grant that request 73% of the time. Based on prescription data from Symphony Health, this strategy has been particularly effective, increasing Contrave's market share from just under 40% to 50% in the branded obesity market (8% of the total market, which includes phentermine) since the consumer campaign started at the beginning of 2017 (see Exhibit 8).

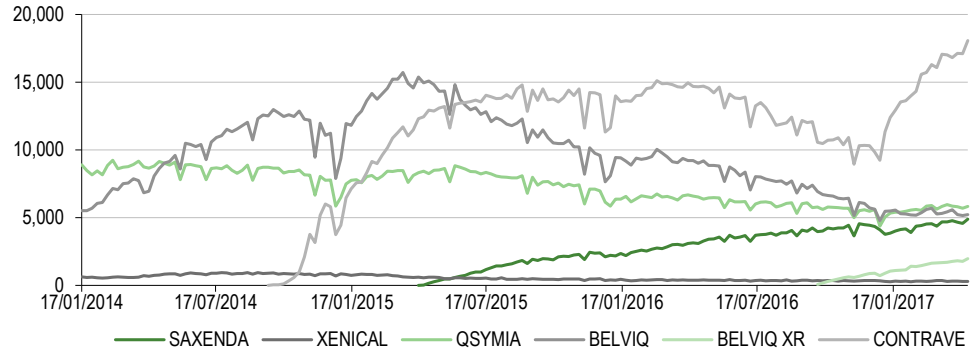
Exhibit 8: Market share in the branded obesity market



Source: Symphony Health

When viewed through the lens of total prescriptions, the growth is even more pronounced; the weekly prescription rate is now c 80% higher than it was at the start of the year (see Exhibit 9).

Exhibit 9: Weekly prescriptions in the branded obesity market



Source: Symphony Health

One thing that remains a work in progress is the reimbursement environment. Historically, obesity medication has not been a covered indication by most insurers due to the perception that it is a "lifestyle" issue. Things have been improving however, with national coverage rates up to 73% in Q117 from just 22% at the beginning in 2015. However, besides having a health plan offer obesity drug coverage, employers also have to opt-in to that coverage, which is a factor in keeping end user coverage rates low. Currently, a little over 20% of Contrave prescriptions are covered by commercial payers.

For the most part, patients need to pay cash for their prescriptions ($90 per month with a Contrave savings card). This relatively high price for a prescription is hurting demand for the product and also is reducing the net realized price that the company collects as they need to deeply discount the product for cash pay patients. As more patients have commercial coverage for Contrave, we expect the average revenue per prescription to increase (which coupled with increasing prescriptions could cause revenue growth to accelerate). Currently, average net revenue per unit sold (including

discounts and any sampling) is $89, up 22% compared to Q116 and up 15% compared to the $77 average for all of 2016.

The telemedicine strategy

In addition to the typical consumer ad-campaign and detailing of physicians, Orexigen is also pursuing a telemedicine strategy where a patient could have a consultation with a physician on-line instead of having to physically attend a doctor's office (there were around 1.2m virtual doctor visits in the US in 2016 according to the American Telemedicine Association). There are several advantages to this:

- Immediacy. Some people suddenly decide to commit to losing weight and want to start taking action immediately. Instead of having to schedule an appointment which could be several days away, they can go on-line and usually get a telemedicine doctor to speak with them the same day.
- Time. The average total time that needs to be invested for a conventional doctor's visit is estimated to be 121 minutes, including 37 minutes of travel time and 84 minutes of clinic time, all for just 20 minutes in front of the doctor[4]. This time commitment can be a real issue for anyone with children and/or a job. With telemedicine, the time that needs to be invested is significantly shorter, often less than 20 minutes.
- Lower anxiety. Many patients are embarrassed to speak with their physician about losing weight or are afraid they will get a lecture. The company estimates that a third of patients are not getting their weight loss medicines because they are uncomfortable with the traditional office visit. The online experience is thought to be less intimidating and more comfortable for many patients.

For Orexigen, a focus on telemedicine has another advantage; phentermine, Qsymia and Belviq are all controlled substances so they cannot be prescribed through telemedicine. Therefore, a patient calling to treat their obesity can only be offered Contrave and the infamously patient unfriendly Xenical. Orexigen expects to have its telemedicine pilot operational in 47 states by the end of May 2017. While we do not expect significant near-term revenues from this channel, it could become a significant driver in the future as telemedicine itself becomes more popular.

Partnering internationally

Orexigen's strategy for Contrave, which is known as Mysimba in most international markets, is to partner the drug region by region. Currently, Orexigen is partnered in a total of 44 countries outside of the US with Contrave/Mysimba launched in 14 of them, including South Korea, Spain and Poland. Launches in the UK and Ireland are expected in Q217. Also, due to a recently signed commercial and distribution agreement with Navamedic ASA, a launch in four Nordic countries (Denmark, Finland, Norway and Sweden) is expected in Q417 (as well as another three launches through other partners. The company hopes to sign partners in a further 10-15 countries over the remainder of 2017. There is little visibility into these markets and Orexigen does not disclose sales by country but as a whole, OUS sales in Q117 were $4.3m, up 139% sequentially as compared to the $1.8m in OUS sales in Q416. Much of this was the sale of product to partners to support the launch and may not be indicative of actual demand.

[4] Ray K et al., *The American Journal of Managed Care*. 2015;21(8):567-574

Exhibit 10: International launch timelines

Country	Partner	Launch Date	Notes
South Korea	Kwangdong	Q216	
Czech Republic	Valeant	Q416	
Slovakia	Valeant	Q416	
Hungary	Valeant	Q416	
Poland	Valeant	Q416	
Romania	Valeant	Q416	
Spain	ROVI	Q117	
Bulgaria	Valeant	Q117	
Estonia	Valeant	Q117	
Lithuania	Valeant	Q117	
Latvia	Valeant	Q117	
Croatia	Valeant	Q117	
Slovenia	Valeant	Q117	
Greece	Valeant	Q217	
UK	Consilient Health	Q217e	
Ireland	Consilient Health	Q217e	
Italy	Bruno	Q417e	
Denmark	Navamedic ASA	Q417e	
Finland	Navamedic ASA	Q417e	
Norway	Navamedic ASA	Q417e	
Sweden	Navamedic ASA	Q417e	
Cyprus	Valeant	Q417e	
Malta	Valeant	Q417e	
Serbia	Valeant	Q118e	
Saudi Arabia	Biologix FZCO	Q118e	Regulatory submission expected Q217
Kuwait	Biologix FZCO	Q118e	Regulatory submission expected Q217
Lebanon	Biologix FZCO	Q118e	Regulatory submission expected Q217
UAE	Biologix FZCO	Q118e	Regulatory submission expected Q217
Canada	Valeant	2018e	Regulatory submission Q117
Australia	Valeant	2018e	Regulatory submission expected Q217
Turkey	Valeant	2018e	Regulatory submission expected Q317
South Africa	Valeant	2018e	Regulatory submission expected Q317

Source: Orexigen

Sensitivities

Orexigen is subject to the execution risks associated with a pharmaceutical company in the midst of a commercial launch. In addition, due to under-reimbursement for medical therapies for obesity, out-of-pocket costs for Contrave are relatively high ($90 per month for those without insurance coverage for Contrave if they have a savings card) making it a tougher sell. Their main competitor, which holds over 80% on the market, is phentermine, part of the amphetamine class and currently generic. While it does have serious side effects normally associated with amphetamines, euphoria and other 'feel good' effects of the drug mean it is unlikely to lose its market leading position without regulatory action.

There are also intellectual property concerns as Contrave is a combination of two generic substances, naltrexone and bupropion. Currently, Contrave is protected by 11 patents listed in the FDA Orange Book, each of which would need to be invalidated, uninfringed or deemed unenforceable for a generic to hit the market (see Exhibit 11).

Exhibit 11: Contrave Orange Book patents

Patent number	Title	Expiration
7,375,111	Compositions for affecting weight loss	26 March 2025
7,462,626	Compositions for affecting weight loss	20 July 2024
8,088,786	Layered pharmaceutical formulations	3 February 2029
8,318,788	Layered pharmaceutical formulations	8 November 2027
8,722,085	Layered pharmaceutical formulations	8 November 2027
8,815,889	Compositions and methods for increasing insulin sensitivity	20 July 2024
8,916,195	Sustained release formulation of naltrexone	2 February 2030
9,107,837	Sustained release formulation of naltrexone	4 June 2027
9,125,868	Methods for administering weight loss medications	8 November 2027
9,248,123	Methods of providing weight loss therapy in patients with major depression	13 January 2032

Source: FDA

Orexigen is currently involved in Paragraph IV litigation with Actavis over their filing for approval of a generic version of Contrave. In April 2015, notice of a Paragraph IV certification regarding an abbreviated new drug application (ANDA), the type of application needed to get a generic approved, was received. In June 2016, following a May 2016 claim construction hearing, the court adopted the company's proposed constructions with regard to the majority of the disputed claim terms in a Markman ruling. While not a definitive victory, adopting one side's claim terms over the other's is an indicator of potential success at trial, which is currently scheduled to begin in June 2017. If Actavis emerges victorious, a generic Contrave could be available after Contrave's exclusivity period expires in September 2017.

We currently assume a 2030 generic entry, as patent 9,248,123 only covers a subset of obesity patients. Our NPV value for the company would decrease if a generic enters the scene prior to that date. If only the 7,375,111 and 7,462,626 patents (known as the Weber/Cowley patents) hold, our valuation per share would fall to $2.07 per share. If the Weber/Cowley patents and some of the patents that expire in 2027 hold, then our NPV per share becomes $6.51 (which is almost 50% lower than our current valuation but still higher than the current share price). On the other hand, as there are Contrave patents currently pending, their issuance could potentially increase the NPV for the company if their expiration dates are after 2030.

Valuation

We are adjusting our valuation from $193m ($12.70/share) to $194m ($12.76/share). This change is due to an increase in our US Orexigen sales estimates (peak sales increased from $329m to $342m) following robust prescription growth and is mitigated by a more conservative launch trajectory for product sales outside of the US (though peak sales are largely the same) and higher SG&A spending estimates ($5.8m higher in 2017 and $5.9m higher in 2018).

Our fair value is based on a NPV analysis of the FCF from Contrave/Mysimba and the company's ongoing costs for R&D and SG&A, to which we apply a 10% discount rate, appropriate for a biotechnology company with an approved and marketed product. Our analysis is highly sensitive to Orexigen's ability to penetrate the vast obesity market, with a large swing factor in fair value on small changes in penetration.

In the US, we currently assume $342m in peak sales, which equates to a 0.29% penetration rate among the obesity population and assumes an eventual normalization of obesity coverage as compared to treatments for other diseases (increasing the net revenue per patient). We assume $175m in peak sales for the rest of the world. This peak sales number is lower than in the US mainly because of reduced penetration assumptions and lower expected net revenue per patient.

Exhibit 12: Orexigen valuation table

Product	Launch	Peak sales ($m)	Royalty rate	NPV ($m)	rNPV/share ($)
Contrave US	Oct-14	342	100%	1,591	104.45
Contrave W. Europe	2016	118	30%	124	8.14
Contrave C. and E. Europe	2016	27	37.5%	35	2.31
Contrave S. Korea	2016	15	37.5%	14	0.93
Contrave ROW	2017	15	37.5%	14	0.91
PV costs inc taxes				(1,533)	(100.66)
Net cash (March 31, 2017)				(51)	(3.32)
Overall valuation (per share based on 15.2m shares outstanding)				194	12.76

Source: Edison Investment Research

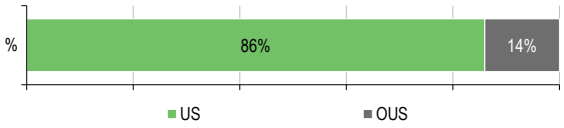
Financials

Sales of Contrave in the US were $14.8m in Q117, up 12% compared to Q116. They also booked $4.3m in sales of Contrave to international partners. Due to an aggressive consumer-focused campaign (which helped increase Contrave prescriptions by 39% in Q117 compared to Q416), operating expenses were $66.8m in the quarter, including $55.2m in SG&A. These expenses are expected to decline over the course of the year. The company is currently guiding for $180-200m in cash operating expenses for 2017. It is important to note that in 2016, the company had guided for $160-180m in cash operating expenses but spent $146m, 9-19% lower than guidance. Due to the recent results, we have increased our revenue estimates in 2017 and 2018. Coupled with increased SG&A estimates, our operating loss estimate is higher for 2017 but lower for 2018. The company had $126.6m in cash, restricted cash and marketable securities at the end of Q117 and is guiding for a cash balance of $40-50m at the end of 2017. Our estimated financing requirement is now $90m through 2020 (not including the $245m in convertible debt principal due in that year) and we continue to expect profitability in 2021. Note that while Orexigen currently lists $177m on its balance sheet, it actually owes $245m in principal value on these notes which will need to be paid in 2020 ($165m by 1 July 2020 and the rest on 1 December). The difference is due to rules related to the fair value accounting of convertible notes with liability and equity components.

Exhibit 13: Financial summary

$'000s	2015	2016	2017e	2018e
Year end 31 December	US GAAP	US GAAP	US GAAP	US GAAP
PROFIT & LOSS				
Revenue	24,459	33,709	87,274	160,251
Cost of Sales	0	(7,995)	(26,104)	(29,680)
Gross Profit	24,459	25,714	61,170	130,572
Research and development	(40,750)	(38,023)	(33,186)	(36,504)
Selling, general & administrative	(43,762)	(118,583)	(163,089)	(164,720)
EBITDA	(60,276)	(134,627)	(135,222)	(70,902)
Operating Profit (before GW and except.)	(60,053)	(130,892)	(135,105)	(70,653)
Intangible Amortisation	0	(3,307)	(7,936)	(5,769)
Exceptionals/Other	0	77,229	(1,400)	0
Operating Profit	(60,053)	(56,970)	(144,441)	(76,422)
Net Interest	(7,219)	(7,228)	(4,104)	(4,834)
Other (includes change in fair value of warrants)	(39)	39,807	(14,215)	0
Profit Before Tax (norm)	(67,272)	(138,120)	(139,209)	(75,487)
Profit Before Tax (FRS 3)	(67,311)	(24,391)	(162,760)	(81,256)
Tax	(1,376)	(133)	0	0
Deferred tax	0	0	0	0
Profit After Tax (norm)	(68,648)	(138,253)	(139,209)	(75,487)
Profit After Tax (FRS 3)	(68,687)	(24,524)	(162,760)	(81,256)
Average Number of Shares Outstanding (m)	13.1	14.6	15.2	15.5
EPS - normalised (c)	(523.81)	(972.82)	(823.44)	(485.89)
EPS - FRS 3 ($)	(5.24)	(9.73)	(8.23)	(4.86)
Dividend per share (c)	0.0	0.0	0.0	0.0
BALANCE SHEET				
Fixed Assets	2,694	79,940	71,628	65,871
Intangible Assets	0	76,061	68,125	62,356
Tangible Assets	1,284	1,044	831	843
Other	1,410	2,835	2,672	2,672
Current Assets	233,895	224,461	95,892	55,355
Stocks	10,802	23,193	20,663	20,663
Debtors	6,828	1,102	6,277	6,277
Cash	214,011	103,993	64,014	23,477
Other	2,254	96,173	4,938	4,938
Current Liabilities	(32,241)	(65,360)	(49,459)	(49,459)
Creditors	(32,241)	(65,360)	(49,459)	(49,459)
Short term borrowings	0	0	0	0
Long Term Liabilities	(170,970)	(178,842)	(210,992)	(230,430)
Long term borrowings	(88,129)	(166,179)	(197,167)	(217,167)
Other long term liabilities	(82,841)	(12,663)	(13,825)	(13,263)
Net Assets	33,378	60,199	(92,931)	(158,663)
CASH FLOW				
Operating Cash Flow	(54,473)	(109,713)	(132,308)	(60,478)
Net Interest	0	0	0	0
Tax	0	0	0	0
Capex	(538)	(330)	(255)	(261)
Acquisitions/disposals	0	(63,504)	(3,414)	0
Financing	64,259	188	0	0
Dividends	0	0	0	0
Other	(3,843)	(15,424)	76,026	188
Net Cash Flow	5,405	(188,783)	(59,951)	(60,551)
Opening net debt/(cash)	(121,629)	(125,882)	62,186	133,153
HP finance leases initiated	0	0	0	0
Exchange rate movements	29	715	0	0
Other	(1,181)	0	(11,016)	(0)
Closing net debt/(cash)	(125,882)	62,186	133,153	193,704

Source: Edison Investment Research

Contact details	Revenue by geography
3344 N. Torrey Pines Court, Suite 200 La Jolla, CA 92037 US +1 858 875 8600 www.orexigen.com	

Management team

CEO: Michael Narachi

Michael Narachi has been CEO of Orexigen since 2009, coming from biotechnology firm REN Pharmaceuticals, where he served as CEO from 2006 to 2009. Previously, he held various positions over a number of years at Amgen, including general manager of Amgen's anemia business, director of clinical operations, VP of development and head of corporate strategic planning. He currently serves on the board of directors of Celladon Corporation and Ultragenyx Pharmaceuticals, as well as PhRMA (Pharmaceutical Research and Manufacturers of America) and BIO (Biotechnology Industry Organization).

Chief Commercial Officer: Thomas Cannell

Thomas Cannell recently joined Orexigen following a long tenure at Merck, where he held various positions. He has considerable experience in global commercialisation, consumer marketing, and sales operations and management. Positions held at Merck include president of Merck Canada, head of marketing and strategy for MSD Japan and general manager roles for a US sales division and as leader of a Merck business unit, managing a multi-billion dollar product portfolio. He also designed and successfully piloted the commercial model for Merck's US business.

CFO: Jason Keyes

Jason Keyes joined Orexigen in 2013 and has held various financial senior leadership positions prior to becoming CFO, including Vice President of Finance, where he led the Company's financial planning and partnership finance functions and served as a key financial advisor to executive management in setting corporate business and financial strategy. Prior to joining Orexigen, Jason was Senior Director of Finance at Amylin Pharmaceuticals, Inc., which was acquired by Bristol-Myers Squibb in 2012. Previously he worked in finance and corporate strategy at Amgen, Inc. and at Baxter Healthcare Corporation.

EVP, General Counsel: Thomas Lynch

Tom joined Orexigen from Novartis where, since 2012, he served as senior legal counsel in two divisions, including leading global legal and compliance support for Novartis Pharma's neuroscience franchise and advising on business development and alliance management with partners in Europe, Japan and the U.S. Earlier, Lynch spent almost ten years with Boston Scientific in a variety of legal roles and nearly six years practicing corporate law at Dorsey & Whitney LLP.

Principal shareholders	(%)
Baupost	14.6%
Foresite Capital	6.6%
BVF	4.8%
Vanguard Group	3.7%
NEA Management	2.4%
GLG	1.6%
Credit Suisse	1.5%

Companies named in this report

Takeda (4502); Vivus (VVUS); Arena (ARNA); Eisai (4523); Roche (ROG); Novo Nordisk (NVO); GSK (GSK); Valeant (VRX); Allergan (AGN)

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