In March 2010, Orexigen® Therapeutics submitted a new drug application (NDA) for approval of naltrexone sustained release (SR)/bupropion SR (Contrave®) for the treatment of obesity in the US. The tablet contains naltrexone SR 32 mg and bupropion SR 360 mg. The drug has been tested in four randomized, double-blind, placebo-controlled, phase III trials and the co-primary endpoints were met in each case. This review discusses the key development milestones and clinical trial program to date.

1. Introduction

Orexigen® Therapeutics is developing a proprietary fixed-dose combination of naltrexone sustained release (SR) and bupropion SR in a single tri-layer tablet, for the treatment of obesity. The tablet contains naltrexone SR 32 mg and bupropion SR 360 mg. The product is awaiting approval in the US. In addition, the combination has been tested in an open-label phase II study for smoking withdrawal in overweight or obese subjects.

Naltrexone is an opioid receptor antagonist marketed in the US for the treatment of narcotic and alcohol dependency, while bupropion is a dopamine and norepinephrine reuptake inhibitor prescribed as an antidepressant and smoking cessation aid. In combination, the agents are thought to stimulate proopiomelanocortin (POMC) neuronal firing and modulate food cravings through an effect on the reward pathways. The naltrexone/bupropion formulation, known as Contrave®, is designed to initiate weight loss and sustain it over a longer period of time by switching off natural compensatory mechanisms involved in the typical weight loss plateau stage.

1.1 Company Agreements

In June 2009, Orexigen secured from Glaxo-SmithKline non-exclusive rights to certain formulation patents related to bupropion in exchange for undisclosed upfront and future milestone payments.[1]

1.2 Key Development Milestones

1.2.1 Obesity

In March 2010, Orexigen submitted an NDA for approval of naltrexone SR/bupropion SR (Contrave®) for the treatment of obesity in the US. The new drug application (NDA) comprises data from the Contrave Obesity Research (COR) clinical program in more than 4500 patients.[2]

The COR program included four randomized, double-blind, placebo-controlled, phase III trials COR-I (NB-301), COR-II (NB-303), COR-Diabetes (NB-304) and COR-BMOD (NB-302). The phase III NB-302 trial (NCT00456521) has been completed, with an enrollment of 793 obese patients. The trial assessed the safety and efficacy of naltrexone 32 mg/bupropion 360 mg dosed daily for 56 weeks. Patients were randomized 3:1 to active therapy (Contrave® plus behavior modification protocol) or behavior modification plus placebo. In January 2009, Orexigen reported that the trial had met its co-primary and key secondary endpoints, with a significant reduction in bodyweight, reductions in selected food craving measures and improvements in markers of cardiovascular risk.[3-5]

Additional
secondary findings were presented in June 2009.\[6\]

All three remaining phase III trials of naltrexone SR/bupropion SR (NB-301, NB-303 and NB-304) have met their co-primary endpoints.\[7\]

In April 2008, patient enrollment was completed in a phase III study (NB-301; NCT00532779) in 1650 patients in 34 centers in the US. This multicenter, randomized, double-blind, placebo-controlled study compared the safety and efficacy of two doses of naltrexone SR/bupropion SR (16 mg/360 mg and 32 mg/360 mg, respectively) for 56 weeks.\[4\]

Orexigen completed a phase III study (NB-304; NCT00474630) evaluating the safety and efficacy of the product over 56 weeks in 525 patients with obesity and type 2 diabetes. The study enrolled patients at 51 centers in the US.\[5,8\]

Patient enrollment of 1500 patients in a phase III trial (NB-303; NCT00567255) was completed in May 2008 at 36 centers in the US. This 56-week study was designed to blind re-randomization of any product recipients who have not responded at week 28 to receive either higher doses of the product or continue on the original dose.\[8,9\]

A phase IIb trial (NB201) of bupropion SR/naltrexone immediate release (IR) in 419 patients with uncomplicated obesity was completed by Orexigen in March 2007. The multicenter, randomized, double-blind study assessed the safety, tolerability and efficacy of three different dosages of naltrexone (16, 32 or 48 mg/day) combined with a single dosage of bupropion (400 mg/day), compared with either agent alone or placebo. The protocol for this study permitted patients to continue receiving naltrexone/bupropion for an additional 24 weeks of open-label treatment. Results from the completed study were presented by Orexigen in October 2007.\[10,11\]

Results from a phase II trial of naltrexone/bupropion in 206 patients with obesity were reported by Orexigen in June 2006. The multi-centre study evaluated the efficacy of naltrexone IR/bupropion SR treatment in combination with a minimal diet and exercise program, compared with monotherapy or placebo. The company used a refined formulation and optimal dose ratio of naltrexone/bupropion in its ongoing phase II/III clinical program.\[12\]

1.2.2 Smoking Withdrawal

Results from an open-label phase II study (NB-401, NCT00563563) of the combination of naltrexone plus bupropion in 30 overweight or obese smokers have been released.\[13\]

1.3 Patent Information

The United States Patent and Trademark Office (USPTO) issued a fourth patent on naltrexone/bupropion in January 2009. The patent (no. 7 462 626) is known as the Weber/Cowley methods patent and will provide protection for Contrave® through mid 2024. It is a companion to the Weber/Cowley composition patent.\[14\]

In May 2008, Orexigen was granted the Weber/Cowley composition-of-matter patent (No. 7 375 111) entitled Compositions for affecting weight loss covering broad claims on the active constituents in Contrave® until March 2025.\[15,16\]

The USPTO also issued a Notice of Allowance to Orexigen’s patient application for what the company refers to as the “Weber/Cowley methods patent” (no. 121/356 839) providing coverage for methods of treating obesity with combinations of naltrexone and bupropion. When issued, this US patent will provide protection for Contrave® through mid 2024.\[17\]

Previously, the USPTO issued a US patent (no. 5 817 665) entitled Composition and method of treating depression using naloxone or naltrexone in combination with a serotonin reuptake inhibitor covering the use of various combinations of weight-loss promoting anti-depressants with opioid antagonists including naltrexone. The patent covers any use of these combinations and not limited to weight loss. The US patent was awarded to Dr Lee Dante, and was exclusively licensed by Orexigen® Therapeutics.\[18\]

The European Patent Office has granted Orexigen a patent covering compositions and uses of bupropion and naltrexone for affecting weight loss. The European patent once validated in individual countries will provide exclusive rights to this combination in those countries until 2024.\[19\]
2. Scientific Summary

2.1 Pharmacokinetics

In a phase I trial in 40 healthy obese volunteers, the maximum concentration (Cmax) value of naltrexone SR was reduced by approximately 25% compared with the naltrexone IR formulation, while retaining approximately 99% of the area under the concentration-time curve (AUC) value. The SR formulation also had a greater time to Cmax (tmax) value compared with the IR formulation (approximately 36 minutes). A reduction in Cmax and similar AUC values were observed in an additional phase I trial. A total of 60 obese volunteers in this study were randomized to receive bupropion SR with either naltrexone SR or IR.[20,21]

2.2 Adverse Events

2.2.1 Obesity

**Phase III:** In the phase III NB-302 trial, naltrexone/bupropion was generally well tolerated. A total of 793 obese patients were randomized to naltrexone/bupropion plus behavior modification or placebo plus behavior modification. The safety profile of the drug was consistent with those of the individual components. No increases in symptoms of depression or suicidality were reported, and mean blood pressure did not worsen. The overall discontinuation rate due to adverse events was 25.9% for patients receiving naltrexone/bupropion vs 13.0% for placebo. The most frequent causes of discontinuation were nausea, urticaria and anxiety. Discontinuation due to nausea was 4.6%. The most frequent adverse events occurring in mild to moderate severity were nausea (34.1% naltrexone/bupropion vs 10.5% placebo), headache (23.8% vs 17.5%) and constipation (24.1% vs 14.0%). The most frequent psychiatric adverse events reported were insomnia (8.7% NB vs 6.0% placebo), anxiety (5.1% vs 3.5%), sleep disorder (2.4% vs 3.0%) and depressed mood (1.9% vs 4.0%). Two serious adverse event cases of cholecystitis were reported in the naltrexone/bupropion arm. Naltrexone/bupropion did not worsen psychiatric symptoms, as assessed by the change in Inventory for Depressive Symptoms-Self-Rated (IDS-SR) total score. The study drug was composed of naltrexone 32 mg/bupropion 360 mg, and dosed daily for 56 weeks.[3,22]

Preliminary analysis of a 24-week blinded data in 3934 evaluable patients showed lower rates of nausea across the four pooled phase III trials compared with pooled 24-week data from the phase IIb (NB-201) trial. The overall rate of early discontinuation due to any adverse events was lower in phase III trials compared with the phase

| Table I. Features and properties |
|----------------------------------|
| Alternate names | Contrave®; Naltrexone SR/bupropion SR |
| Originator | Orexigen Therapeutics |
| Highest development phase | Preregistration (USA) |
| Active development-indications | Obesity |
| Class | Morphine-derivatives, Propiophenones |
| Mechanism of action | Adrenergic receptor antagonists; Dopamine uptake inhibitors; Opioid receptor antagonists |
| Route of administration | PO |
| Pharmacodynamics | Significantly improves HDL, triglycerides and hsCRP levels in obese patients, compared with placebo, when used in conjunction with a behavior modification program; reduces food intake in mice, and increases neuronal firing in the ventral tegmental area |
| ATC codes | WHO ATC code: A08 (Antiobesity Preparations, Excl. Diet Products), N06A-X12 (Bupropion), N07B-A (Drugs used in nicotine dependence), N07B-B04 (Naltrexone) EphMRA ATC code: A8 (Antiobesity Preparations, Excluding Dietetics), N7B (Antismoking Products), N7F (Drugs Used In Opioid Dependence) |
**Table II. Drug development history**

| Date               | Comment                                                                 |
|--------------------|-------------------------------------------------------------------------|
| 7 April 2010       | inThought Analysis for Obesity Updated                                  |
| 31 March 2010      | Preregistration for Obesity in USA (PO)                                 |
| 21 July 2009       | Top-line efficacy data from three phase III trials (NB-301, NB-303, NB-304) inobesity released by Orexigen Therapeutics[7] |
| 11 June 2009       | Orexigen secures non-exclusive rights to certain formulation patents related to bupropion from GlaxoSmithKline[1] |
| 6 June 2009        | Additional efficacy and adverse events data from a phase III (NB-302) trial in Obesity presented at the 69th Annual Scientific Sessions of the American Diabetes Association (ADA-2009)[6,22,25] |
| 21 May 2009        | Clinical trials in Smoking withdrawal in USA (PO)                       |
| 21 May 2009        | Efficacy and adverse events data from a clinical trial in smoking withdrawal presented at the 162nd Annual Meeting of the American Psychiatric Association (APA-2009)[13] |
| 8 January 2009     | Efficacy, adverse events and pharmacodynamics data from the phase III NB-302 trial in Obesity released by Orexigen[3] |
| 9 October 2008     | Final safety and pharmacokinetics data in volunteers and preliminary pooled safety data from phase III trials in Obesity presented at the 2008 Obesity Society Annual Scientific Meeting[20] |
| 10 June 2008       | Additional efficacy data from a phase IIb trial in obesity released by Orexigen® Therapeutics[29] |
| 9 May 2008         | Orexigen® completes enrollment in a phase III program for type 2 diabetes in USA         |
| 22 April 2008      | Orexigen® completes enrollment in its second phase III trial (NB-301) for Obesity in USA |
| 12 December 2007   | OREXIGEN™ initiates enrollment in a fourth phase III trial for Obesity in USA |
| 30 November 2007   | Orexigen® completes enrollment in its first phase III trial (NB-302) for Obesity in USA |
| 31 October 2007    | Data presented at the 007 Annual Meeting of the North American Association for the Study of Obesity (NAASO-2007) added to the Obesity therapeutic trials section[28] |
| 24 October 2007    | Data presented at the Obesity Society’s Annual Scientific Meeting (NAASO-2007) added to the adverse events and Obesity pharmacodynamics and therapeutic trials sections[15,23] |
| 4 October 2007     | Clinical data added to the adverse events and pharmacokinetics sections[21] |
| 26 September 2007  | OREXIGEN™ initiates third phase III trial for Obesity in USA |
| 29 June 2007       | Data presented at the 67th Scientific Sessions of the American Diabetes Association (ADA-2007) added to the Obesity therapeutic trials section[26,27] |
| 24 May 2007        | Final results from a phase IIb clinical study in patients with Obesity to the Obesity therapeutic trials sections[5] |
| 22 May 2007        | OREXIGEN™ initiates enrollment in second phase III trial for obesity in USA |
| 30 April 2007      | OREXIGEN™ initiates enrollment in first phase III trial for obesity in USA |
| 28 September 2006  | Top line results from a phase IIb clinical study in patients with obesity have been added to the adverse events and Obesity therapeutic trials sections[11] |
| 30 April 2005      | Phase II clinical trials in Obesity in USA (PO) |
| 30 April 2005      | New Profile                                                             |

Phase II: There were no serious adverse events related to naltrexone/bupropion treatment in a phase IIb trial (NB-201) in 419 patients with obesity. The study assessed three different dosages of naltrexone (16, 32 or 48 mg/day) combined with a single dosage of bupropion (400 mg/day), compared with either agent alone or placebo. The naltrexone 32 mg/bupropion 400 mg group experienced the lowest rate of discontinuation due to adverse events, at just under 16%. The most common adverse event was nausea which typically occurred on initial drug exposure and was transient and mild. Discontinuations due to nausea through 24 weeks were substantially lower in the naltrexone 32 mg/bupropion 400 mg group (7.9%) than in the naltrexone 48 mg/bupropion 400 mg group (18.0%). Other adverse events included headache, dizziness and insomnia. There was also no evidence to suggest that naltrexone/bupropion treatment had an adverse effect on vital signs including blood pressure, pulse, electrocardiogram (ECG) intervals, laboratory evaluations or on a scale evaluating depression.[10,11]
**Phase I:** In a phase I trial in 40 healthy obese volunteers, fewer participants receiving naltrexone SR experienced an adverse event, compared with participants receiving naltrexone IR. In another phase I study in 60 obese volunteers, naltrexone SR was associated with fewer gastrointestinal (GI), CNS and other adverse events, compared with volunteers in the naltrexone IR group (GI: 10.3% vs 16.7%, CNS: 10.3% vs 23.3%, respectively). The rate of participants experiencing concurrently occurring adverse events was also lower in the naltrexone SR group.[20,21]

**2.2.2 Smoking Withdrawal**

Transient, mild to moderate nausea, insomnia, and constipation are the most common adverse events associated with naltrexone plus bupropion in a 24-week open-label study in overweight or obese smokers (n = 30).[13]

**2.3 Pharmacodynamics**

**2.3.1 Obesity**

**Phase III:** In the phase III NB-302 trial, patients receiving naltrexone SR/bupropion SR experienced significant improvements over placebo, in high density lipoprotein (HDL), triglycerides and high sensitivity C-reactive protein (hsCRP), markers of cardiovascular risk. A total of 793 obese patients were randomized to naltrexone SR/bupropion SR plus behavior modification (counseling, diet and exercise) or placebo plus behavior modification. The study drug was composed of naltrexone 32 mg/bupropion 360 mg, and dosed daily for 56 weeks.[3]

**Preclinical studies:** In a preclinical study in lean mice, treatment with bupropion, naltrexone or a combination of both agents resulted in food intake reductions of 34%, 67% and 77%, respectively. In obese mice, treatment with bupropion, naltrexone or a combination of both agents resulted in food intake reductions of 27%, 49% and 94%, respectively. A separate study demonstrated that administration of naltrexone plus bupropion to the ventral tegmental area (VTA) was associated with a significant and synergistic reduction of food intake.[23]

**2.4 Therapeutic Trials**

**2.4.1 Drug Withdrawal**

In a 24-week, open-label study, combination therapy with naltrexone and bupropion plus behavioral counseling decreased nicotine use and limited nicotine withdrawal symptoms while preventing weight gain in overweight or obese smokers (n = 30). A total of 48% and 41% of subjects were continuously abstinent from smoking from week 4 through weeks 12 and 24 (primary endpoint). Nicotine withdrawal scores remained unchanged, except a significant increase on week 5. A total of 78% and 74% of subjects had 10 ppm CO at weeks 12 and 24, respectively. Tobacco use decreased from 129 to 15 and 18 cigarettes/week at weeks 12 and 24, respectively.[13]

**2.4.2 Obesity**

**Phase III:** Three phase III trials of 32 mg naltrexone/360 mg bupropion (NB-301, NB-303, NB-304) have met their co-primary endpoints (n = 4500). Naltrexone/bupropion produced a weight loss of 6.1%, 6.4, and 5% in these trials compared to 1.3%, 1.2% and 1.8% with placebo, respectively; 48%, 56.3% and 44.5% of patients lost ≥5% of weight with naltrexone/bupropion compared to 16.4%, 17.1% and 18.9% with placebo, respectively; naltrexone/bupropion reduced glycosylated hemoglobin (HbA1C) by 0.6%.

**Table III. Forecasts**

| Indication | Approval Date Estimate | inThought Approvability Index | Last Update |
|------------|------------------------|-------------------------------|-------------|
| Obesity    | 1 Mar 2011              | 77%                           | 7 Apr 2010  |

| Indication | 2009 | 2010 | 2011 | 2012 | 2013 | 2014 | 2015 | 2016 | 2017 | Last Update |
|------------|------|------|------|------|------|------|------|------|------|-------------|
| Obesity    | 0    | 0    | 74   | 186  | 301  | 490  | 590  | 673  | 722  | 5 Feb 2010  |

*All numbers in $US millions.*
compared with 0.1% by placebo in NB-304; patients with a HbA1C of >8% taking naltrexone/bupropion experienced a mean reduction of 1.1%, which was significantly greater than placebo. In all cases, the difference was significant (p < 0.001, intent-to-treat population). Naltrexone/bupropion also significantly improved cardiovascular and metabolic risk factors, such as waist circumference, visceral fat, HDL cholesterol and triglycerides. Patients receiving naltrexone/bupropion also experienced reductions in the frequency and strength of food cravings and an increased ability to control their eating compared with placebo.[7,24]

The phase III NB-302 trial met its co-primary and key secondary endpoints, with a significant reduction in bodyweight and reductions in selected food craving measures. Naltrexone/bupropion produced placebo-subtracted weight loss of up to 4.7% at 6 months in obese patients. A total of 793 obese patients were randomized to naltrexone/bupropion plus behavior modification (counseling, diet and exercise) or placebo plus behavior modification. At 56 weeks, change in bodyweight was −9.29 ± 0.40% for naltrexone/bupropion (n = 482) and −5.08 ± 0.60% for placebo (n = 193) [p < 0.001]. More patients treated with naltrexone/bupropion achieved bodyweight loss of ≥5% (66.4% naltrexone/bupropion vs 42.5% placebo), ≥10% (41.5% vs 20.2%) and ≥15% (29.1% vs 10.9%); all results were significant (p < 0.001). Waist circumference also decreased significantly from baseline in patients on active treatment, compared with placebo. Those on active treatment also demonstrated improvements in quality of life, as measured by the Impact of Weight on Quality of Life-Lite total scores (−16.65 for naltrexone/bupropion vs −12.77 for placebo, p < 0.001). The study drug was composed of naltrexone 32 mg/bupropion 360 mg, and dosed daily for 56 weeks. Additional secondary data from this trial showed that patients receiving naltrexone/bupropion had significant improvements in eating control and overall quality of life compared with placebo recipients, improved physical function and self-esteem that occurred early in treatment and maintained over 1 year.[3,25] Additional secondary data from this trial showed that patients receiving naltrexone SR/bupropion SR had significant improvements in eating control and overall quality of life compared with placebo recipients, improved physical function and self-esteem that occurred early in treatment and maintained over 1 year.[6]

**Phase II:** In a phase IIb trial (NB-201) of naltrexone IR/bupropion SR in 419 patients with obesity, optimal treatment results were observed in the naltrexone 32 mg/bupropion 400 mg dose group. The study assessed three different dosages of naltrexone (16, 32 or 48 mg/day) combined with a single dosage of bupropion (400 mg/day), compared with either agent alone or placebo. Compared with the placebo and monotherapy groups, patients in the naltrexone 32 mg/bupropion 400 mg group demonstrated significantly greater improvements in fasting glucose and insulin resistance, as evaluated by the quantitative insulin-sensitivity check index (QUICKI) and log (HOMA) measurements. Significant improvements were also observed when compared with at least one of the control groups in waist circumference, insulin, triglycerides and homeostatic model assessment of insulin resistance (HOMA). In a subset of patients who had a DEXA scan or abdominal CAT scan at baseline and week 24, the mean reduction in visceral fat ranged from 13.7% to 16% across all naltrexone/bupropion groups, compared with a 0.1% to 4.6% mean reduction for patients receiving either of the monotherapies of placebo. At 48 weeks, weight loss from baseline bodyweight across the three naltrexone/bupropion groups ranged from 5.0% to 6.6% (last observation carried forward analysis) and from 8.0% to 10.7% (completer analysis). Additionally, patients experiencing a clinical response at 24 weeks continued to lose additional weight through 48 weeks.[5,10,11,26-28]

A review of data from a phase IIb study showed that in patients who completed 24 weeks of treatment with naltrexone IR/bupropion SR, the percentage of patients with metabolic syndrome decreased from 31% to 15% (p < 0.05). Among patients in the placebo group, the percentage of patients with metabolic syndrome decreased from 38% to 30%. There were also evident improvements in key markers of metabolic and cardiovascular disease.[29]
In an earlier phase II trial, naltrexone/bupropion treatment was associated with a greater weight loss over 6 months, compared with either monotherapy or placebo. More than 50% of patients completing the trial demonstrated 5% weight loss over 24 weeks, while 18% of patients demonstrated 10% weight loss. Additionally, the trajectory of these weight loss curves showed no evidence of a plateau.[12]

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