CADTH

CADTH COMMON DRUG REVIEW

Clinical Review Report

NALTREXONE HYDROCHLORIDE AND BUPROPION HYDROCHLORIDE (CONTRAVE)

(Bausch Health, Canada Inc.)

Indication: An adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adults with an initial body mass index of 30 kg/m^2 or greater (obese) or 27 kg/m^2 or greater (overweight) in the presence of at least one weight-related comorbidity (e.g., controlled hypertension, type 2 diabetes mellitus, or dyslipidemia).

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About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

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Abbreviations

AE	adverse event
ANCOVA	analysis of covariance
bpm	beats per minute
BMI	body mass index
BOCF	baseline observation carried forward
CDR	CADTH Common Drug Review
CI	confidence interval
COE	Control of Eating
CPH	Cox proportional hazards
CrI	credible interval
CTFPHC	Canadian Task Force on Preventive Health Care
EMA	European Medicines Agency
FCI	Food Craving Inventory
GRADE	Grading of Recommendations Assessment, Development, and Evaluation
HbA1c	glycated hemoglobin
HDL	high-density lipoprotein
HRQoL	health-related quality of life
IDS-SR	Inventory of Depressive Symptomology – Subject-Rated
ITT	intention to treat
IWQoL-Lite	Impact of Weight on Quality of Life – Lite Questionnaire
LOCF	last observation carried forward
LSM	least squares mean
MACE	major adverse cardiovascular event
MCS	mental component summary
MDD	major depressive disorder
MI	myocardial infarction
MID	minimal important difference
mITT	modified intention to treat
NB	naltrexone and bupropion

NI	noninferiority
NMA	network meta-analysis
OBQoL	obesity quality quality of life
PCS	physical component summary
PP	per protocol
PT	phentermine-topiramate
RCT	randomized controlled trial
SAE	serious adverse event
SD	standard deviation
SF-12	Short-Form (12) Health Survey
SF-36	Short-Form (36) Health Survey
VAS	Visual Analogue Scale
WDAE	withdrawal due to adverse event

Drug	Naltrexone hydrochloride and bupropion hydrochloride (Contrave)
Indication	Indicated as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adults with an initial body mass index of: • 30 kg/m^2 or greater (obese) or • 27 kg/m^2 or greater (overweight) in the presence of at least one weight-related comorbidity (e.g., controlled hypertension, type 2 diabetes mellitus, or dyslipidemia).
Reimbursement request	As per indication
Dosage form(s)	Extended-release naltrexone hydrochloride 8 mg and bupropion hydrochloride 90 mg tablets
NOC date	February 13, 2018
Sponsor	Bausch Health, Canada Inc.

Executive Summary

Introduction

Obesity is characterized by excess adiposity and weight gain and is associated with many chronic comorbidities, including cardiovascular disease, type 2 diabetes mellitus, osteoarthritis, hypertension, dyslipidemia, and certain forms of cancer. Patients are considered to be overweight or obese according to their body mass index (BMI), which takes both weight and height into account. A BMI of 25 to 30 kg/m^2 signifies an overweight condition and a BMI of 30 kg/m2 or greater corresponds with obesity. According to the 2016 and 2017 Canadian Health Measures Survey and the 2017 Canadian Community Health Survey, 34% of Canadians were overweight and 27% had obesity.

Canadian recommendations for managing obesity and overweight consider dietary and physical activity interventions to be appropriate for adults who are overweight or obese. The addition of a pharmacologic drug for overweight or obese adults who do not attain or maintain clinically important weight loss through diet and exercise therapy alone may be appropriate. Orlistat and liraglutide are approved in Canada for chronic weight management, but are associated with gastrointestinal adverse events. If pharmacotherapy is not effective, bariatric surgery may be appropriate for some patients with a BMI of 40 kg/m^2 or 35 kg/m^2 or greater with severe comorbid disease. However, bariatric surgery, in addition to issues with limited access, is associated with a risk of mortality or serious complications and is typically used as a last resort for weight loss.

Contrave is a fixed-dose combination of naltrexone hydrochloride 8 mg and bupropion hydrochloride 90 mg extended-release tablets for oral administration. The recommended dosage is two tablets twice daily for a total daily dose of 32 mg of naltrexone hydrochloride and 360 mg of bupropion hydrochloride. Naltrexone and bupropion (NB) is indicated as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adults with an initial BMI of 30 kg/m^2 or greater (obese) or 27 kg/m^2 or greater (overweight) in the presence of at least one weight-related comorbidity (e.g., controlled hypertension, type 2 diabetes mellitus, or dyslipidemia).

The objective of the review is to perform a systematic review of the beneficial and harmful effects of naltrexone hydrochloride 8 mg and bupropion hydrochloride 90 mg (Contrave) extended-release tablets, as an adjunct to a reduced-calorie diet and

increased physical activity for chronic weight management in adults with an initial BMI of 30 kg/m^2 or greater (obese) or 27 kg/m^2 or greater (overweight) in the presence of at least one weight-related comorbidity (e.g., controlled hypertension, type 2 diabetes mellitus, or dyslipidemia).

Stakeholder Engagement

Patient Input

Two patient groups, Obesity Canada and the Canadian Spondylitis Association, provided input for this submission. Obesity Canada is a national organization for professionals and patients. It aims to improve the lives of Canadians affected by obesity through the advancement of anti-discrimination, prevention, and treatment efforts. Its goals are to address the social stigma associated with obesity, change the way policy-makers and health professionals approach obesity, and improve access to evidence-based prevention and treatment resources. The Canadian Spondylitis Association is a registered not-for-profit patient association that supports, educates, and advocates for those living with spondylarthritis. Patient input submitted by Obesity Canada was based on 45 responses to an online survey of persons living with obesity and five interviews with individuals living with obesity, all of whom had experience with NB. Patient input submitted by the Canadian Spondylitis Association was based on 61 responses (49 females and 12 males) to an online survey and one-on-one discussions with five participants. Participants were individuals with a spondyloarthritic condition who were also diagnosed with obesity.

In addition to the numerous mental and physical health–related symptoms and conditions and chronic diseases that can result from obesity, patients also described difficulty exercising, difficulty losing weight, difficulty performing daily activities, preoccupation with weight, fatigue, low self-esteem due to perceived appearance, adverse effects on mood, and depression. Patients tend to struggle with varying degrees of success with available weight-loss options and often try several treatments, with weight regain identified as a significant issue.

Beyond weight loss, patients are interested in improvements in quality-of-life measures for issues related to obesity. Examples include improvement in comorbidities, such as diabetes, hypertension, and sleep apnea. Other outcomes of interest include productivity, energy levels, sleep, activity, and mental health. Individuals living with a spondyloarthritic condition and obesity commented that losing weight would allow them to improve mental and physical quality of life and in turn reduce or relieve pain and fatigue and improve mobility. Patients who take other medications (e.g., for a spondyloarthritic condition) are looking for medications with fewer side effects. Patients who had experience with NB noted a reduction in food cravings and a corresponding ability to focus on other aspects of their lives.

Clinician Input

Most Canadians living with obesity do not have access to obesity treatments. Few interdisciplinary behavioural intervention programs are available, less than 10% of Canadians currently have access to anti-obesity medications (even in private drug benefit plans), and wait times for surgery range from two to five years or longer (where bariatric surgery services exist). Behavioural interventions may be effective in the short term, but most patients experience difficulties maintaining weight loss through diet and exercise alone. Given the heterogeneous nature of obesity, one medication is not expected to work

for every patient. Instead, certain medications may work well in certain patients but prove ineffective in others. Use of medications in a patient can also be limited by adverse events (AEs) or contraindications to a specific drug. There is therefore a clear need for a range of effective medications to treat obesity, rather than a single drug.

As with any other pharmacotherapy for obesity, NB should always be considered an adjunct to behavioural interventions. It may reduce appetite and food cravings and increase tolerability of a calorie-restricted diet. In turn, this would help a patient achieve weight loss and prevent or attenuate weight gain. The other two available pharmacological therapies are limited by issues with tolerability for orlistat and the need for daily subcutaneous injection for liraglutide. Given these considerations, NB has the potential to be a first-line treatment as an adjunct to behavioural interventions.

As with any obesity treatment, patients who stand to benefit the most from weight loss are those who already present with obesity-related comorbidities. However, given the progressive nature of obesity, preventive use of medications to limit further weight gain in other patients may reduce complications in the long-term. Patients with contraindications to naltrexone and/or bupropion would not be suitable for treatment with NB. In addition, anti-obesity medications in general should not be used for short-term weight loss or for cosmetic reasons. There are no established predictors of response treatment with NB. However, patients who show an early weight-loss response are more likely to achieve and sustain clinically meaningful weight loss in the long term.

In general terms, a 5% sustained reduction in body weight is considered a clinically relevant response in most individuals, as this degree of weight loss has been shown to be beneficial in patients with obesity-related comorbidities such as hypertension or type 2 diabetes. Greater degrees of weight loss may be required to achieve clinically relevant benefits for other conditions, such as obstructive sleep apnea or osteoarthritis. Treatment response should be assessed both by weight trajectory as well as clinically relevant improvement in obesity-related comorbidities and quality of life. Treatment with NB can also be used to stabilize weight in patients who have already lost weight through any of the aforementioned interventions but are at risk of regaining weight. In these cases, a reduction in body weight while on NB would not be required to continue treatment. Treatment should be discontinued in patients who do not tolerate or do not respond to this medication.

Clinical Evidence

Pivotal Studies and Protocol-Selected Studies

Description of Studies

Five multi-centre, double-blind, placebo-controlled, parallel-group randomized controlled trials (RCTs) for NB in a fixed-dose combination conducted by the original sponsor (Orexigen Therapeutics, Inc.) were identified, including four 56-week pivotal phase III trials:

- COR-I (N = 1,742; 2007 to 2009) randomized patients 1:1:1 to naltrexone 16 mg/bupropion 360 mg daily (not a recommended dosage in the product monograph), naltrexone 32 mg/bupropion 360 mg daily, or matching placebo
- COR-II (N = 1,496; 2007 to 2009) randomized patients 1:1 to naltrexone 32 mg/bupropion 360 mg daily or matching placebo. From week 28 to 44, patients who did not lose at least 5% of body weight were re-randomized to continue or to receive

naltrexone 48 mg/bupropion 360 mg daily (not a recommended dosage in the product monograph)

- COR-BMOD (N = 793; 2007 to 2008) randomized patients 3:1 to 32 mg naltrexone/ 360 mg bupropion daily or matching placebo
- COR-DM (N = 505; 2007 to 2009) randomized patients with type 2 diabetes mellitus 2:1 to 32 mg naltrexone/360 mg bupropion daily or matching placebo.

In the COR-I, COR-II, and COR-DM studies, all patients received instructions to follow a hypocaloric diet and a prescription for walking at least 30 minutes a day three days a week, while patients in the COR-BMOD study participated in an intensive behaviour-modification program that included dietary instruction, 28 closed-group sessions, and prescribed exercise. Patients in the COR-I, COR-II, and COR-BMOD studies were non-diabetic and had a BMI of 30 kg/m^2 to 45 kg/m^2 with uncomplicated obesity or a BMI of 27 kg/m^2 to 45 kg/m^2 with controlled hypertension and/or dyslipidemia. Patients in the COR-DM study had type 2 diabetes that was not treatable with injectable antidiabetic medication or inhaled insulin, and a BMI of 27 kg/m^2 to 45 kg/m^2. The pivotal trials assessed change in weight from baseline for the co-primary end points (percent change in body weight from baseline and percentage of patients with at least 5% weight loss) and for one secondary end point (percentage of patients with at least 10% weight loss). Secondary end points were part of a sequential, hierarchical, closed testing procedure and other relevant secondary end points were the Impact of Weight on Quality of Life – Lite version (IWQoL-Lite), a disease-specific measure of health-related quality of life (HRQoL) total score; the item-19 ("Generally, how difficult has it been to control your eating?") score on the 21-item Control of Eating questionnaire (COE); the Inventory of Depressive Symptomology – Subject-Rated total score, a measure of severity of symptoms of depression; and the Food Craving Inventory (a measure of severity of food craving) sweet and carbohydrates or starches subscale scores. The mental and physical component summary scores of the Short-Form (36) Health were assessed in the COR-II study as exploratory end points, and the percentage of patients requiring a change in dose of oral antidiabetic medication was assessed in the COR-DM study as a secondary end point.

One RCT, the LIGHT study (N = 8,910), was a cardiovascular-outcomes trial of patients with a BMI of 27 kg/m^2 to 45 kg/m^2 and cardiovascular disease or type 2 diabetes with at least two cardiovascular risk factors. All patients participated in a comprehensive, web-based weight-management program. The LIGHT study was a noninferiority trial assessing time to first confirmed occurrence of a major adverse cardiovascular event (MACE) using a noninferiority margin of 1.4 for the hazard ratio to rule out increased risk of MACE with NB versus placebo. The required follow-up duration to accumulate the planned number of events was expected to be three to four years. Due to public release of the 25% interim results, the LIGHT study was terminated early by the investigators after 64% of planned events.

Efficacy Results

The co-primary end points (percent change in body weight from baseline and percentage of patients with at least 5% weight loss) were met in all four pivotal trials, and superiority of NB over placebo for weight loss was demonstrated (Table 1). The primary analyses were conducted by imputing the last observation carried forward in the full analysis sets, which comprised randomized patients who received at least one dose of the study drug and had at least one post-baseline measurement. Sensitivity analyses of the co-primary end points in the set of all randomized patients (or the full analysis set in the COR-BMOD study) with

imputation of the baseline observation carried forward (BOCF) yielded results consistent with the primary analyses, although the observed treatment effect in all four pivotal trials was consistently smaller for the co-primary end points compared with the primary analyses (Table 1). The percentage of patients with at least 10% weight loss, which was a secondary end point, was also statistically significantly different between groups in the COR-I, COR-II, and COR-BMOD studies (Table 1). In the COR-DM study, hypothesis testing ended at a secondary end point further up the testing hierarchy. Sensitivity analyses in all randomized patients using BOCF imputation were not performed for this end point. The LIGHT study did not control for multiplicity in body weight outcomes and was therefore at risk of type I error.

Subgroup analyses of the co-primary end points in the pivotal trials according to baseline BMI category (less than or at least the median baseline BMI) or the presence of hypertension or dyslipidemia did not find any notable differences between subgroups in treatment effect.

The primary end point in the LIGHT study was time to first occurrence of MACE (defined as cardiovascular death, non-fatal myocardial infarct, or non-fatal stroke). In the main analysis using an unadjusted Cox proportional hazards model, the hazard ratio for NB versus placebo using the final data cut-off was 0.95 (99.7% confidence interval, 0.65 to 1.38) with a P value of 0.0013 for ruling out a hazard ratio of 1.4 or greater and a P value of 0.6953 for demonstrating superiority. However, the study was terminated early (with 64% of expected events available) and conclusions were not drawn by the investigators based on the interim analysis of 50% of expected events or the analysis of the final dataset (64% of expected events). The trial was not stopped based on an unfavourable safety profile or a favourable benefit-to-risk profile.

The IWQoL-Lite total score was used to assess HRQoL and was in the statistical testing hierarchy of secondary end points in the pivotal trials. In COR-I, COR-II, and COR-BMOD, the improvement in IWQoL-Lite total score from baseline to week 56 (week 28 in the COR-II study) was statistically significantly greater in the NB group compared with the placebo group. Statistical testing was halted before this end point was reached in the hierarchy of the COR-DM study. Between-group differences in all pivotal trials did not meet the lower end of the range of minimal important differences (MIDs) identified for the IWQoL-Lite total score. Besides the IWQoL-Lite total score, the only other outcome for which a statistically significant between-group difference was found was for the item-19 score for the COE in the COR-I study, but the validity of using a single-item score from the COE is unknown.

Harms Results

In the pivotal trials, AEs were more common in the NB group than in the placebo group (Table 1). The AEs that consistently occurred more commonly in the NB group versus the placebo group were constipation (15.7% to 24.1% versus 5.6% to 14.0%), dry mouth (6.3% to 9.1% versus 1.0% to 3.0%), nausea (29.2% to 42.3% versus 5.3% to 10.5%), vomiting (8.5% to 18.3% versus 2.0% to 6.5%), dizziness (6.9% to 14.6% versus 2.6% to 5.3%), headache (13.8% to 23.8% versus 8.7% to 17.5%), and insomnia (7.5% to 11.1% versus 5.1% to 6.7%). In the pivotal trials, serious adverse events (SAEs) were reported in less than 5% of each treatment group (Table 1). SAEs reported in more than 1% of a treatment group were angina pectoris and atrial fibrillation, each occurring in two patients in the COR-DM study placebo group. In the LIGHT study, 9.7% of patients in the placebo group and 10.4% in the NB group reported an SAE. No SAEs were reported in at least 1% of either treatment group.

Gastrointestinal disorders and psychiatric disorders identified in the systematic review protocol as notable harms were more common in the NB group than in the placebo group in the pivotal trials (Table 1). Aside from gastrointestinal disorders, the most common notable AEs (expressed as ranges for NB and placebo, respectively) included anxiety (1.6% to 5.4% and 1.2% to 4.3%), increased blood pressure (1.7% to 4.5% and 0.9% to 3.0%), increased heart rate (0% to 3.4% and 0% to 1.6%), and hypertension (1.9% to 9.9% and 1.6% to 4.1%).

In the pivotal trials, withdrawals due to adverse events (WDAEs) were more common in the NB group than in the placebo group (Table 1). Reasons for WDAE reported by at least 1% in at least one treatment group were nausea, dizziness, headache, anxiety, disturbance in attention, vomiting, and urticaria. In the LIGHT study, the percentage of WDAEs was 9.0% in the placebo group and 29.0% in the NB group. Reasons for WDAE reported by at least 1% in at least one treatment group were nausea, constipation, vomiting, tremor, dizziness, and headache.

In all the pivotal trials, increases from baseline at two consecutive visits in pulse rate (of at least five beats per minutes or 10 beats per minutes), systolic blood pressure (of at least 10 mm Hg or 15 mm Hg), and diastolic blood pressure (of at least 5 mm Hg or 10 mm Hg) were more common in patients receiving NB than in patients receiving placebo (data not shown).

Table 1: Summary of Key Results from Pivotal and Protocol-Selected Studies

	COR-I		COR-II (week 28 results)		COR-BMOD		COR-DM	
	PL	**NB**	**PL**	**NB**	**PL**	**NB**	**PL**	**NB**
Main analyses: LOCF imputation, FA set	**N = 511**	**N = 471**	**N = 456**	**N = 825**	**N = 193**	**N = 482**	**N = 159**	**N = 265**
Co-primary end point: Mean body weight, kg								
Baseline (SD)	99.29 (14.33)	100.17 (16.26)	99.29 (15.97)	100.69 (16.65)	101.91 (15.04)	100.69 (15.43)	104.99 (17.13)	106.35 (19.11)
End point[a] (SD)	98.03 (15.21)	94.17 (17.40)	97.21 (16.18)	94.19 (17.61)	96.38 (17.07)	91.02 (17.13)	103.03 (17.33)	100.97 (19.67)
LSMD in % change, NB vs. PL (95% CI)	–4.81 (–5.63 to –3.99) **P < 0.001**		–4.56 (–5.19 to –3.93) **P < 0.001**		–4.21 (–5.56 to –2.86) **P < 0.001**		–3.28 (–4.34 to –2.22) **P < 0.001**	
Co-primary end point: Patients with ≥ 5% decrease in body weight,[b] n (%)	84 (16.4)	226 (48.0)	80 (17.5)	459 (55.6)	82 (42.5)	320 (66.4)	30 (18.9)	118 (44.5)
Odds ratio, NB vs. PL (95% CI)	4.86 (3.60 to 6.57) **P < 0.001**		6.61 (4.95 to 8.84) **P < 0.001**		2.89 (2.02 to 4.13) **P < 0.001**		3.44 (2.15 to 5.50) **P < 0.001**	
Secondary end point: Patients with ≥ 10% decrease in body weight[b], n (%)	38 (7.4)	116 (24.6)	32 (7.0)	225 (27.3)	39 (20.2)	200 (41.5)	9 (5.7)	49 (18.5)
Odds ratio, NB vs. PL (95% CI)	4.19 (2.82 to 6.23) **P < 0.001**		5.36 (3.60 to 7.98) **P < 0.001**		2.92 (1.95 to 4.37) **P < 0.001**		3.75 (1.79 to 7.88)	

	COR-I		COR-II (week 28 results)		COR-BMOD		COR-DM	
Sensitivity analyses: BOCF imputation, all randomized patients	**N = 581**	**N = 583**	**N = 495**	**N = 1,001**	**N = 202**	**N = 591**	**N = 170**	**N = 335**
Mean body weight, kg								
Baseline (SD)	99.45 (14.31)	99.70 (15.88)	99.21 (15.86)	100.31 (16.55)	101.88 (14.96)	100.16 (15.42)	105.08 (16.99)	104.22 (18.93)
End point[a] (SD)	98.59 (14.91)	95.77 (16.90)	97.57 (15.96)	95.50 (17.42)	97.50 (16.66)	93.90 (17.14)	103.60 (17.29)	100.91 (19.15)
LSMD in % change, NB vs. PL (95% CI)	–3.12 (–3.81 to –2.42) P < 0.001		–3.28 (–3.88 to –2.69) P < 0.001		–1.91 (–3.21 to –0.61) P = 0.004		–1.72 (–2.68 to –0.77) P < 0.001	
Patients with ≥ 5% decrease in body weight,[b] n (%)	67 (11.5)	180 (30.9)	69 (13.9)	421 (42.1)	64 (33.2) **FA set N = 193**	242 (50.2) **FA set N = 482**	24 (14.1)	94 (28.1)
Odds ratio, NB vs. PL (95% CI)	3.61 (2.63 to 4.94) P < 0.001		4.93 (3.68 to 6.62) P < 0.001		2.17 (1.51 to 3.11) P < 0.001		2.35 (1.44 to 3.86) P < 0.001	
Treatment discontinuations, n (% of randomized patients)	291 (50.1)	287 (49.2)	228 (46.1)	463 (46.3)	84 (41.6)	249 (42.1)	70 (41.2)	160 (47.8)
AEs; safety set	**N = 569**	**N = 573**	**N = 492**	**N = 992**	**N = 200**	**N = 584**	**N = 169**	**N = 333**
Patients with > 0 AEs, n (%)	390 (68.5)	476 (83.1)	370 (75.2)	852 (85.9)	176 (88.0)	547 (93.7)	144 (85.2)	301 (90.4)
Patients with > 0 SAEs, n (%)	8 (1.4)	9 (1.6)	7 (1.4)	21 (2.1)	1 (0.5)	22 (3.8)	8 (4.7)	13 (3.9)
WDAEs, n (%)	56 (9.8)	112 (19.5)	68 (13.8)	241 (24.3)	25 (12.5)	150 (25.7)	26 (15.4)	98 (29.4)
Notable AEs								
Gastrointestinal disorders (SOC)	136 (23.9)	292 (51.0)	131 (26.6)	532 (53.6)	78 (39.0)	380 (65.1)	53 (31.4)	215 (64.6)
Psychiatric disorders (SOC)	62 (10.9)	85 (14.8)	75 (15.2)	205 (20.7)	45 (22.5)	145 (24.8)	20 (11.8)	75 (22.5)
Hypertension	14 (2.5)	17 (3.0)	8 (1.6)	19 (1.9)	4 (2.0)	14 (2.4)	7 (4.1)	33 (9.9)

AE = adverse event; BOCF = baseline observation carried forward; CI = confidence interval; FA = full analysis; LOCF = last observation carried forward; LSMD = least squares mean difference; NB = naltrexone and bupropion; PL = placebo; SAE = serious adverse event; SD = standard deviation; SOC = system organ class; vs. = versus; WDAE = withdrawal due to adverse event.

Note: The FA set included patients who were randomized, had a baseline weight measurement, and had at least one post-baseline weight measurement while on the study drug. The LOCF approach used post-baseline observations made while on treatment (up to one day after last confirmed dose of study medication). Continuous end points were analyzed using an analysis of covariance model. Categorical end points were analyzed using a logistic regression model. For the COR-I, COR-II, and COR-BMOD studies, the model adjusted for study centre and baseline body weight. For the COR-DM study, the model adjusted for glycated hemoglobin category (≤ or > 8%), sulfonylurea use (with or without), and baseline body weight.

[a] Week 56 (week 28 in the COR-II study).

[b] From baseline to week 56 (week 28 in the COR-II study).

Source: Clinical Study Reports for the COR-I, COR-II, COR-BMOD, and COR-DM studies.

Critical Appraisal

The main limitation common to all the trials was the large proportion of treatment and study discontinuations (see Table 1 for treatment discontinuations). Additionally, rates of discontinuation due to AEs and lack of efficacy were imbalanced between treatment groups in each trial. Discontinuation due to AEs was more common in the NB groups and discontinuation due to lack of efficacy (including those who did not achieve at least 2% weight loss in the LIGHT study by week 16) was more common in the placebo groups.

The primary analyses in the pivotal trials was in the full analysis set (all randomized patients with a baseline weight measurement and at least one post-baseline weight measurement while on the study drug) using imputation of the last observation carried forward for missing data. The use of the full analysis set rather than a true intention-to-treat (ITT) set resulted in exclusion of any patients who discontinued treatment before the week 4 visit. The percentage of patients discontinuing the study treatment during the first four weeks was significant and imbalanced between treatment groups, ranging from 5.9% to 10.8% in the placebo groups and from 18.3% to 22.1% in the NB groups. Consequently, patients were not missing at random, and using the full analysis set instead of the set of all randomized patients likely biased the results in favour of NB as patients who discontinued in the first four weeks were less likely than the rest of the patients to receive treatment benefit. The BOCF method assigned no overall benefit from weight loss to patients who discontinued treatment. This method is in line with input from the clinical expert consulted for this review, who indicated that patients who discontinue treatment are expected to return to their baseline weight and that there is no evidence for an overall benefit from temporary weight loss. While a 5% decrease in weight may be of clinical benefit and was a co-primary end point, the clinical expert indicated that patients generally require weight loss of at least 10% to 15% to be satisfied with efficacy and continue treatment. Some patients in the trials who were considered responders for the co-primary end point would have been more likely to discontinue due to perceived lack of efficacy, outside of a clinical trial setting, experience weight regain, and therefore receive minimal overall benefit.

Maintenance of weight following weight loss is a key challenge for patients with obesity, and patients are expected to continue pharmacotherapy for weight management indefinitely, according to the clinical expert. The pivotal trials did not provide efficacy results beyond one year of treatment and most patients in the LIGHT study discontinued treatment after less than one year. Evidence for the long-term efficacy of NB past one year of treatment is therefore limited.

The major limitation in the LIGHT study was its early termination and the inability to draw conclusions based on the 50% interim analysis or the final data cut-off analysis, given the reduction in statistical power. In addition, the large proportions of patients discontinuing treatment early may have biased the results toward the null (which is problematic in a noninferiority study), as the risk of cardiovascular events could be positively associated with duration of treatment exposure and/or negatively associated with time since treatment discontinuation.

Indirect Comparisons

Description of Studies

One relevant published network meta-analysis (NMA) was included in the review. The NMA compared weight loss and discontinuations due to AEs between five FDA-approved weight-

loss drugs (orlistat, lorcaserin, NB, phentermine-topiramate, and liraglutide) for long-term use in obese (BMI of at least 30 kg/m^2) or overweight (BMI of at least 27 kg/m^2) patients with at least one weight-related comorbidity. The primary efficacy outcome for the NMA was the proportion of patients with at least 5% weight loss at one year of follow-up, relative to baseline weight. Other efficacy outcomes assessed were the proportion of patients with at least 10% weight loss and the change in weight in kilograms relative to baseline weight in excess of placebo after one year of follow-up.

A total of 28 primary RCTs were included in the NMA evidence network: 16 RCTs of orlistat versus placebo, two of liraglutide versus placebo, four of NB versus placebo, three of lorcaserin versus placebo, two of phentermine-topiramate versus placebo, and one three-armed trial comparing orlistat and liraglutide with placebo.

Efficacy Results

In the main analyses of the three efficacy outcomes, the 95% credible intervals (CrIs) excluded values of 1 for odds ratios and 0 for mean differences for the comparisons of NB versus placebo and NB versus orlistat (and not for the comparison of NB versus liraglutide).

For the primary outcome, the proportion of patients with at least 5% weight loss, the odds ratios were 0.71 (95% CrI, 0.46 to 1.04) for NB versus liraglutide; 1.47 (95% CrI, 1.09 to 1.96) for NB versus orlistat; and 3.96 (95% CrI, 3.03 to 5.11) for NB versus placebo.

For the proportion of patients with at least 10% weight loss, the odds ratios were 0.83 (95% CrI, 0.50 to 1.30) for NB versus liraglutide; 1.74 (95% CrI, 1.22 to 2.47) for NB versus orlistat; and 4.19 (95% CrI, 3.08 to 5.72) for NB versus placebo.

For the mean change in weight in excess of placebo (in kilograms), the mean differences were as follows: 0.32 (95% CrI, –0.92 to 1.59) for NB versus liraglutide; –2.36 (95% CrI, –3.43 to –1.28) for NB versus orlistat; and –4.95 (95% CrI, –5.94 to –3.96) for NB versus placebo.

Harms Results

For the percentage of patients discontinuing due to AEs, the odds ratios were as follows: 0.90 (95% CrI, 0.58 to 1.35) for NB versus liraglutide; 1.44 (95% CrI, 1.07 to 1.95) for NB versus orlistat; and 2.64 (95% CrI, 2.1 to 3.35) for NB versus placebo.

Critical Appraisal

The main limitations affecting the interpretation of the NMA results were the high risk of attrition bias in all the primary RCTs due to the proportions of study discontinuations ranging from 30% to 45% (according to the authors' quality assessment), and bias in favour of NB for efficacy and against NB for harms due to use of the full analysis set compared with the modified intention-to-treat (mITT) set in the other RCTs, In addition variation in study design characteristics and potential effect modifiers may have undermined the assumption of clinical similarity between pairwise comparisons. Inconsistency between main analyses and worst-case scenario sensitivity analyses for the 5% and 10% weight-loss outcomes (i.e., 95% CrIs for odds ratios no longer excluding 1), coupled with the identified limitations, meant that superior efficacy of NB over orlistat could not be concluded. Similarly, the identified limitations meant that superiority of orlistat over NB in discontinuations due to AEs could not be established. There was no evidence for a difference in any of the outcomes between NB and liraglutide.

Conclusions

The pivotal trials demonstrated that NB results in greater weight loss versus placebo in adult patients who are obese (BMI of at least 30 kg/m^2) or overweight (BMI of at least 27 kg/m^2) in the presence of at least one weight-related comorbidity. Whether this greater weight loss, measured as percent change in weight and percentage of patients who achieve at least 5% weight loss, translates to a clinically meaningful benefit is unclear, given that improvement in, or prevention of, weight-related comorbidities were either not assessed in the trials or could not be statistically tested. No evidence was found for a clinically meaningful benefit from NB over placebo in HRQoL or food craving, and other outcomes important to patients were not assessed.

Treatment discontinuation was common in the pivotal trials, often due to AEs. A limited subgroup of patients of the indicated population may achieve weight loss with NB that they find satisfactory when balanced against AEs, but no predictive markers for identifying these patients prior to initiating treatment are available. There was insufficient evidence to demonstrate maintenance of weight loss with NB past one year of treatment, which is a major limitation considering the progressive nature of the disease and the expectation that patients will remain on the treatment indefinitely.

The most common AEs associated with NB in the pivotal trials were gastrointestinal and nervous disorders that are generally considered manageable. The LIGHT study was designed to rule out the possibility of increased risk of major adverse cardiovascular outcomes with NB treatment based on higher pulse rate and blood pressure associated with NB in the pivotal trials, but conclusions could not be drawn due to its early termination. Until results are available from a planned second cardiovascular-outcomes study, the potential cardiovascular harms associated with NB remain uncertain.

In one NMA, there was no evidence for a difference in weight loss or discontinuations due to AEs between NB and the other available pharmacotherapies for weight management, orlistat and liraglutide.

Introduction

Disease Background

Obesity is characterized by excess adiposity and weight gain and is associated with many chronic comorbidities, including cardiovascular disease, type 2 diabetes mellitus, osteoarthritis, hypertension, dyslipidemia, and certain forms of cancer.[1,2] Obesity occurs when there is an imbalance between energy intake and energy expenditure, and the causes of this imbalance are complex and multifactorial.[1,2] Identified determinants of obesity include physical activity, diet, socioeconomic status, ethnicity, immigration, and environmental factors.[3] Patients are considered to have overweight or obese according to their BMI, which takes weight and height into account. A BMI of 25 kg/m^2 to 30 kg/m^2 corresponds with overweight and a BMI of over 30 kg/m^2 corresponds with obesity. According to the 2016 and 2017 Canadian Health Measures Survey and the 2017 Canadian Community Health Survey, 34% of Canadian were overweight and 27% were obese.[4] Obesity prevalence has increased in recent decades, with an approximate doubling of obesity evident in a comparison of 1981 and 2007-to-2009 surveys.[3]

Obesity, overweight, and its associated conditions can have a myriad of negative impacts that are detrimental to the physical, mental, and social well-being of patients. Patient input submitted for this review highlighted the following negative effects of obesity: pain, difficulty exercising and performing daily activities, fatigue, preoccupation with food, worrying about weight, low self-esteem due to perceived appearance, adverse effects on mood, and depression.

As noted by the clinical expert consulted for this review, those with obesity may experience weight bias and discrimination. Mental health issues can be a product of obesity and influence behaviour that promotes further weight gain by increased caloric intake and avoidance of physical activity. In addition to the comorbidities of obesity listed above, existing health conditions can become more difficult to treat and manage in the presence of excess adiposity, and certain diagnostic procedures may become more difficult to perform.

Standards of Therapy

Canadian recommendations for managing obesity and overweight consider dietary and physical activity interventions to be appropriate for adults who have overweight or obesity.[1,2] The Canadian Task Force on Preventive Health Care (CTFPHC) 2015 guideline recommends structured behavioural interventions aimed at weight loss (involving several sessions or interactions over weeks to months and a focus on diet, exercise, making lifestyle changes, or any combinations of these) for adults with obesity and at high risk of diabetes (strong recommendation) and adults who have overweight or obesity (weak recommendation).[1] The 2006 Canadian clinical practice guidelines on the management and prevention of obesity in adults and children were developed by a panel of experts convened by Obesity Canada, a not-for-profit organization.[2] Obesity Canada guidelines strongly recommend an energy-reduced diet and regular physical activity as the first treatment option for adults and children who are overweight or obese to achieve clinically important weight loss and reduce obesity-related symptoms.[2]

In addition to the drug under review, the two other pharmacologic therapies approved in Canada for chronic weight management are orlistat and liraglutide. The CTFPHC recommends that practitioners not routinely offer pharmacologic interventions such as

orlistat or metformin aimed at weight loss, due to concerns with AEs and the generalizability of clinical trials of metformin or orlistat for weight loss (weak recommendation).[1] At the same time, the CTFPHC acknowledges that pharmacologic therapy may be suitable for some patients.[1] Obesity Canada guidelines suggest adding a pharmacologic drug for selected adults with overweight or obesity who do not attain or maintain clinically important weight loss with diet and exercise therapy alone (intermediate recommendation).[2] Both guidelines were published prior to the original marketing date in Canada for liraglutide (Saxenda) an NB. Orlistat and liraglutide are associated with gastrointestinal AEs; orlistat with fatty or oily stools, fecal incontinence, and increased defecation; and liraglutide with mild or moderate nausea, constipation, diarrhea, and vomiting.[5]

If pharmacotherapy is not effective, bariatric surgery may be appropriate for some patients with a BMI of at least 40 kg/m^2 or 35 kg/m^2 with severe comorbid disease.[2] However, bariatric surgery is associated with a risk of mortality or serious complications and is typically used as a last resort for weight loss.[6] Although the volume of bariatric surgeries in Canadian hospitals has almost quadrupled from the fiscal year 2006 to 2007 to the year 2012 to 2013, wait times for publicly covered bariatric surgery can range from months to several years.[6]

According to patient input submitted for this review, patients struggle with varying degrees of success with available options to lose weight. Additionally, weight regain is a significant issue. Patients have tried a variety of nonpharmacologic methods to lose weight, including commercial programs, physical activity, mental health interventions, behavioural interventions, and medically supervised nutrition interventions. Patients often attempt several different treatments. They also have trouble accessing medical and surgical interventions for obesity, as few provinces and territories have obesity-treatment programs, there are few interdisciplinary teams for obesity prevention and management, medications for obesity are not covered by provincial public drug benefit programs, and access to bariatric surgery is limited.

Beyond weight loss, patients are looking for a treatment that improves comorbidities as well as pain, fatigue, mobility, productivity, energy levels, sleep, activity, and mental health. Improvements in these aspects are expected to lead to improved mental and physical well-being. Some patients who had experience with NB (Contrave) noted that the treatment mitigated constant obsessions with food and cravings and allowed them to focus on other aspects of life.

Drug

Contrave is a fixed-dose combination of naltrexone hydrochloride 8 mg and bupropion hydrochloride 90 mg extended-release tablets for oral administration. Naltrexone is an opioid antagonist and bupropion is a relatively weak inhibitor of the neuronal reuptake of dopamine and norepinephrine. The recommended dosage is two tablets twice daily for a total daily dose of 32 mg of naltrexone hydrochloride and 360 mg of bupropion hydrochloride. Contrave is indicated as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adults with an initial BMI of 30 kg/m^2 or greater (obese) or 27 kg/m^2 or greater (overweight) in the presence of at least one weight-related comorbidity (e.g., controlled hypertension, type 2 diabetes mellitus, or dyslipidemia).

Table 2: Key Characteristics of Naltrexone-Bupropion, Liraglutide, and Orlistat

	Naltrexone-bupropion	Liraglutide	Orlistat
Mechanism of action	Non-clinical studies suggest that naltrexone and bupropion affect two separate areas of the brain involved in the regulation of food intake: the hypothalamus (appetite regulatory centre) and the mesolimbic dopamine circuit (reward system). The exact neurochemical effects leading to weight loss are not fully understood.	Acylated human GLP-1 receptor agonist. GLP-1 is a physiological regulator of appetite and food intake.	Reversible inhibitor of lipases acting in the lumen of the stomach and small intestine.
Indication[a]	Indicated as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adults with an initial BMI of: • 30 kg/m^2 or greater (obese) or • 27 kg/m^2 or greater (overweight) in the presence of at least one weight-related comorbidity (e.g., controlled hypertension, type 2 diabetes, or dyslipidemia).	Indicated as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adult patients with an initial BMI of: • 30 kg/m^2 or greater (obese), or • 27 kg/m^2 or greater (overweight) in the presence of at least one weight-related comorbidity (e.g., hypertension, type 2 diabetes, or dyslipidemia) and who have failed a previous weight management intervention.	When used in conjunction with a mildly hypocaloric diet, is indicated for: • obesity management including weight loss and weight maintenance • reducing the risk of weight regain in patients after prior weight loss. These indications apply to obese patients with a BMI ≥ 30 kg/m^2 or a BMI ≥ 27 kg/m^2 in the presence of other risk factors (e.g., hypertension, type 2 diabetes, dyslipidemia, excess visceral fat).
Route of administration	Oral	Subcutaneous injection	Oral
Recommended dosage	Two 8 mg naltrexone/90 mg bupropion extended-release tablets taken twice daily for a total daily dose of 32 mg/360 mg. At initiation, dosage should be escalated as follows: • Week 1: 1 tablet in the a.m. • Week 2: 1 tablet in the a.m. and 1 tablet in the p.m. • Week 3: 2 tablets in the a.m. and 1 tablet in the p.m. • Week 4 onwards: 2 tablets in the a.m. and 2 tablets in the p.m. The maximum recommended daily dose is 1 tablet in the a.m. and p.m. each for patients with moderate-to-severe renal impairment. Treatment should be discontinued after 12 weeks at the maintenance dosage if the patient has not lost at least 5% of initial body weight.	In adults with an initial BMI of 27 kg/m^2 or greater, the recommended daily maintenance dose is 3.0 mg/day. Daily doses higher than 3.0 mg are not recommended. At initiation, dosage should be escalated in 0.6 mg increments every week to reduce the likelihood of gastrointestinal symptoms. Treatment should be discontinued after 12 weeks at the maintenance dosage if the patient has not lost at least 5% of initial body weight.	One 120 mg capsule three times daily with each main meal.
Serious side effects and safety Issues	Contraindicated in: • Uncontrolled hypertension • Seizure disorder or a history of seizures • Use of other bupropion hydrochloride–containing products	Contraindicated in patients: • With a personal or family history of medullary thyroid carcinoma or in patients	Contraindicated in patients with: • Chronic malabsorption syndrome • Cholestasis

	Naltrexone-bupropion	Liraglutide	Orlistat
	• With a current or prior diagnosis of bulimia or anorexia nervosa • Chronic opioid or opiate agonist (e.g., methadone) or partial agonists (e.g., buprenorphine) use, or acute opiate withdrawal • Patients undergoing an abrupt discontinuation of alcohol, benzodiazepines or other sedatives, and antiepileptic drugs • Concomitant administration of monoamine oxidase inhibitors or thioridazine • Pregnancy • Severe hepatic impairment • End-stage renal failure • Hypersensitivity to this drug or to any ingredient in the formulation or component of the container. Warnings based on experience with bupropion: • Potential association with behavioural and emotional changes, including self-harm • Seizures • Antidepressant treatment can precipitate a manic, mixed, or hypomanic episode (increased risk with bipolar disorder) • Patients with major depression treatment with bupropion have been reported to show a variety of neuropsychiatric signs and symptoms • Anaphylactic reactions or shock, erythema multiforme, Stevens-Johnson syndrome, and symptoms suggestive of delayed hypersensitivity associated with bupropion have been reported.	with multiple endocrine neoplasia syndrome type 2 • Who are hypersensitive to liraglutide or to any ingredient in the formulation • Who are pregnant or breast-feeding. Serious warning: Dose-dependent and treatment-duration-dependent thyroid C-cell tumours at clinically relevant exposures in both genders of rats and mice. Warnings: • Increase in heart rate and PR interval prolongation have been observed in clinical trials Severe hypoglycemia was observed in clinical trials in patients with type 2 diabetes • Acute pancreatitis and gallbladder disease have been observed in clinical trials • Hypersensitivity reactions have been reported • Monitor patients for depression, suicidal ideation, or unusual mood/behaviour changes.	• Known hypersensitivity to the drug. Warnings: • Cases of rectal bleeding have been reported • There have been rare post-marketing reports of severe liver injury with hepatocellular necrosis or acute hepatic failure • There have been reports of convulsions with concomitant treatment with antiepileptic drugs.

BMI = body mass index; GLP-1 = glucagon-like peptide-1.

[a] Health Canada indication.

Source: Product monographs for Contrave, Saxenda, and Xenical.[7-9]

Stakeholder Engagement

Patient Group Input

This section was prepared by CADTH staff based on the input provided by patient groups.

Brief Description of Patient Group(s) Supplying Input

Two patient groups, Obesity Canada and the Canadian Spondylitis Association, provided input for this submission.

Obesity Canada is a national organization for professionals and patients. It aims to improve the lives of Canadians affected by obesity through the advancement of anti-discrimination, prevention, and treatment efforts. Its goals are to address the social stigma associated with obesity, change the way policy-makers and health professionals approach it, and improve access to evidence-based prevention and treatment resources. Obesity Canada consulted with other patient associations who have submitted patient input to CADTH.

The Canadian Spondylitis Association is a registered not-for-profit patient association that supports, educates, and advocates for those living with spondylarthritis.

Condition-Related Information

Obesity Canada engaged persons living with obesity with an online survey sent through a newsletter to 4,300 people between April 23 and May 14 of 2019 and received 45 responses. Obesity Canada conducted five interviews with individuals living with obesity with experience with NB (Contrave). Additionally, Obesity Canada engaged with researchers who helped prepare the Obesity Canada Report Card on Access to Obesity Treatments for Canadian Adults and surveyed clinicians and scientists for information about clinical practice guidelines, obesity management, and weight bias and discrimination.

The Canadian Spondylitis Association gathered information from 61 responses (49 females and 12 males) to an online survey in April and May of 2019 and one-on-one discussions with five females. Participants were individuals with a spondyloarthritic condition who were also diagnosed with obesity.

Obesity is a chronic relapsing condition characterized by excessive fat accumulation and weight gain. It is a heterogeneous condition that results from complex interactions with many social, psychological, and biological factors. Individuals living with obesity may experience numerous mental and physical health–related symptoms and conditions, and chronic diseases that can result from obesity include type 2 diabetes, non-alcoholic fatty liver disease, high blood pressure, heart disease, stroke, arthritis, and many forms of cancer. Once obesity occurs, neuro-hormonal factors can impede weight loss and contribute to weight regain if loss occurs.

Many aspects of social and economic well-being are also affected by obesity. One respondent stated, “I need to lose weight so I can have the energy and mobility to play with my kids/grandkids” and “I am so preoccupied with worrying about my weight that my productivity and mental health suffer, if I can lose some weight, everything else will get better.” Other specific impacts of obesity that were outlined by individuals with spondyloarthritic conditions included pain, difficulty exercising, difficulty losing weight,

difficulty performing daily activities, fatigue, low self-esteem due to perceived appearance, adverse effects on mood, and depression. For example, one participant stated,

> I hate being so over-weight. My Rheumatologist keeps telling me I need to lose weight. It's hard when you can't bend and are in constant pain. My hips, lower back, knees and feet hurt the most. I hate looking at myself. I was never over weight when I was younger. It's very hard to find a man who wants a relationship with me. I feel very depressed.

Current Therapy-Related Information

Obesity Canada summarized that patients feel that there are many limitations characterizing currently available treatment options for obesity in Canada. Few provinces and territories have obesity-treatment programs and few interdisciplinary teams are available for obesity prevention and management. Medications for obesity are not covered by provincial public drug benefit programs and access to bariatric surgery is limited. Obesity Canada noted that many of their patient supporters were not aware of Health Canada–approved medications for obesity and that there was interest in more information about Contrave. Despite this, nearly all (> 95%) of the respondents to the Obesity Canada survey indicated that anti-obesity medications need to be covered under public and private insurance plans in the same manner as treatments for any other chronic disease state.

Patients struggle with varying degrees of success with available options to lose weight. Additionally, weight regain is a significant issue. Respondents to the Canadian Spondylitis Association survey have tried a variety of non-drug methods to lose weight, including commercial programs such as Weight Watchers (33%), physical activity (33%), and mental health interventions (25%). Respondents have tried a variety of treatments — and often several at once — to try to lose weight. Some have tried behavioural interventions (16%) or medically supervised nutrition intervention (18%). Two individuals tried bariatric surgery. One respondent to the Canadian Spondylitis Association survey commented, "I have tried too many treatments to possibly count." Another respondent commented, "I've had gastric bypass surgery in January 2017. It was successful. Now two years later, I am struggling with emotional eating and starting to regain weight?" Another respondent stated, "I try different diets and programs. Some work, some don't. If I do lose weight, it's not enough to really help me. And the weight doesn't stay off long-term. It's like a yo-yo and is very frustrating. Sometimes I just want to give up on life."

The submissions described the struggle that patients experience with the lack of affordability of available medications to treat obesity, particularly when combined with medications for other conditions. One respondent stated,

> When choosing a treatment for obesity, the first thing I have to look at is the cost, even before I see what the potential outcomes might be, because my drug plans do not cover obesity treatments so I would be out of pocket for anything. Even if the medication cured everything and made all my weight-related issues go away, I would still consider the financial aspect of it first. I have responsibilities and obligations and do not have the disposable income to make this a non-issue.

Expectations About the Drug Being Reviewed

Patients are interested in outcomes beyond weight loss. Obesity Canada summarized that, beyond weight loss, individuals with obesity are much more interested in improvements in quality-of-life measures related to obesity. Examples include improvement in comorbidities, such as diabetes, hypertension, and sleep apnea. Other outcomes of interest include productivity, energy levels, sleep, activity, mental health, and reduced stress associated with other conditions. These outcomes could positively affect social aspects of life such as comfort in group situations. Respondents reported that cost was the most significant factor when choosing a therapy for obesity. For individuals living with a spondyloarthritic condition and obesity, the majority of respondents commented that weight loss would allow them to improve mental and physical quality of life, which would in turn reduce or relieve pain and fatigue and improve mobility. Patients who take other medications (e.g., for a spondyloarthritic condition), are looking for medications with fewer side effects.

For patients who took Contrave, the impact on food cravings was noted. For example, one patient reported it was “as if a heavy burden was lifted allowing for some clarity and mental space being opened up. The constant obsession or thinking about food was replaced with the ability to focus on other areas of my life.” One patient with experience commented,

> I hope that Contrave will continue to improve my quality of life by allowing me to no longer obsess over food and my weight. Take control of my cravings which would allow me to free up a massive amount of mental real estate. This will allow me to be more productive, more functional, a better father and husband, and allow me to enjoy life. This in turn will positively impact my physical health by allowing me to manage my weight better, improve function and reduce pain. Contrave has the potential to have such far reaching benefits to my quality of life that go way beyond any weight loss.

Only one patient noted any adverse effects of Contrave. This patient experienced hot flashes, nausea, and unbearable tinnitus that was not reversible two months after drug discontinuation.

Additional Information

The Obesity Canada submission acknowledged that it is likely that Contrave would not work for all patients and was supportive of the stopping rule incorporated into the Contrave product monograph.

Clinician Input

All CADTH review teams include at least one clinical specialist with expertise regarding the diagnosis and management of the condition for which the drug is indicated. Clinical experts are a critical part of the review team and are involved in all phases of the review process (e.g., providing guidance on the development of the review protocol, assisting in the critical appraisal of clinical evidence, and interpreting the clinical relevance of the results and providing guidance on the potential place in therapy). This section was prepared by CADTH based on input provided by one clinical specialist with expertise in the diagnosis and management of obesity and overweight conditions.

Current Treatment Paradigm

All current obesity guidelines (national and international) call for long-term treatment of obesity as a chronic disease using a combination of multidisciplinary behavioural management, medication (aside from NB, this would be orlistat and liraglutide), and/or surgery. Both medication and surgery promote weight loss by targeting the primary driver of weight gain, i.e., increased appetite, by inhibiting hunger (including cravings) and promoting satiety, thereby reducing caloric consumption. In addition, medication and surgery, through their biological modes of action, inhibit the biological homeostatic response to weight loss and allow patients to sustain a greater degree of weight loss over the long term (as long as the treatment continues).

Treatment Goals

The overall goals of treatment are alleviating symptoms and improving health and well-being in all aspects of patients' lives, specifically for weight-related comorbidities and existing health conditions that are exacerbated by the presence of excess adiposity. These include the mental (e.g., depression, low self-esteem, and social anxiety/avoidance), metabolic (e.g., type 2 diabetes, hypertension, fatty liver disease, gall bladder disease, and polycystic ovary syndrome), and mechanical (e.g., osteoarthritis in weight-bearing joints, obstructive sleep apnea, gastroesophageal reflux disease, and urinary incontinence) impacts of obesity, as well as impacts on social and work life due to weight bias and discrimination.

Unmet Needs

As outlined in the 2019 Obesity Canada Report Card on Access to Obesity Treatments for Adults, most Canadians living with obesity do not have access to obesity treatments. Few interdisciplinary behavioural intervention programs are available, less than 10% of Canadians currently have access to anti-obesity medications (even in private drug benefit plans), and wait times for surgery range from two to five years or longer (where bariatric surgery services exist). It is therefore fair to say that the vast majority of Canadians living with obesity are currently not receiving treatment for their condition. As a direct consequence, the incidence of severe obesity (BMI of over 35 kg/m^2) is rising, as can be expected when a progressive chronic disease remains uncontrolled.

There are a number of limitations regarding the currently available treatment options for obesity in Canada. Behavioural interventions may be effective in the short term, but most patients have difficulty maintaining weight loss through diet and exercise alone. The long-term effectiveness of behavioural interventions is limited due to the body's tendency to defend body weight by limiting weight loss (e.g., through a decrease in metabolic rate) and promoting weight gain (e.g., through an increase in appetite). Living in an obesogenic environment (e.g., one that encourages unhealthy eating or discourages physical activity) may also contribute to these difficulties.

Pharmacological options for obesity treatment are extremely limited. This is especially true when the paucity of pharmacological options for obesity treatment are compared to the relative abundance of drugs for the treatment of other common chronic disorders. Given the heterogeneous nature of obesity, one medication is not expected to work for every patient. Instead, certain medications can be expected to work well in certain patients but prove ineffective in others. Use of medications in a patient can also be limited by adverse effects

or contraindications to a specific drug. There is therefore a clear need for a range of effective medications to treat obesity, rather than a single drug.

Place in Therapy

As with any other pharmacotherapy for obesity, NB should always be considered an adjunct to behavioural interventions. The mechanism of action of NB, which centrally suppresses appetite, is unique among the medications available for chronic weight management. It may reduce appetite and food cravings and increase tolerability of a calorie-restricted diet. In turn, this would help a patient lose weight and prevent or attenuate weight gain. The other two available pharmacological therapies are limited by issues with tolerability (in the case of orlistat, stemming from significant gastrointestinal adverse effects) and the need for daily subcutaneous injection (in the case of liraglutide). Given these considerations, NB has the potential to be a first-line treatment as an adjunct to behavioural interventions.

Patient Population

Current indications for obesity medications are based on BMI, with or without the presence of obesity-related comorbidities. There is considerable underdiagnosis of obesity, especially at lower BMI values, as BMI is not routinely assessed by all clinicians. As with any obesity treatment, patients who stand to benefit the most from weight loss are those who already present with obesity-related comorbidities. However, given the progressive nature of obesity, preventive use of medications to limit further weight gain in other patients may reduce complications over the long term.

There are no established predictors of response treatment with NB. However, patients who show an early weight-loss response are more likely to achieve and sustain clinically meaningful weight loss over the long term.

Patients with contraindications to naltrexone and/or bupropion are not suitable for treatment with NB. In addition, anti-obesity medications in general should not be used for short-term weight loss or for cosmetic reasons.

Assessing Response to Treatment

In general terms, a 5% sustained reduction in body weight is considered a clinically relevant response in most individuals, as this degree of weight loss has been shown to be beneficial in patients with obesity-related comorbidities such as hypertension or type 2 diabetes.[10] Greater degrees of weight loss may be required to achieve clinically relevant benefits for other conditions, such as obstructive sleep apnea or osteoarthritis. Treatment response should be assessed both by weight trajectory as well as clinically relevant improvement in obesity-related comorbidities and quality of life. Although the frequency of assessment varies from patient to patient depending on weight-related comorbidities and other factors, patients may be assessed more frequently when pharmacotherapy is initiated (perhaps every four to six weeks) followed by approximately every three to six months, when a stable dose is achieved. The drug could also be used to stabilize weight loss in patients who have already lost weight through any of the aforementioned interventions but are at risk of weight regain. In these cases, a reduction in body weight while on NB would not be required to continue treatment.

Discontinuing Treatment

Use of NB should be discontinued in patients who do not tolerate or do not respond to this medication. Since an early weight-loss response is a predictor of long-term weight loss and maintenance, there is a stopping rule aimed at limiting the ongoing use of NB in patients who are clearly not responding. The product monograph for Contrave states: "If a patient has not lost at least 5% of baseline body weight, discontinue Contrave, as it is unlikely that the patient will achieve and sustain clinically meaningful weight loss with continued treatment."[7]

Prescribing Conditions

Treatment with NB can be prescribed and monitored in a family medicine practice and no specialty is required to diagnose, treat, and monitor patients who receive NB.

Clinical Evidence

The clinical evidence included in this review is presented in three sections. The systematic review includes pivotal studies provided in the sponsor's submission to CADTH and Health Canada, as well as those studies that were selected according to an a priori protocol. The second section includes indirect evidence from the sponsor (if submitted) and indirect evidence selected from the literature that met the selection criteria specified in the review. This is followed by a review of sponsor-submitted long-term extension studies and additional relevant studies to address important gaps in the evidence included in the systematic review.

Systematic Review (Pivotal and Protocol-Selected Studies)

Objectives

To perform a systematic review of the beneficial and harmful effects of naltrexone hydrochloride 8 mg and bupropion hydrochloride 90 mg (Contrave) extended-release tablets as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adults with an initial BMI of 30 kg/m^2 or greater (obese) or 27 kg/m^2 or greater (overweight) in the presence of at least one weight-related comorbidity (e.g., controlled hypertension, type 2 diabetes mellitus, or dyslipidemia).

Methods

Studies selected for inclusion in the systematic review included pivotal studies provided in the sponsor's submission to CADTH and Health Canada, as well as those meeting the selection criteria presented in Table 3.

Table 3: Inclusion Criteria for the Systematic Review

Patient population	Adults with an initial BMI of 30 kg/m^2 or greater (obese) or 27 kg/m^2 or greater (overweight) in the presence of at least one weight-related comorbidity (e.g., controlled hypertension, type 2 diabetes, or dyslipidemia) Subgroups: • Baseline BMI • Number and/or type of weight-related comorbidities
Intervention	Naltrexone hydrochloride 8 mg and bupropion hydrochloride 90 mg extended-release tablets with two tablets taken twice daily as an adjunct to a reduced-calorie diet and increased physical activity

Comparators	• A reduced-calorie diet and increased physical activity with the following:
	  ○ Placebo
	  ○ Orlistat
	  ○ Liraglutide
	  ○ Bariatric surgery
	
	• Intensive behaviour or lifestyle modification

Outcomes	**Efficacy outcomes** • Mortality (e.g., all-cause, CV, cancer) • Body weight • BMI • Health-related QoL[a] • Physical functioning[a,b] • Impact on work and daily activities[a,b] • Impact on sleep (e.g., duration, quality)[a,b] • Severity of depression[a] • Food craving[a,b] • Fatigue[a,b] • Pain intensity[a,b] • Non-fatal CV event (e.g., myocardial infarction, stroke, TIA, revascularization, hospitalization for unstable angina) • Weight-related comorbidity (e.g., hypertension, dyslipidemia, OSA, OA, urinary incontinence, GERD, POS, NAFLD, respiratory disease, cancer) • Development of type 2 diabetes • Health care resource utilization (e.g., need for bariatric surgery) • Dose reduction or complete withdrawal of concomitant medications for weight-related comorbidities • Elimination of non-drug interventions for weight-related comorbidities **Harms outcomes** • AEs, SAEs, WDAEs • Notable harms (e.g., gastrointestinal AEs, mental or psychiatric symptoms [e.g., depression, anxiety, suicidal ideation, agitation-type events, psychosis, insomnia, mania], MACE [e.g., CV death, non-fatal MI, non-fatal stroke], increase in blood pressure or resting heart rate, seizures, hypoglycemia, angle closure glaucoma, hypersensitivity)
Study design	Published and unpublished phase III and IV RCTs

AE = adverse event; BMI = body mass index; CV = cardiovascular; GERD = gastroesophageal reflux disease; MACE = major adverse cardiovascular event; MI = myocardial infarction; NAFLD = non-alcoholic fatty liver disease; OA = osteoarthritis; OSA = obstructive sleep apnea; POS = polycystic ovary syndrome; QoL = quality of life; RCT = randomized controlled trial; SAE = serious adverse event; TIA = transient ischemic attack; WDAE = withdrawal due to adverse event.

[a] These outcomes were identified as being of particular importance to patients in the input received by CADTH from patient groups.

[b] Using a validated scale.

The literature search for clinical studies was performed by an information specialist using a peer-reviewed search strategy according to the Peer Review of Electronic Search Strategies checklist (https://www.cadth.ca/resources/finding-evidence/press).[11]

Published literature was identified by searching the following bibliographic databases: MEDLINE All (1946–) via Ovid, Embase (1974–) via Ovid, and PubMed. The search strategy comprised both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were Contrave, Mysimba, and naltrexone/bupropion. Clinical trial registries searched included the US National Institutes of Health's clinicaltrials.gov and the World Health Organization's International Clinical Trials Registry Search Portal.

No filters were applied to limit retrieval by study type. Retrieval was not limited by publication date or by language. Conference abstracts were excluded from the search results. See Appendix 1 for the detailed search strategies.

The initial search was completed on May 30, 2019. Regular alerts updated the search until the meeting of the CADTH Canadian Drug Expert Committee on January 15, 2020.

Grey literature (literature that is not commercially published) was identified by searching relevant websites from the following sections of the *Grey Matters: A Practical Tool For Searching Health-Related Grey Literature* checklist (https://www.cadth.ca/grey-matters):[12] Health Technology Assessment (HTA) Agencies, Health Economics, Clinical Practice Guidelines, Drug and Device Regulatory Approvals, Advisories and Warnings, Drug Class Reviews, Clinical Trials Registries, and Databases (Free). Google was used to search for additional internet-based materials. These searches were supplemented by reviewing bibliographies of key papers and through contacts with appropriate experts. In addition, the sponsor of the drug was contacted for information regarding unpublished studies. See Appendix 1 for more information on the grey literature search strategy.

Two CADTH clinical reviewers independently selected studies for inclusion in the review based on titles and abstracts, according to the predetermined protocol. Full-text articles of all citations considered potentially relevant by at least one reviewer were acquired. Reviewers independently made the final selection of studies to be included in the review, and differences were resolved through discussion.

Findings From the Literature

Five studies were identified from the literature for inclusion in the systematic review (Figure 1). The included studies are summarized in Table 4 and Table 5. A list of excluded studies is presented in Appendix 2.

Figure 1: Flow Diagram for Inclusion and Exclusion of Studies

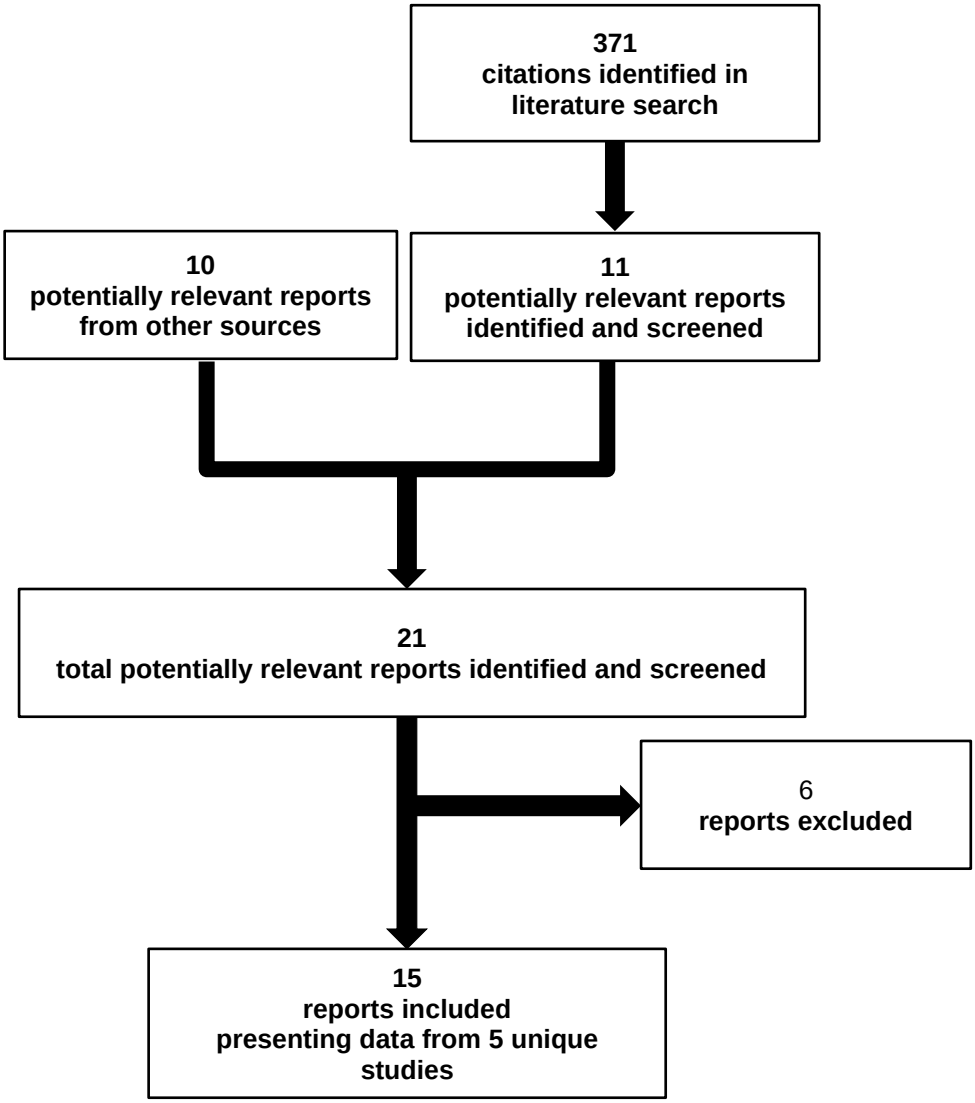


Table 4: Details of the Pivotal Trials

		COR-I	COR-II	COR-BMOD	COR-DM
Designs and Populations	**Study design**	Multi-centre, DB, placebo-controlled trial			
	Locations	34 sites in the US	36 sites in the US	9 sites in the US	53 sites in the US
	Randomized (N)	1,742	1,496	793	505

	Inclusion criteria	• Age 18 to 65 years
		• One of the following:
		  ○ BMI of 30 to 45 kg/m^2, inclusive, with uncomplicated obesity
		  ○ BMI of 27 to 45 kg/m^2, inclusive, with obesity and controlled hypertension and/or dyslipidemia
		• Systolic BP ≤ 140 mm Hg and diastolic BP ≤ 90 mm Hg
		• Medications for hypertension or dyslipidemia must be stable for 6 weeks before randomization
		• IDS-SR score < 2 on sadness, irritability, anxiety/tension, and suicidality items; total score < 30
				• Age 18 to 65 years
				• One of the following:
				  ○ BMI of 30 to 45 kg/m^2, inclusive, with uncomplicated obesity
				  ○ BMI of 27 to 45 kg/m^2, inclusive, with obesity and controlled hypertension and/or dyslipidemia
				• Systolic BP ≤ 140 mm Hg and diastolic BP ≤ 90 mm Hg
				• Medications for hypertension or dyslipidemia must be stable for 8 weeks before randomization
				• IDS-SR score < 2 on sadness, irritability, anxiety or tension, and suicidality items; total score < 30
				• Non-smoker with no tobacco or nicotine use in the previous 6 months
				• Beta-blockers not allowed
				• LDL < 190 mg/dL
				• Completed a food diary for 6 of 7 consecutive days during screening
					• Age 18 to 70 years
					• BMI of 27 to 45 kg/m^2, inclusive
					• Type 2 DM diagnosis, on no injectable antidiabetic medication or inhaled insulin for > 3 months prior to randomization
					• If on oral hypoglycemic medications, dose was stable for ≥ 3 months prior to randomization
					• Systolic BP ≤ 140 mm Hg and diastolic BP ≤ 90 mm Hg
					• Medications for hypertension or dyslipidemia must be stable for ≥ 4 weeks before randomization
					• HbA1c between 7% and 10%, fasting blood glucose < 270 mg/dL, and fasting triglycerides < 400 mg/dL
					• IDS-SR score < 2 on sadness, irritability, anxiety or tension, and suicidality items; total score < 30

	Exclusion criteria	• Obesity of known endocrine origin • Serious medical condition • History of or current serious psychiatric illness • Recent suicide attempt or current active suicidal ideation • Recent hospitalization due to psychiatric illness • Presence of bipolar disorder based on screening questions • Needed medication for psychiatric disorder in the previous 6 months • Type 1 or 2 DM (not applicable in the COR-DM study) • The following concomitant medications: psychotropic drugs (except for low-dose benzodiazepine or hypnotic drugs for insomnia), anorectic or weight loss drugs, over-the-counter dietary supplements with psychoactive, appetite, or weight effects, alpha-adrenergic blockers, dopamine agonists, clonidine, coumadin, theophylline, cimetidine, oral corticosteroids, cholestyramine, colestipol, Depo-Provera, smoking cessation drugs, opioid or opioid-like medications • History of surgical or device (e.g., lap band) intervention for obesity			Identical to the exclusion criteria for COR-I, COR-II, and COR-BMOD, with the addition of the following: • Type I DM • “Brittle diabetes” or hospitalization or emergency room visit due to poor diabetic control within 6 months prior to screening • Change of > 5 kg in the previous 3 months • Severe microvascular or macrovascular complications of diabetes

		COR-I	COR-II	COR-BMOD	COR-DM
		• History of seizures or of predisposition to seizures • Use of drugs, herbs, or dietary supplements potentially affecting body weight or participation in a weight-loss-management program in the previous month • Change of > 4 kg in the previous 3 months (not applicable in COR-DM) • Any condition which, in the opinion of the investigator, makes the patient unsuitable for inclusion			• Concomitant use of beta-blockers
DRUGS	**Intervention**	Randomization to a maintenance daily dosage of NAL/BUP of 32 mg/360 mg or 16 mg/360 mg taken as 2 tablets twice a day Weekly fixed-dose escalation during the first 4 weeks	Maintenance daily dosage of NAL/BUP of 32 mg/360 mg taken as 2 tablets twice a day. Patients were randomized to fast or slow dose escalation of NAL From week 28 to 44, patients who did not lose ≥ 5% of body weight were re-randomized to continue or to receive NAL/BUP 48 mg/360 mg daily	Maintenance daily dosage of NAL/BUP of 32 mg/360 mg taken as 2 tablets twice a day Weekly fixed-dose escalation during the first 4 weeks	Maintenance daily dosage of NAL/BUP of 32 mg/360 mg taken as 2 tablets twice a day Weekly fixed-dose escalation during the first 4 weeks
	Comparator(s)	Placebo matched in appearance and number of tablets			
	Ancillary therapy	See paragraph text for more information			
DURATION					
	Screening	Up to 4 weeks			
	Double-blind	4 weeks of titration followed by 52 weeks of maintenance			
	Follow-up	2-week discontinuation period	None		
OUTCOMES	**Co-primary end points**	• Percentage change in body weight from baseline to week 56 (week 28 for COR-II) • Proportion of patients with ≥ 5% reduction in body weight from baseline to week 56 (week 28 for COR-II)			
	Other end points	Unless otherwise indicated, change was measured from baseline to week 56 in COR-I and to week 28 in COR-II Secondary efficacy end points, from top to bottom of testing hierarchy: • % change in total body weight from baseline to week 56 using weighted LOCF analysis (COR-II only) • Proportion of patients with ≥ 5% decrease in total body weight from baseline to week 56 using weighted LOCF analysis (COR-II only) • Proportion of patients with ≥ 10% decrease in total body weight		Change was measured from baseline to week 56 Secondary efficacy end points, from top to bottom of testing hierarchy: • Proportion of patients with ≥ 10% decrease in body weight • Change in: ○ IWQoL-Lite total score ○ IDS-SR total score ○ FCI sweets subscale and	Change was measured from baseline to week 56 Secondary efficacy end points, from top to bottom of testing hierarchy: • Proportion of patients with ≥ 10% decrease in body weight • % of patients requiring rescue medications for diabetes • % of patients requiring reduction in dose of oral antidiabetic medication

		COR-I	COR-II	COR-BMOD	COR-DM
		• Change from baseline in: ○ IWQoL-Lite total score ○ COE questionnaire item 19 ○ IDS-SR total score ○ FCI sweets subscale and carbohydrates/starches subscale scores Exploratory end points: • SF-36 MCS and PCS scores (COR-II only) Safety end points: • AEs, SAEs • Increases in pulse rate, systolic BP, and diastolic BP		carbohydrates/starches subscale scores ○ 21-item COE questionnaire Safety end points: • AEs, SAEs • Increases in pulse rate, systolic BP, and diastolic BP	• Change in: ○ IWQoL-Lite total score ○ COE questionnaire item 19 ○ IDS-SR total score ○ FCI sweets subscale and carbohydrates/starches subscale scores Safety end points: • AEs, SAEs • Increases in pulse rate, systolic BP, and diastolic BP
NOTES	**Publications**	Greenway et al. (2010)[13]	Apovian et al. (2013)[14]	Wadden et al. (2011)[15]	Hollander et al. (2013)[16]

AE = adverse event; BMI = body mass index; BP = blood pressure; BUP = bupropion; COE = Control of Eating; DB = double-blind; DM = diabetes mellitus; ECG = electrocardiogram; FCI = Food Craving Inventory; HbA1c = glycated hemoglobin; IDS-SR = Inventory of Depressive Symptomology – Subject-Rated; IWQoL-Lite = Impact of Weight on Quality of Life – Lite; LDL = low-density lipoprotein cholesterol; LOCF = last observation carried forward; MCS = mental component summary; NAL = naltrexone; PCS = physical component summary; SAE = serious adverse event; SF-36 = Short-Form (36) Health Survey.

Note: Four additional reports were included: Health Canada reviewer's report;[21] FDA Medical Review of Contrave;[22] FDA Statistical Review of Contrave;[23] European Medicines Agency assessment report for Mysimba;[24] National Institute for Health and Care Excellence appraisal consultation document for naltrexone-bupropion.[25]

Source: Clinical Study Reports for the COR-I, COR-II, COR-BMOD, and COR-DM studies.[17-20]

Table 5: Details of the Cardiovascular-Outcomes Trial (LIGHT Study)

		LIGHT
DESIGNS AND POPULATIONS	**Study design**	Multi-centre, DB, placebo-controlled trial
	Locations	266 sites in the US
	Randomized (N)	8,910
	Inclusion criteria	• Age ≥ 50 years (women) or age ≥ 45 years (men) • BMI of 27 to 50 kg/m^2, inclusive • Waist circumference ≥ 88 cm (women) or ≥ 102 cm (men) • At increased risk of adverse CV outcomes (≥ 1 of the following): ○ CV disease (confirmed diagnosis or at high likelihood of CV disease) with ≥ 1 of the following: ▪ Documented MI more than 3 months prior to screening ▪ History of coronary revascularization ▪ History of carotid or peripheral revascularization ▪ Angina with ischemic changes ▪ Ankle brachial index < 0.9 in the last 2 years ▪ A ≥ 50% stenosis of a coronary, carotid, or lower extremity artery in the last 2 years ○ Type 2 diabetes with ≥ 2 of the following: ▪ Concurrent hypertension ▪ Dyslipidemia in the last 12 months ▪ Documented low HDL in the last 12 months ▪ Current smoker

		LIGHT
	Exclusion criteria	• MI within 3 months of screening • Angina pectoris grade III or IV • History of large vessel stroke • History of tachyarrhythmia other than sinus tachycardia • BP ≥ 145 mm Hg/95 mm Hg • Change in weight > 3% within 3 months of screening • Planned bariatric surgery, cardiac surgery, or coronary angioplasty • History of seizures or of predisposition to seizures • History of mania or current diagnosis of active psychosis, active bulimia or anorexia nervosa • At risk for suicide attempts based on the judgment of the investigator • Acute depressive illness including new onset of depression or acute exacerbation of symptoms (stable subjects on chronic treatment for depression for at least 3 months were not excluded) • Any condition with life expectancy anticipated to be less than 4 years
DRUGS	**Intervention**	Maintenance daily dosage of NAL/BUP of 32 mg/360 mg taken as 2 tablets twice a day Weekly fixed-dose escalation during the first 4 weeks Patient discontinued study medication if they: • had not lost ≥ 2% of body weight at week 16; or • were experiencing sustained increases in systolic or diastolic blood pressure of ≥ 10 mm Hg at week 8 or week 16
	Comparator(s)	Placebo matching in appearance and number of tablets
	Ancillary therapy (all patients)	Comprehensive, web-based weight-management program
DURATION	Lead-in	2 weeks of DB treatment with 1 tablet per day with randomization (1:1) to 1 week of intervention followed by 1 week of comparator or 1 week of comparator followed by 1 week of intervention
	Double-blind and/or follow-up	3 to 4 years planned
OUTCOMES	**Primary end point**	Time to first confirmed occurrence of 3-point MACE (CV death, non-fatal MI, and non-fatal stroke)
	Other end points	Efficacy end points: • Time to first confirmed occurrence of 4-point MACE (3-point MACE plus non-fatal unstable angina requiring hospitalization) • Time to confirmed occurrence of CV death • Time to confirmed occurrence of death from any cause • % change in body weight from baseline to week 52 • Proportion of patients with ≥ 10% body weight loss from baseline to week 52 • Proportion of patients with ≥ 5% body weight loss from baseline to week 26 and week 52 • Time to first confirmed occurrence of 5-point MACE (4-point MACE plus coronary revascularization) Safety end points: • AEs, SAEs • Increases in pulse rate, systolic BP, and diastolic BP
NOTES	**Publications**	Nissen et al. (2016)[26]

AE = adverse event; BMI = body mass index; BP = blood pressure; BUP = bupropion; CV = cardiovascular; DB = double-blind; HDL = high-density lipoprotein cholesterol; MACE = major adverse cardiovascular event; MI = myocardial infarction; NAL = naltrexone; SAE = serious adverse event.

Note: Four additional reports were included: Health Canada reviewer's report,[21] FDA Medical Review of Contrave,[22] FDA Statistical Review of Contrave,[23] European Medicines Agency assessment report for Mysimba,[24] National Institute for Health and Care Excellence appraisal consultation document for naltrexone-bupropion.[25]

Source: Clinical Study Report for the LIGHT study.[27]

Description of Studies

Five multi-centre, double-blind, placebo-controlled, parallel-group RCTs for NB in a fixed-dose combination conducted by the original sponsor (Orexigen Therapeutics, Inc.) were identified. The RCTs were conducted at multiple centres in the US.

Four RCTs were 56-week pivotal phase III trials:

- COR-I (N = 1,742; 2007 to 2009) randomized patients 1:1:1 to naltrexone 16 mg/bupropion 360 mg daily (not a recommended dosage in the product monograph), naltrexone 32 mg/bupropion 360 mg daily, or matching placebo. All patients received instructions to follow a hypocaloric diet and a prescription for walking at least 30 minutes a day most days of the week.
- COR-II (N = 1,496; 2007 to 2009) randomized patients 1:1 to naltrexone 32 mg/bupropion 360 mg daily or matching placebo. From week 28 to 44, patients who did not lose at least 5% of body weight were re-randomized to continue or to receive naltrexone 48 mg/bupropion 360 mg daily (not a recommended dosage in the product monograph). All patients received instructions to follow a hypocaloric diet and a prescription for walking at least 30 minutes a day three days a week.
- COR-BMOD (N = 793; 2007 to 2008) randomized patients 3:1 to 32 mg naltrexone/ 360 mg bupropion daily or matching placebo. All patients participated in an intensive behaviour-modification program, which included dietary instruction, 28 closed-group sessions, and prescribed exercise.
- COR-DM (N = 505; 2007 to 2009) randomized patients with type 2 diabetes 2:1 to 32 mg naltrexone/360 mg bupropion daily or matching placebo. All patients received instructions to follow a hypocaloric diet, dietary counselling, and a prescription for walking at least 30 minutes a day three days a week.

In the pivotal trials, study visits occurred at baseline and then every four weeks.

One RCT, the LIGHT study (N = 8,910; 2012 to 2015), was a cardiovascular-outcomes trial that randomized patients with cardiovascular risk factors 1:1 to naltrexone 32 mg/bupropion 360 mg daily or matching placebo with an expected treatment period of three to four years for most patients. Prior to the treatment period in the LIGHT study, patients were randomized 1:1 for a two-week lead-in period to receive naltrexone 8 mg/bupropion 90 mg or placebo in the first week followed by the other treatment in the second week. Patients who discontinued the study drug or experienced a suspected MACE during the lead-in period were not eligible for randomization to the treatment period. The purpose of the lead-in period was to exclude patients likely to have low treatment adherence from the treatment period. All patients participated in a comprehensive, web-based weight-management program. Study visits occurred at baseline and weeks 2, 8, 16, and 26, followed by visits every 26 weeks.

The LIGHT study was conducted to exclude an increased cardiovascular risk in patients receiving naltrexone 32 mg/bupropion 360 mg daily and an interim analysis of the first 25% of the planned number of events was required for the FDA to grant marketing authorization. The FDA also required completion of the trial in the post-approval setting, and when it discovered that the interim results were disseminated more widely than anticipated, the FDA determined that a new cardiovascular-outcomes trial was required (while encouraging completion of the LIGHT study). Due to subsequent public release of the 25% interim results, the LIGHT study was terminated early by the investigators after 64% of planned

events. The new trial is to be completed by July 2021, with the final report to be submitted by January 2022.[28]

Populations

Inclusion and Exclusion Criteria

Detailed information on inclusion and exclusion criteria for the four pivotal phase III trials is provided in Table 4. The COR-I, COR-II, and COR-BMOD studies enrolled patients aged 18 to 65 years with a BMI of 30 kg/m^2 to 45 kg/m^2 (or 27 kg/m^2 to 45 kg/m^2 with controlled hypertension and/or dyslipidemia), systolic and diastolic blood pressure no greater than 140 mm Hg and 90 mm Hg, respectively, fasting glucose of less than 126 mg/dL, and fasting triglycerides of less than 400 mg/dL. Obesity could not be of known endocrine origin and patients could not have diabetes mellitus, clinically significant cardiac abnormality, a history of surgical or device intervention for obesity, or a recent change in weight greater than 4 kg. Patients were screened based on the Inventory of Depressive Symptomology – Subject-Rated (IDS-SR) scale and were excluded if they exhibited or had a history of serious psychiatric illness, needed medication for a psychiatric disorder (except for short-term insomnia) in the previous six months, had bipolar disorder, had a recent suicide attempt or current active suicidal ideation, or had a history of or predisposition to seizures. In the COR-BMOD study, patients had to be non-smokers who had adhered to a food diary during screening. Study selection criteria in the COR-DM study were similar to those of the other three phase III trials, except that patients had to have a BMI of 27 kg/m^2 to 45 kg/m^2 and type 2 diabetes, glycated hemoglobin (HbA1c) between 7% and 10%, and fasting glucose of less than 270 mg/dL.

In the LIGHT study, patients were at least 50 years (women) or 45 years (men) of age with a BMI of 27 kg/m^2 to 50 kg/m^2 and at increased risk of adverse cardiovascular outcomes. Specifically, patients had to have cardiovascular disease by confirmed diagnosis or high likelihood or type 2 diabetes with two cardiovascular risk factors (hypertension, dyslipidemia, low high-density lipoprotein [HDL] cholesterol, and/or be a smoker). Patients were excluded if they had a recent myocardial infarction (MI) or had angina pectoris grade III or IV, history of large vessel stroke, history of tachyarrhythmia (sinus tachycardia excluded), blood pressure above 145 mm Hg/95 mm Hg, or a history of seizures or predisposition to seizures. Patients with a history of mania or current diagnosis of active psychosis, active bulimia, or anorexia nervosa, those at risk for suicide attempts, and those with acute depressive illness were excluded. Unlike in the pivotal trials, stable patients on chronic treatment for depression were not excluded.

Baseline Characteristics

Detailed information on baseline characteristics in the pivotal trials is available in Table 6. There were no notable imbalances between the NB and placebo group in each phase III trial, other than a greater percentage of patients in the placebo group using alcohol in the COR-DM study (40.6% versus 28.7%). In the COR-I, COR-II, and COR-BMOD studies, mean age ranged from 43.7 to 45.9 years and the percentage of female patients ranged from 85.1% to 91.6%. In contrast, mean age was 53.5 to 54.0 years and the percentage of female patients was 52.9% to 58.2% in the COR-DM study. In all four pivotal trials, most patients were white, and mean BMI ranged from 36.09 kg/m^2 to 36.96 kg/m^2. Most patients had a BMI of at least 30 kg/m^2, and 0.9% to 5.4% were in the overweight category (BMI of less than 30 kg/m^2). Percentages of patients with hypertension and mean systolic blood pressure were higher in the COR-DM study compared with the other pivotal trials (60.6% to

63.3% versus 14.6% to 22.3% for hypertension and systolic blood pressure of 124.7 mm Hg to 125.3 mm Hg versus 116.6 mm Hg to 119.2 mm Hg, respectively). Dyslipidemia was also present in more patients in the COR-DM study than in the other phase III trials (85.3% to 85.6% versus 40.1% to 55.9%). While patients in the COR-I, COR-II, and COR-BMOD studies did not have diabetes, 21.7% to 28.0% had impaired fasting glucose. Of the patients in the COR-DM study, 48% used sulfonylureas and 34.3% to 38.8% had HbA1c levels of greater than 8%. Across the pivotal trials, 8.2% to 15.4% of patients had depression, 3.0% to 6.1% had anxiety, and 4% or less had other psychiatric disorders.

Concomitant use of medications for obesity-related morbidities in the pivotal trials is summarized in Table 7. There were no notable imbalances between the NB and placebo groups in each pivotal trial. Among the COR-I, COR-II, and COR-BMOD studies, the most frequently used medications were angiotensin-converting enzyme inhibitors (6.4% to 8.9%), glucocorticoids (7.1% to 12.3%), statins (8.4% to 13.1%), other lipid-modifying drugs (7.9% to 11.2%), platelet-aggregation inhibitors excluding heparin (6.7% to 11.9%), and proton-pump inhibitors (9.3% to 12.9%). In the COR-DM study, the most frequently used medications were angiotensin-converting enzyme inhibitors (34.7% to 42.7%), metformin (80.0% to 80.6%), statins (45.9% to 49.3%), platelet-aggregation inhibitors excluding heparin (32.8% to 37.1%), sulfonylureas (48.7% to 54.1%), and thiazolidinediones (32%).

Table 6: Summary of Baseline Characteristics (Pivotal Trials)

	COR-I randomized		COR-II randomized		COR-BMOD randomized		COR-DM randomized	
	PL N = 581	NB N = 583	PL N = 495	NB N = 1,001	PL N = 202	NB N = 591	PL N = 170	NB N = 335
Mean age, years (SD)	43.7 (11.1)	44.4 (11.1)	44.4 (11.4)	44.3 (11.2)	45.6 (11.4)	45.9 (10.4)	53.5 (9.8)	54.0 (9.1)
Female, n (%)	496 (85.4)	496 (85.1)	420 (84.8)	847 (84.6)	185 (91.6)	528 (89.3)	90 (52.9)	195 (58.2)
Male, n (%)	85 (14.6)	87 (14.9)	75 (15.2)	154 (15.4)	17 (8.4)	63 (10.7)	80 (47.1)	140 (41.8)
Race, n (%)								
White	440 (75.7)	440 (75.5)	414 (83.6)	835 (83.4)	149 (73.8)	405 (68.5)	140 (82.4)	261 (77.9)
Black	110 (18.9)	106 (18.2)	72 (14.5)	133 (13.3)	44 (21.8)	145 (24.5)	18 (10.6)	63 (18.8)
Asian	4 (0.7)	6 (1.0)	4 (0.8)	12 (1.2)	2 (1.0)	6 (1.0)	5 (2.9)	7 (2.1)
Native Hawaiian or Pacific Islander	4 (0.7)	5 (0.9)	1 (0.2)	3 (0.3)	0	1 (0.2)	0	1 (0.3)
American Indian or Alaska Native	17 (2.9)	18 (3.1)	2 (0.4)	10 (1.0)	1 (0.5)	7 (1.2)	2 (1.2)	2 (0.6)
Other	6 (1.0)	8 (1.4)	2 (0.4)	8 (0.8)	6 (3.0)	27 (4.6)	5 9 (2.9)	1 (0.3)
Mean BMI, kg/m^2 (SD)	36.18 (4.00)	36.10 (4.35)	36.09 (4.27)	36.22 (4.45)	36.96 (4.18)	36.34 (4.16)	36.40 (4.50)	36.40 (4.75)
BMI category, n (%)								
BMI < 30 kg/m^2	5 (0.9)	18 (3.1)	14 (2.8)	25 (2.5)	1 (0.5)	8 (1.4)	11 (6.5)	18 (5.4)
BMI ≥ 30 and < 35 kg/m^2	217 (37.3)	224 (38.4)	186 (37.6)	398 (39.8)	64 (31.7)	207 (35.0)	49 (28.8)	111 (33.1)
BMI ≥ 35 and < 40 kg/m^2	229 (39.4)	204 (35.0)	191 (38.6)	316 (31.6)	79 (39.1)	230 (38.9)	64 (37.6)	110 (32.8)

	COR-I randomized		COR-II randomized		COR-BMOD randomized		COR-DM randomized	
BMI ≥ 40 kg/m^2	130 (22.4)	137 (23.5)	104 (21.0)	262 (26.2)	58 (28.7)	146 (24.7)	46 (27.1)	96 (28.7)
Mean height, cm (SD)	165.6 (8.3)	165.9 (8.4)	165.5 (8.2)	166.1 (8.4)	165.9 (7.8)	165.7 (7.8)	169.7 (9.7)	168.9 (10.1)
Mean weight, kg (SD)	99.5 (14.3)	99.7 (15.9)	99.2 (15.9)	100.3 (16.6)	101.9 (15.0)	100.2 (15.4)	105.1 (17.0)	104.2 (18.9)
Hypertension,[a] n (%)	114 (19.6)	130 (22.3)	106 (21.4)	212 (21.2)	37 (18.3)	86 (14.6)	103 (60.6)	212 (63.3)
Mean systolic blood pressure, mm Hg (SD)	119.2 (9.9)	119.2 (9.7)	118.2 (10.5)	118.1 (10.1)	116.7 (10.9)	116.6 (10.1)	124.7 (9.7)	125.3 (10.9)
Mean diastolic blood pressure, mm Hg (SD)	77.4 (6.8)	77.3 (7.1)	76.8 (6.9)	76.9 (7.1)	77.1 (7.4)	78.0 (7.3)	77.6 (7.0)	77.3 (7.5)
Mean pulse rate, bpm (SD)	71.9 (8.1)	71.9 (8.7)	71.5 (8.5)	71.3 (8.4)	70.2 (8.9)	70.7 (8.4)	73.2 (9.1)	73.0 (8.7)
Dyslipidemia,[b] n (%)	288 (49.6)	284 (48.7)	263 (53.1)	560 (55.9)	81 (40.1)	270 (45.7)	145 (85.3)	280 (83.6)
Impaired fasting glucose,[c] n (%)	140 (24.1)	148 (25.4)	127 (25.7)	280 (28.0)	49 (24.3)	128 (21.7)	NR	NR
HbA1c > 8%, n (%)	NR	NR	NR	NR	NR	NR	66 (38.8)	115 (34.3)
Sulfonylurea use, n (%)	NR	NR	NR	NR	NR	NR	81 (47.6)	160 (47.8)
Current smoker, n (%)	65 (11.2)	65 (11.1)	52 (10.5)	108 (10.8)	0	0	15 (8.8)	38 (11.3)
Alcohol use, n (%)	244 (42.0)	254 (43.6)	217 (43.8)	462 (46.2)	100 (49.5)	251 (42.5)	69 (40.6)	96 (28.7)
Depression, n (%)	73 (12.6)	66 (11.3)	76 (15.4)	131 (13.1)	31 (15.3)	83 (14.0)	14 (8.2)	29 (8.7)
Anxiety, n (%)	18 (3.1)	29 (5.0)	30 (6.1)	47 (4.7)	7 (3.5)	19 (3.2)	9 (5.3)	10 (3.0)
Other psychiatric disorders, n (%)	4 (0.7)	5 (0.9)	8 (1.6)	17 (1.7)	0	6 (1.0)	7 (4.1)	9 (2.7)
Antidepressant use, n (%)	63 (10.9)	59 (10.1)	62 (12.5)	116 (11.6)	30 (14.9)	67 (11.3)	9 (5.3)	17 (5.1)
Anxiolytic use, n (%)	9 (1.6)	11 (1.9)	7 (1.4)	15 (1.5)	8 (4.0)	9 (1.5)	1 (0.6)	6 (1.8)
Other psychotropic drug use, n (%)	4 (0.7)	4 (0.7)	7 (1.4)	12 (1.2)	0	9 (1.5)	8 (4.7)	10 (3.0)

BMI = body mass index; bpm = beats per minute; HbA1c = glycated hemoglobin; NB = naltrexone and bupropion; NR = not reported; PL = placebo; SD = standard deviation.

[a] Hypertension was defined as a diagnosis of hypertension or prescription for anti-hypertensive medication.

[b] Dyslipidemia was defined as a diagnosis of dyslipidemia, hypercholesterolemia, hypertriglyceridemia, hyperlipidemia, low high-density lipoprotein cholesterol or one of the following: triglycerides ≥ 200 mg/dL, low-density lipoprotein cholesterol ≥ 160 mg/dL, total cholesterol ≥ 240 mg/dL, high-density lipoprotein cholesterol < 40 mg/dL.

[c] Impaired fasting glucose was defined as fasting glucose ≥ 100 mg/dL.

Source: Clinical Study Reports for the COR-I, COR-II, COR-BMOD, and COR-DM studies.[17-20]

Table 7: Select Common Concomitant Medications (Pivotal Trials)

	COR-I randomized		COR-II randomized		COR-BMOD randomized		COR-DM randomized	
	PL N = 581	NB N = 583	PL N = 495	NB N = 1,001	PL N = 202	NB N = 591	PL N = 170	NB N = 335
Patients with ≥ 1 concomitant medication by class, n (%)								
ACE inhibitors	45 (7.7)	52 (8.9)	39 (7.9)	86 (8.6)	14 (6.9)	38 (6.4)	59 (34.7)	143 (42.7)
Angiotensin II antagonists	32 (5.5)	34 (5.8)	31 (6.3)	56 (5.6)	13 (6.4)	25 (4.2)	36 (21.2)	75 (22.4)
Beta-blocking drugs, selective	15 (2.6)	16 (2.8)	20 (4.0)	60 (6.0)	0	4 (0.7)	23 (13.5)	38 (11.3)
Metformin or metformin hydrochloride	3 (0.5)	2 (0.3)	0	5 (0.5)	1 (0.5)	1 (0.2)	137 (80.6)	268 (80.0)
Glucocorticoids	53 (9.1)	46 (7.9)	61 (12.3)	86 (8.6)	20 (9.9)	42 (7.1)	13 (7.6)	28 (8.4)
Statins	50 (8.6)	67 (11.5)	65 (13.1)	117 (11.7)	17 (8.4)	54 (9.1)	78 (45.9)	165 (49.3)
Statins with other lipid-modifying drugs	10 (1.7)	6 (1.0)	9 (1.8)	13 (1.3)	0	11 (1.9)	14 (8.2)	20 (6.0)
Natural opium alkaloids	29 (5.0)	30 (5.1)	16 (3.2)	36 (3.6)	11 (5.4)	33 (5.6)	6 (3.5)	13 (3.9)
Other lipid-modifying drugs	52 (9.0)	46 (7.9)	49 (9.9)	111 (11.1)	21 (10.4)	66 (11.2)	32 (18.8)	50 (14.9)
Platelet-aggregation inhibitors excluding heparin	39 (6.7)	54 (9.3)	59 (11.9)	105 (10.5)	14 (6.9)	62 (10.5)	63 (37.1)	110 (32.8)
Proton-pump inhibitors	54 (9.3)	65 (11.1)	58 (11.7)	112 (11.2)	22 (10.9)	76 (12.9)	25 (14.7)	59 (17.6)
Selective $ß_2$ adrenoreceptor agonists	19 (3.3)	31 (5.3)	31 (6.3)	59 (5.9)	6 (3.0)	26 (4.4)	8 (4.7)	16 (4.8)
Sulfonamides, urea derivations	0	0	0	0	0	0	92 (54.1)	163 (48.7)
Thiazolidinediones	0	0	0	0	0	0	54 (31.8)	107 (31.9)

ACE = angiotensin-converting-enzyme; NB = naltrexone and bupropion; PL = placebo.

Note: Only medications used by ≥ 5% of patients in ≥ one treatment group were included.

Source: Clinical Study Reports for the COR-I, COR-II, COR-BMOD, and COR-DM studies.[17-20]

Detailed information on baseline characteristics and medication use in the LIGHT study is available in Table 8. There were no notable imbalances between treatment groups in baseline characteristics, including cardiovascular history and medication use. Mean age in the LIGHT study was higher than in the pivotal RCTs (60.9 to 61.1 years) and distributions of patients based on sex, race, and BMI category were similar to those in the COR-DM study (although mean BMI in the LIGHT study was higher: 37.2 to 37.4 kg/m^2). According to the study entry criteria, 31.8% to 32.5% of patients had cardiovascular disease, 84.9% to 85.5% had type 2 diabetes, and 16.7% to 18.0% had both. In patients with type 2 diabetes, the mean duration of DM was 9.5 years. Hypertension (93% of patients) and dyslipidemia requiring medication (92% of patients) were present in most patients, 9% of patients were current smokers, and 22.4% to 23.1% of patients had depression. In terms of cardiovascular history, 26% of patients had undergone coronary revascularization, 13% had experienced an MI more than three months before the study, and 3.5% to 4.2% had angina with ischemic changes. Carotid revascularization, peripheral revascularization, lower extremity atherectomy, femoral bypass, and popliteal bypass were each reported in no more than 1.2% of patients. With regards to medication use, 92% of patients were using an anti-hypertensive drug, 75% were using at least one antidiabetic drug (23.3% using insulin [compared with no recent insulin use in the COR-DM study], 57% using metformin, and

25% using a sulfonylurea), 87% were using a lipid-altering medication (79% used statins), and 14.8% to 16.0% were using a selective serotonin-reuptake inhibitor.

Patients in the LIGHT study only underwent randomization for the treatment period if they successfully completed the two-week lead-in period (i.e., they tolerated the treatment well, did not demonstrate characteristics that would predict lack of adherence, and did not have a suspected MACE event). Also, patients discontinued study treatment if they had not lost at least 2% of body weight at week 16 or were experiencing consecutive, sustained increases in systolic or diastolic blood pressure of at least 10 mm Hg at week 8 or week 16.

Table 8: Summary of Baseline Characteristics (LIGHT Study)

	ITT set	
	PL N = 4,450	**NB N = 4,455**
Mean age, years (SD)	60.9 (7.4)	61.1 (7.3)
Female, n (%)	2,419 (54.4)	2,437 (54.7)
Male, n (%)	2,031 (45.6)	2,018 (45.3)
Race, n (%)		
White	3,698 (83.1)	3,738 (83.9)
Black	648 (14.6)	656 (14.7)
Asian	27 (0.6)	19 (0.4)
Native Hawaiian or Pacific Islander	6 (0.1)	6 (0.1)
American Indian or Alaska Native	20 (0.4)	11 (0.2)
Other	49 (1.1)	24 (0.5)
Mean BMI, kg/m^2 (SD)	37.4 (5.4)	37.2 (5.3)
BMI category, n (%)		
BMI < 35 kg/m^2	1,719 (38.6)	1,692 (38.0)
BMI ≥ 35 and < 40 kg/m^2	1,383 (31.1)	1,476 (33.2)
BMI ≥ 40 kg/m^2	1,348 (30.3)	1,284 (28.8)
Mean height, cm (SD)	169.0 (10.0)	168.8 (10.0)
Mean weight, kg (SD)	106.3 (19.2)	105.6 (19.1)
Mean waist circumference, cm (SD)	119.6 (13.3)	119.4 (13.3)
CV risk group, n (%)		
CV disease	1,447 (32.5)	1,415 (31.8)
Type 2 DM	3,803 (85.5)	3,784 (84.9)
CV disease without type 2 diabetes	646 (14.5)	670 (15.0)
CV disease with type 2 diabetes	801 (18.0)	745 (16.7)
Type 2 DM without CV	3,002 (67.5)	3,039 (68.2)
No CV or type 2 diabetes	1 (0.02)	1 (0.02)
Mean duration of type 2 diabetes, years (SD)	9.5 (7.7) N = 3,728	9.5 (7.4) N = 3,699
Hypertension, controlled < 145 mm Hg/95 mm Hg, n (%)	4,117 (92.5)	4,162 (93.4)
Mean systolic blood pressure, mm Hg (SD)	125.5 (12.6)	125.9 (12.5)
Mean diastolic blood pressure, mm Hg (SD)	74.4 (9.1)	74.5 (9.0)
Mean pulse rate, bpm (SD)	72.1 (11.0)	72.1 (11.0)
Dyslipidemia requiring pharmacotherapy, n (%)	4,070 (91.5)	4,100 (92.0)
Mean total cholesterol, mg/dL (SD)	172.8 (42.3)	171.3 (41.4)

	ITT set	
Mean HDL, mg/dL (SD)	46.6 (12.7)	46.3 (12.7)
Mean LDL, mg/dL (SD)	88.8 (35.0)	87.5 (33.3)
Mean triglycerides, mg/dL (SD)	195.6 (144.9)	196.6 (141.7)
HbA1c > 7%, n (%)	2,033 (53.5) N = 3,799	1,961 (51.9) N = 3,780
Current smoker, n (%)	416 (9.3)	405 (9.1)
Depression, n (%)	995 (22.4)	1,031 (23.1)
CV history		
MI > 3 months prior to screening	589 (13.2)	593 (13.3)
Coronary revascularization	1,169 (26.3)	1,138 (25.5)
Carotid revascularization	55 (1.2)	27 (0.6)
Peripheral revascularization	36 (0.8)	27 (0.6)
Lower extremity atherosclerotic disease atherectomy	18 (0.4)	6 (0.1)
Femoral bypass	20 (0.5)	10 (0.2)
Popliteal bypass	6 (0.1)	6 (0.1)
Angina with ischemic changes	155 (3.5) N = 4,438	187 (4.2) N = 4,440
ABI < 0.9 by simple palpation in past 2 years	24 (0.5) N = 4,409	29 (0.7) N = 4,412
Coronary artery stenosis ≥ 50% in past 2 years	162 (3.7) N = 4,427	157 (3.6) N = 4,428
Carotid artery stenosis ≥ 50% in past 2 years	33 (0.8) N = 4,426	28 (0.6) N = 4,429
Lower extremity artery stenosis ≥ 50% in past 2 years	5 (0.1) N = 4,427	11 (0.3) N = 4,431
Medication use, n (%)		
Anti-hypertensive	4,082 (91.7)	4,108 (92.2)
Beta blocker	1,705 (38.3)	1,768 (39.7)
Diuretic	1,413 (31.8)	1,470 (33.0)
ACE inhibitor/angiotensin II receptor blocker	3,407 (76.6)	3,440 (77.2)
Calcium channel blocker	845 (19.0)	905 (20.3)
Antidiabetic	3,346 (75.2)	3,339 (74.9)
Insulin	1,038 (23.3)	1,038 (23.3)
Thiazolidinediones	297 (6.7)	282 (6.3)
Metformin	2,543 (57.1)	2,525 (56.7)
GLP-1/DPP-4	714 (16.0)	776 (17.4)
Sulfonylurea	1,096 (24.6)	1,129 (25.3)
Lipid-altering	3,863 (86.8)	3,889 (87.3)
Statins	3,518 (79.1)	3,534 (79.3)
Antidepressant	1,015 (22.8)	1,042 (23.4)
Selective serotonin-reuptake inhibitor	659 (14.8)	711 (16.0)

ABI = ankle brachial index; ACE = angiotensin-converting enzyme; BMI = body mass index; bpm = beats per minute; CV = cardiovascular; DPP-4 = dipeptidyl peptidase-4; GLP-1 glucagon-like peptide-1; HbA1c = glycated hemoglobin; HDL = high-density lipoprotein; ITT = intention to treat; LDL = low-density lipoprotein; MI = myocardial infarction; NB = naltrexone and bupropion; PL = placebo; SD = standard deviation.

Source: Clinical Study Report for the LIGHT study.[27]

Interventions

Patients were allocated to a treatment group using an interactive voice or web response system and a computer-generated randomization schedule prepared by the clinical supply management company in the COR-I, COR-II, and COR-DM studies and by the sponsor or a delegate in the COR-BMOD study. Randomization was stratified by study site in the COR-1, COR-II, and COR-BMOD studies and by baseline HbA1c (less than or at least 8%) and sulfonylurea use (yes or no) in COR-DM. In the LIGHT study, permuted blocks were used with no stratification factors and an interactive voice or web response system was used for allocation. Further details on the randomization methods were not described in the clinical study reports. Placebo tablets were identical in appearance to the NB tablets and were given in the same numbers as the NB tablets. Patients, investigators, and study personnel (including the committee adjudicating cardiovascular events in the LIGHT study) were blinded to treatment assignment.

In the COR-I study, patients in the NB treatment groups were re-randomized at week 56 to undergo sudden or tapered withdrawal of study medication. From week 28 to week 44 in the COR-II study, patients in the NB group who did not lose at least 5% of body weight were re-randomized to continue on the same dosage or to increase dosage to naltrexone 48 mg/bupropion 360 mg daily. This increased dosage exceeds the maximum recommended dosage according to the Health Canada–approved product monograph for Contrave[7] and results for these patients are not included in the present report. In the LIGHT study, patients were randomized at the start of the two-week lead-in phase and those who did not discontinue were re-randomized to the treatment phase.

In all the trials, the maintenance dosage of NB was naltrexone 32 mg/bupropion 360 mg daily, distributed as two tablets of naltrexone 8 mg/bupropion 90 mg taken twice a day (once in the morning and once in the evening). The COR-I study included a treatment group receiving naltrexone 16 mg/bupropion 360 mg daily (which is not a recommended dosage in the product monograph) and results for this group are not summarized in the present report. The dosage was escalated to the maintenance dosage according to schedules outlined in Table 4. The dose escalation schedules in the pivotal trials match the schedule outlined in the Health Canada–approved product monograph for Contrave,[7] with the exception of the slower escalation schedule in half of the NB group in the COR-II study (escalation to 32 mg naltrexone daily by week 5 rather than week 4). Because the clinical expert consulted by CADTH did not expect this difference in dose escalation to have a significant impact on the study results, the COR-II study was included in the systematic review.

In addition to NB or placebo, all patients received ancillary therapy to encourage a hypocaloric diet and increased physical activity. In the COR-I, COR-II, and COR-DM studies, patients were instructed to follow a hypocaloric diet representing a deficit of 500 kcal/day based on the WHO algorithm for resting metabolic rate. Patients in these studies also received written instruction on behavioural-modification techniques and a prescription for walking at least 30 minutes a day most days of the week (COR-I study) or three days a week (COR-II and COR-DM studies). In the COR-DM study, dietary counselling was provided according to American guidelines for counselling diabetics. Patients in the COR-BMOD study participated in an intensive behaviour-modification program that included dietary instruction, 28 closed-group sessions (10 to 20 patients per 90-minute session), moderately intense exercise increasing from 30 minutes to 60 minutes a day, and daily food and physical activity diaries. The sessions focused on modifying

behaviour related to eating and exercise and were conducted weekly for the first 16 weeks, biweekly for the next 12 weeks, and monthly onwards. In the LIGHT study, patients were encouraged to participate in a comprehensive, web-based weight-management program regardless of whether they had discontinued study treatment.

In the COR-DM study, patients on insulin therapy for more than 14 consecutive days were discontinued from the study. Adjustments to antidiabetic medications were considered based on HbA1c values and fasting glucose concentrations with minimal changes prior to week 16. Once the full dose was reached on current antidiabetic medications, new medications were added in a stepwise manner in the following order: metformin, sulfonylurea (or metformin if already on sulfonylurea alone), and dipeptidyl peptidase-4 inhibitor or thiazolidinedione. In patients who improved in glycemic control during the study, medications were reduced in the reverse order.

In the pivotal trials, the medications listed under the exclusion criteria in Table 4 were also prohibited during the trials and their use was recorded. In the LIGHT study, patients continued to receive routine medical care from their usual health care providers and standard medical management for high blood pressure was allowed (which could include discontinuation of study medication). Patients who used concomitant NB, loriciferan, or any drug activating a sympathetic tone were discontinued from study medication and a protocol deviation was recorded. Use of other weight-loss medications were also considered protocol deviations, although study medication was not discontinued.

Outcomes

A description and appraisal of outcome measures, including body weight, is presented in Appendix 4.

Body Weight

The FDA draft guidance on developing drugs for weight management[29] and the European Medicines Agency (EMA) guideline on clinical evaluation of medicinal products used in weight management[30] both recommend change in weight as the primary end point for assessing efficacy of drugs for weight management. The FDA draft guidance specifies that both mean percent loss in baseline body weight and the proportion of patients who lose at least 5% of baseline body weight after one year of treatment should be assessed. The EMA guideline specifies that analyses of absolute and percentage change in body weight as well as the proportion of patients who lose at least 5% and 10% of baseline body weight should be conducted after 12 months of treatment.

Data from RCTs and meta-analyses of RCT data on weight-loss interventions and assessment of mortality, weight-related comorbidities, and HRQoL are summarized in Appendix 4. Overall, the results were mixed and reporting of percentage of weight loss was inconsistent. No analyses were reported specifically for patients who lost at least 5% or 10% of baseline body weight. Some evidence suggests all-cause mortality can be reduced with behavioural or lifestyle weight-loss interventions and cardiovascular mortality can be reduced with pharmacologic weight-loss interventions. Evidence was found for a reduction in onset of new type 2 diabetes with pharmacologic or behavioural/lifestyle interventions in patients with impaired glucose tolerance and obesity. No RCT evidence could be found for clinically meaningful improvements in HRQoL with weight-loss interventions and non-RCT evidence suggests that weight loss of greater than 10% would be needed to achieve clinically meaningful improvements.

Body weight was measured at each study visit in all five RCTs and change in body weight from baseline to week 56 (week 28 in the COR-II study) was evaluated for the co-primary end points in the pivotal trials. Percent change in weight from baseline and the percentage of patients with at least 5% weight loss from baseline were co-primary end points in the pivotal RCTs. The percentage of patients with at least 10% weight loss from baseline was a secondary end point in the pivotal RCTs. In the LIGHT study, percent change in body weight from baseline to week 52, the percentage of patients with at least 10% weight loss at week 52, and the percentage of patients with at least 5% weight loss at weeks 26 and 52 were exploratory end points.

Mortality

All-Cause

Deaths were reported in the pivotal studies as part of the safety evaluation alongside AEs. Time from treatment period randomization to confirmed occurrence of death from any cause was reported as an exploratory end point in the LIGHT study.

Cardiovascular

In the LIGHT study, cardiovascular events were validated and classified by a clinical events committee, which was made up of multidisciplinary experts in cardiovascular events adjudication. The independent committee was blinded to treatment assignment and adjudicated whether the case was a confirmed event, a non-event, or lacked sufficient documentation to confirm an event.

In the LIGHT study, the primary end point was time from treatment period randomization to first confirmed occurrence of MACE, defined as cardiovascular death, non-fatal MI, or non-fatal stroke. Time to confirmed occurrence of cardiovascular death was reported as an exploratory outcome. There were also exploratory four-point composite (the MACE included in the primary end point plus non-fatal unstable angina requiring hospitalization) and five-point composite (the four-point composite end point plus coronary revascularization procedure) end points.

Cardiovascular death was not reported outside of AEs reported for the pivotal trials.

Health-Related Quality of Life

No outcomes assessing HRQoL were reported in the LIGHT study.

Impact of Weight on Quality of Life – Lite Questionnaire

The Impact of Weight on Quality of Life – Lite (IWQoL-Lite) questionnaire, a disease-specific instrument designed to assess the effect of obesity on quality of life, was administered at baseline and weeks 8, 16, 28, and 56 in the COR-I, COR-BMOD, and COR-DM studies and at baseline and weeks 28 and 56 in the COR-II study. The IQWoL-Lite has 31 self-administered items with five domains: self-esteem (seven items), sexual life (four items), physical function (11 items), public distress (five items), and work (four items).[31] The items all begin with “Because of my weight…”; for example, “Because of my weight, I experience ridicule, teasing, or unwanted attention.”[31] Five response options are provided for each item, ranging from “always true” (score of 5) to “never true” (score of 1).[31] The domain score is the sum of all the item scores, and all domains are added to create the total score. Total scores and subscale scores on the IWQoL-Lite are transformed to a range from 0 to 100; with 100 being the best and 0 being the poorest quality of life.[31] There is no specific recall period.[31]

There is evidence of the validity and reliability of the IWQoL-Lite total score in patients with obesity seeking treatment and in the community-based population with obesity. The MID for an improvement in the IWQoL-Lite total score ranges from 7.7 to 12, depending on the baseline score. Further information on the IWQoL-Lite questionnaire is provided in Appendix 4.

The total score and subscale scores were reported in the pivotal trials. Change in the IWQoL-Lite total score from baseline to week 56 (week 28 in the COR-II study) was a secondary end point in the pivotal trials.

Short-Form (36) Health Survey

The 36-Item Short-Form (36) Health Survey (SF-36) measures general health and has been used extensively in clinical trials.[32] There are eight health domains in the SF-36 and for each a subscale score can be determined: physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional, and mental health.[32] Two component summaries, the physical component summary (PCS) and the mental component summary (MCS), are derived from a scoring algorithm from the eight domains.[32] Scores on the PCS and MCS range from 0 to 100, with a higher score indicating a better health status.[32] Scoring for the summary scales uses norm-based methods; the general US population is used to derive the regression weights and constants. The PCS and MCS scales are transformed to have a mean of 50 and a standard deviation (SD) of 10 in the general US population.[33] The SF-36 has been validated in a variety of disease conditions.[34]

There is evidence for the validity of the SF-36 MCS and PCS in the community-based population with obesity. An MID for the SF-36 MCS and PCS was not found for patients with obesity. Further information on the SF-36 is provided in Appendix 4.

The SF-36 was administered at baseline and at week 28 and 56 in the COR-II study. Change in the MCS and PCS scores from baseline to weeks 28 and 56 were exploratory end points in the COR-II study.

Severity of Depression

Inventory of Depressive Symptomology – Subject-Rated Scale

The IDS-SR is a 30-item self-reporting tool that measures the severity of depressive symptoms. It is also available in a clinician-rated format.[35] The 30 items include diagnostic criteria for major depressive disorder (MDD) from the fourth edition of the *Diagnostic and Statistical Manual of Mental Disorders*; symptom domain content includes insomnia, sad mood, appetite or weight change, concentration, outlook, suicidal ideation, involvement, energy or fatigability, psychomotor function, anxiety, mood reactivity, mood quality anhedonia, libido and self-criticalness.[35] Scores are generated by summing the responses to 28 of 30 items (for two pairs of items, only one item is rated).[35] Each symptom item is scored on a scale of 0 to 3, with higher scores indicating greater severity of symptoms.[35] Total scores range from 0 to 84.[35]

No information about an estimated MID for the IDS-SR or the psychometric properties of the IDS-SR in patients with obesity was found. Further information on the IDS-SR is provided in Appendix 4.

The IDS-SR was administered at each study visit in COR-I, COR-II, and COR-BMOD and at baseline and weeks 8, 16, 28, and 56 in COR-DM. Change in the IDS-SR total score

from baseline to week 56 (week 28 in the COR-II study) was a secondary end point in the pivotal trials.

Food Craving

The Food Craving Inventory (FCI) and Control of Eating (COE) questionnaire were administered in the pivotal trials at baseline and weeks 8, 16, 28, and 56. Food craving was not assessed in the LIGHT study.

Food Craving Inventory

The FCI is a 28-item self-administered questionnaire designed to assess specific food cravings.[36] A craving is defined as an intense desire to consume a particular food (or food type) that was difficult to resist over the past month.[36] The FCI is organized into four subscales (high fats, sweets, carbohydrates or starches, and fast-food fats), each composed of an item representing specific foods.[36] Subjects rate the frequency of craving for each of the items using a five-point scale (1 = never, 2 = rarely, 3 = sometimes, 4 = often, and 5 = always or almost every day).[36] There is a one-month recall period.[36] The original 28-item FCI scale did not include cooked vegetables, fruit juices, raw vegetables, canned fruit, or raw fruit. However, the version used in the pivotal trials did; the impact of these items on the total scale score, subscale scores and psychometric properties of the FCI are unclear. The subscale and total scores are calculated by summing the relevant item scores, with higher scores indicating more cravings.[37]

For patients with obesity in the community, there is evidence of acceptable internal consistency, and evidence of content validity and convergent validity. An MID was not found for the FCI. Further information on the FCI is provided in Appendix 4.

Change in the sweets and carbohydrates subscale scores from baseline to week 56 (week 28 in the COR-II study) were secondary end points in the pivotal trials. The range of scores was 8 to 40 for the sweets subscale, 9 to 45 for the carbohydrates or starches subscale, and 28 to 140 for the total score.

COE Questionnaire

The COE questionnaire is a 21-item, self-administered questionnaire that assesses the type and intensity of food cravings and the subjective sensations of appetite and mood.[38] There are six sections that relate to general appetite, overall mood, craving frequency, craving intensity, specific cravings, and perceived level of control over resisting a nominated food item.[38] Items are scored using a Visual Analogue Scale (VAS), and one question asks the participant to identify a craved food.[38] A food craving is defined as a strong urge to eat a particular food or drink. Patients are instructed to read each question carefully and place a mark at the point that best represents their experience over the last seven days using a 100 mm VAS with extremes of 0 (“not at all”) to 100 (“extremely,” “very often,” or “after every one”).[38]

Change in the item-19 score (“Generally, how difficult has it been to control your eating?”) from baseline to week 56 (week 28 in the COR-II study) was a secondary end point in the pivotal trials. The validity of administering a single question of the COE questionnaire as a study end point is unclear. Further information on the COE questionnaire is provided in Appendix 4.

Non-Fatal Cardiovascular Events

As mentioned under the description of outcomes related to cardiovascular mortality, the primary end point in the LIGHT study was time from treatment period randomization to a three-point composite of cardiovascular death, non-fatal MI, and non-fatal stroke. Analyses were also performed for similar four-point and five-point composites. Times to first confirmed occurrence of the following were also reported individually (including fatal or non-fatal events) for MI, stroke, unstable angina requiring hospitalization, and coronary revascularization.

In the pivotal trials, non-fatal cardiovascular events were not reported outside of AE reporting.

Dose Reduction or Complete Withdrawal of Concomitant Medications for Weight-Related Comorbidities

In the COR-DM study, antidiabetic medications were recorded at each study visit and the percentage of patients requiring a dose reduction in oral antidiabetic medication during the study was a secondary end point. The percentage of patients requiring rescue medications for diabetes (defined as either a dose increase in antidiabetic medication or initiation of a new antidiabetic medication) during the study was also a secondary end point. Although the latter outcome does not represent a dose reduction or complete withdrawal of concomitant medication as specified in the review protocol, it may provide information on potential benefits regarding the medical management of diabetes. Changes in medications for other weight-related comorbidities were not reported in any of the trials.

Unreported Efficacy Outcomes

The following outcomes identified in the systematic review protocol were not reported in the RCTs: BMI, impact on sleep, fatigue, pain intensity, weight-related comorbidity, development of type 2 diabetes, health care resource utilization, and elimination of non-drug interventions for weight-related comorbidities. The outcomes of physical functioning and impact on work and daily activities were reported, but assessed as part of the physical function and work subscales of the IWQoL-Lite, and no MID was found for these subscales. Therefore, the subscale scores were not included in the present report.

AEs, SAEs, and WDAEs

All AEs, including SAEs and WDAEs, were recorded in all the RCTs.

In the pivotal trials, treatment-emergent AEs were defined as those with an onset date after treatment initiation within seven days (30 days in the COR-BMOD study) of the last confirmed dose of study medication. In the LIGHT study, AEs were only collected if they were SAEs or if they led to discontinuation of study medication. Treatment-emergent AEs were those occurring from the baseline visit to either study discontinuation or 30 days after study medication discontinuation (whichever date came first).

Increase in Pulse Rate and Blood Pressure (Notable Harms)

In the pivotal trials, increases above pre-specified thresholds in pulse rate, systolic blood pressure, and diastolic blood pressure with respect to baseline values recorded for at least two consecutive study visits (or at least one if it was the last assessment) or occurring at least once were reported. In the LIGHT study, increases recorded for at least two

consecutive study visits were reported. Study visits occurred every four weeks in the pivotal trials and every 26 weeks (following visits as weeks 2, 8, 16, and 26) in the LIGHT study.

Statistical Analysis

Primary End Point

For the pivotal trials, the co-primary end points were percent change in weight from baseline to week 56 (week 28 for the COR-II study) and the proportion of patients with at least a 5% reduction weight from baseline to week 56 (week 28 for the COR-II study). The main analyses of the co-primary end points was in the full analysis set (defined in "Analysis Populations"), with missing data imputed using the last observation carried forward (LOCF) approach incorporating post-baseline observations while on study medication (up to one day following the last confirmed dose of study medication). Percent change in weight was analyzed using an analysis of covariance (ANCOVA) model with type III sums of squares, and the proportion of responders was analyzed using a logistic regression model. The two-sided significance level for rejecting the null hypothesis that there was no difference between the NB and placebo groups was 0.05 for each co-primary end point. For the COR-I, COR-II, and COR-BMOD studies, the models were adjusted for study centre and baseline body weight. For the COR-DM study, the models adjusted for the HbA1c category (no more than or greater than 8%), sulfonylurea use (with or without), and baseline body weight. In the COR-I study, co-primary end points compared the naltrexone 32 mg/bupropion 360 mg group versus the placebo group and the comparison between the naltrexone 16 mg/bupropion 360 mg group and the placebo group was only performed if the first comparison was statistically significant (although these results are not included in the present report).

For the LIGHT study, the primary end point was time from treatment period randomization to first confirmed occurrence of MACE, defined as cardiovascular death, non-fatal MI, or non-fatal stroke in the ITT population (defined in "Analysis Populations"). The primary end points was tested for three null hypotheses: One, the hazard ratio for NB versus placebo is at least 2 (noninferiority; to be tested in interim analysis of 25% of expected events); two, the hazard ratio for NB versus placebo is at least 1.4 (noninferiority; to be tested in interim analyses of 50% and 75% of expected events and in final analysis); and three, the hazard ratio for NB versus placebo is at least 1.0 (superiority; to be tested in interim analyses of 50% and 75% of expected events and in final analysis).

Group sequential testing at the interim and final analyses used an O'Brien-Fleming design with the monitoring boundaries based on a one-sided 97.5% confidence interval (CI) for the unadjusted hazard ratio. Rejection of the first null hypothesis at the 25% interim analysis was required to justify a decision to resubmit to the FDA for approval (as the original submission to the FDA did not receive approval due to concerns with the cardiovascular safety profile). The LIGHT trial could be terminated due to an unfavourable safety profile if the 50% or 75% interim analyses ruled out a hazard ratio of NB versus placebo of 1.0 or less based on the O'Brien-Fleming monitoring boundaries. It could also be terminated due to a favourable benefit-to-risk profile if the interim analyses rejected the third null hypothesis based on the O'Brien-Fleming stopping boundary for superiority. If there was no early termination, rejection of the second and third null hypotheses in the final analysis was required to establish cardiovascular safety and cardiovascular superiority of NB, respectively.

Due to the public release of the 25% interim results, the executive steering committee of the trial determined that the scientific integrity of the LIGHT trial was compromised, and the trial was terminated early after 64% of the planned events. The primary analysis following termination was amended to the planned 50% interim analysis, with a sensitivity analysis using the final data cut-off and the monitoring boundaries specified for the 50% interim analysis. Results from the final data cut-off are presented in this report.

Sensitivity Analyses

Several sensitivity analyses were performed for primary end points and the combinations of model type, analysis set, and method for handling missing data are provided in Table 9. In the pivotal trials, weight-regain imputation assumed a rate of 0.3 kg gained per month until baseline weight was reached, after which baseline weight was imputed. For patients who did not return after enrolment, baseline weight was carried forward. Mixed-effects models with repeated measures were also used for the co-primary end points. Mixed-effects models in all trials used an unstructured covariance structure and the Kenward-Rogers approximation to estimate the denominator degrees of freedom.

In the LIGHT study, sensitivity analyses of the primary end point and other time to cardiovascular event end points were performed in the ITT and per-protocol (PP) sets using a Cox proportional hazards (CPH) model adjusted for the following: age, cardiovascular risk group, race (white or non-white), and sex. Sensitivity analyses were also performed with the unadjusted model in the on-treatment ITT set, in which patients were censored for 365 days following treatment discontinuation, and the PP set, in which patients were censored 30 days following treatment discontinuation.

Table 9: Summary of Primary End Point Analyses

Model type	Factors and covariates	Analysis set	Data imputation approach
Pivotal trials			
Primary analysis			
ANCOVA/ logistic regression	COR-I, COR-II, and COR-BMOD studies: Study centre, baseline weight COR-DM study: HbA1c category,[a] sulfonylurea use,[b] baseline weight	Full analysis	LOCF
Sensitivity analyses			
Mixed effects with repeated measures (% change in weight outcome only)	Random effect: patient Covariate: baseline weight Fixed effects for the COR-I, COR-II, and COR-BMOD studies: treatment, time (week), study centre, treatment by time Fixed effects for the COR-DM study: treatment, time (week), treatment by time, HbA1c category, sulfonylurea use[b]	Full analysis, mITT	None
ANCOVA/ logistic regression	Same as for primary analysis	All: Completers, PP COR-I, COR-II, and COR-DM only: mITT	LOCF

Model type	Factors and covariates	Analysis set	Data imputation approach
ANCOVA/ logistic regression	Same as for primary analysis	COR-I, COR-II, and COR-DM: All randomized patients COR-BM: Full analysis	BOCF
ANCOVA/ logistic regression	Same as for primary analysis	All randomized patients	COR-I, COR-II, and COR-DM: weight regain
ANCOVA/ logistic regression	Same as for primary analysis	Full analysis	None (visit-wise observed cases)
LIGHT study			
Primary analysis			
CPH model	None	ITT	NA
Sensitivity analyses			
CPH model	None	On-treatment ITT (censored 365 days following treatment discontinuation), PP	NA
CPH model	Age, CV risk group, race,[c] and sex	ITT, PP	NA

ANCOVA = analysis of covariance; BOCF = baseline observation carried forward; CPH = Cox proportional hazards; CV = cardiovascular; ITT = intention to treat; LOCF = last observation carried forward; mITT = modified intention to treat; NA = not applicable; PP = per protocol.

[a] Less than or equal to 8% or greater than 8%.

[b] With or without sulfonylurea use.

[c] White or non-white.

Source: Clinical Study Reports for the COR-I, COR-II, COR-BMOD, COR-DM, and LIGHT studies.[17-20,27]

Subgroup Analyses

In the pivotal trials, the co-primary end points were analyzed in the full analysis set in the following pre-specified subgroups:

- BMI category: patients with below-median baseline BMI; patients with median baseline BMI or greater
- Patients with hypertension at baseline, defined as a diagnosis of hypertension or a prescription for concomitant anti-hypertensive medications
- Patients with dyslipidemia at baseline, defined as a diagnosis of dyslipidemia (or hypercholesterolemia, hypertriglyceridemia, hyperlipidemia, or low HDL cholesterol in the COR-I, COR-II, and COR-DM studies) or low-density lipoprotein cholesterol greater than 160 mg/dL, total cholesterol greater than 240 mg/dL, or triglycerides of at least 200 mg/dL (or HDL cholesterol less than 40 mg/dL in the COR-BMOD study).

The subgroup analyses for change in weight were conducted using an ANCOVA model with treatment, subgroup, and subgroup-by-treatment interaction as factors and baseline weight as a covariate. The subgroup analyses for the dichotomous co-primary end point were conducted using a logistic regression model with the same factors and covariate as for the continuous co-primary end point.

In the LIGHT study, the efficacy end points were analyzed in the ITT and PP sets in the following pre-specified subgroups:

- BMI category: patients with a below-median baseline BMI; patients with median baseline BMI or greater
- Cardiovascular risk category: type 2 diabetes and no cardiovascular disease; cardiovascular disease and no type 2 diabetes; type 2 diabetes and cardiovascular disease

The LIGHT study subgroup analyses for time-to-event end points were conducted using a CPH model with treatment, cardiovascular risk group, race (white or non-white), sex, subgroup, and treatment-by-subgroup interaction as factors and age as a covariate. A likelihood ratio test was used to compare the models with and without the treatment-by-subgroup interaction term.

Other Efficacy Analyses

The efficacy analyses for secondary and exploratory outcomes in the pivotal trials used similar models as the co-primary end points. Continuous variables were analyzed using an ANCOVA model adjusted for study centre and baseline value in the COR-I, COR-II, and COR-BMOD studies and adjusted for HbA1c category (at least or greater than 8%), sulfonylurea use (with or without), and baseline value in the COR-DM study. The full analysis set and the LOCF approach for missing data were used.

Study centres in the COR-I, COR-II, and COR-BMOD studies were pooled for analysis if they had fewer than nine patients with a non-missing post-baseline weight measurement. In the COR-II study, weighted LOCF analysis in the full analysis set was used for secondary end points evaluated at week 56. In this approach, patients in the NB group who did not lose at least 5% of body weight and were re-randomized to continue on the same dosage regimen were assigned a statistical weight double that of patients in the placebo group. Patients re-randomized to the higher dosage were excluded from the analysis. Due to methodological concerns with this method (i.e., loss of randomization), the weighted LOCF analysis results from week 56 are not presented in this report.

In the pivotal trials, the secondary efficacy outcomes were only to be tested if both co-primary end points were met. The secondary efficacy outcomes were tested in a hierarchy such that each secondary outcome was tested only if the significance level of 0.05 was met for all the preceding outcomes. The order of relevant secondary end points within the hierarchy is detailed in Table 4.

If fewer than half of the item scores were missing for a subscale in the IWQoL-Lite, the missing subscale score was imputed by multiplying the average of the non-missing subscale item scores with the total number of items in that subscale. The same approach was used for the total score if 25% or less of the item scores were missing. The same imputation approach was used for total scores and subscale scores in the COE questionnaire, IDS-SR, and FCI if less than 20% of the item scores were missing. If the percentage of missing item scores exceeded the threshold, the total or subscale score was set to missing.

End points in the LIGHT study that were not event-based were analyzed in the ITT set using the LOCF approach and a general linear model (continuous outcomes) or logistic regression model (categorical outcomes) adjusting for the same factors and covariates as for the CPH model sensitivity analyses (with the addition of a baseline value). The same

end points were also analyzed in the PP set without imputation. For body-weight end points, the LOCF approach used only observations made while on study medication (no more than 30 days after treatment discontinuation).

Sample Size Calculations

The assumptions upon which sample size calculations were based for the pivotal trials are summarized in Table 10. In the LIGHT study, the underlying hazard ratio for the primary end point in the NB group versus the placebo group was assumed to be 1.0. With a noninferiority (NI) margin of 1.4, a total of 371 events would have a 90% power to establish the upper bound of a one-sided 97.5% CI lower than the NI margin. Assuming a recruitment period of half a year, a maximum follow-up of four years, an annual rate of 1.2% of patients lost to follow-up, and an annualized event rate of 1.5% in the placebo group, a sample size of 3,448 patients per treatment group was required. A sample size of 4,450 patients was chosen to accommodate uncertainty in the assumptions and dropout.

Table 10: Summary of Sample Size Assumptions (Pivotal Trials)

Trial and outcome	NB effect	PL effect	SD	Statistical test	Power	Alpha	Dropout	Randomized sample size required
COR-I								
Weight loss	≥ 6%	1%	7%	2-sample t-test	99%	0.05	20%	1,650 (1:1:1)
≥ 5% weight loss	64%	50%	NA	2-sample chi-square test	99%	0.05	20%	1,650 (1:1:1)
COR-II								
Weight loss	≥ 6%	1%	7%	2-sample t-test	99%	0.05	40%	1,500 (2:1)
≥ 5% weight loss	64%	50%	NA	2-sample chi-square test	99%	0.05	20%	1,500 (2:1)
COR-BMOD								
Weight loss	10%	5%	5%	2-sample t-test	99%	0.05	NR	800 (3:1)
≥ 5% weight loss	64%	50%	NA	2-sample chi-square test	99%	0.05	NR	800 (3:1)
COR-DM								
Weight loss	≥ 6.5%	1.5%	5%	2-sample t-test	99%	0.05	20%	525 (2:1)
≥ 5% weight loss	27.5%	15%	NA	2-sample chi-square test	79%	0.05	20%	525 (2:1)

NA = not applicable; NB = naltrexone and bupropion; NR = not reported; PL = placebo; SD = standard deviation.

Source: Clinical Study Reports for the COR-I, COR-II, COR-BMOD, and COR-DM studies.[17-20]

Analysis Populations

In the pivotal trials, the definitions of the analysis sets were as follows:

- Full analysis (primary efficacy analysis set): All randomized patients who had a baseline weight measurement and at least one post-baseline weight measurement while on study drug
- mITT: All randomized patients who had a baseline weight measurement and at least one post-baseline weight measurement during the defined treatment phase
- Completers: All randomized patients who had a baseline weight measurement and a post-baseline weight measurement, and who completed 56 weeks of treatment. The

COR-II study had two completers analysis sets; one for completion of 28 weeks of treatment and one for completion of 56 weeks of treatment

- PP: Patients in the full analysis set who received at least 28 weeks of study treatment and had at least 70% adherence to treatment
- Safety: All randomized patients who received at least one tablet of study treatment and had at least one investigator contact or assessment at any time after the start of study treatment.

In the full analysis, mITT, completers, and PP sets, patients were analyzed according to randomized treatment-group assignment. In the safety set, patients were analyzed according to the study treatment administered on the first day of treatment following randomization. The set of all randomized patients was also used for sensitivity analyses.

In the LIGHT study, the ITT set consisted of all patients randomized to the treatment period and dispensed study medication, and patients were analyzed according to randomized treatment group assignment. For the on-treatment sensitivity analysis of the ITT set, patients were censored after 365 days following study medication discontinuation. The PP set consisted of all ITT patients who took at least one dose of study medication in the treatment period according to protocol and did not have exclusionary notable protocol deviations (which were determined prior to database lock), or received study medication that led to treatment change. In the PP set, patients were censored after 30 days following discontinuation of study treatment.

Results

Patient Disposition

Details of patient disposition in the pivotal trials are provided in Table 11. The percentage of randomized patients who completed the full course of study treatment ranged from 49.9% to 58.8%. There were notable and consistent imbalances in study treatment discontinuation due to AEs and insufficient weight loss, with the former more common in the NB groups and the latter more common in the placebo groups. Discontinuation due to AEs was reported for 9.6% to 15.3% of the placebo groups and 19.2% to 29.3% of the NB groups, with the highest rates in the COR-DM study. Discontinuation due to insufficient weight loss was reported for 3.0% to 6.9% of the placebo groups and for 0.5% to 2.1% of the NB groups. The imbalances in discontinuations due to AEs were already apparent in the dose escalation period (weeks 1 to 4), with rates ranging from 2.0% to 4.7% for the placebo groups and 9.8% to 17.3% in the NB groups. The early discontinuations may have contributed to imbalances between treatment groups in patients eligible for the full analysis set. As a percentage of randomized patients, the full analysis set accounted for 88.0% to 95.5% of the placebo groups and 79.1% to 82.4% of the NB groups.

Patients who discontinued study treatment early were encouraged to return as soon as possible to complete an early study-termination visit at which end-of-study assessments were performed. Patients were also encouraged to return for body-weight measurements every four weeks (or at weeks 28 and 56 in the COR-II study) and waist-circumference measurements at weeks 28 and 56.

Table 11: Patient Disposition (Pivotal Trials)

	COR-I		COR-II		COR-BMOD		COR-DM	
	PL	NB	PL	NB	PL	NB	PL	NB
Screened, N	2,930		2,237		NR		1,625	
Randomized, N	581	583	495	1,001	202	591	170	335
Completed study treatment, N (%)	290 (49.9)	296 (50.8)	267 (53.9)	538 (53.7)	118 (58.4)	342 (57.9)	100 (58.8)	175 (52.2)
Discontinued study treatment, N (%)	291 (50.1)	287 (49.2)	228 (46.1)	463 (46.3)	84 (41.6)	249 (42.1)	70 (41.2)	160 (47.8)
Adverse event	56 (9.6)	112 (19.2)	68 (13.7)	241 (24.1)	25 (12.4)	150 (25.4)	26 (15.3)	98 (29.3)
Death	0	1 (0.2)	0	0	0	0	0	0
Drug nonadherence	15 (2.6)	17 (2.9)	5 (1.0)	10 (1.0)	5 (2.5)	13 (2.2)	3 (1.8)	8 (2.4)
Insufficient weight loss	40 (6.9)	12 (2.1)	33 (6.7)	19 (1.9)	6 (3.0)	3 (0.5)	6 (3.5)	5 (1.5)
Lost to follow-up	66 (11.4)	65 (11.1)	48 (9.7)	77 (7.7)	17 (8.4)	22 (3.7)	15 (8.8)	22 (6.6)
Other	3 (0.5)	2 (0.3)	3 (0.6)	0	1 (0.5)	5 (0.8)	0	1 (0.3)
Patient moved	7 (1.2)	4 (0.7)	5 (1.0)	13 (1.3)	5 (2.5)	5 (0.8)	NR	NR
Pregnancy	3 (0.5)	5 (0.9)	0	6 (0.6)	1 (0.5)	1 (0.2)	NR	NR
Protocol violation	7 (1.2)	9 (1.5)	8 (1.6)	20 (2.0)	0	4 (0.7)	4 (2.4)	3 (0.9)
Selection criteria not met	1 (0.2)	0	0	1 (0.1)	0	0	0	2 (0.6)
Study drug not dispensed	3 (0.5)	0	2 (0.4)	1 (0.1)	0	3 (0.5)	1 (0.6)	0
Withdrew consent	90 (15.5)	60 (10.3)	56 (11.3)	75 (7.5)	24 (11.9)	43 (7.3)	15 (8.8)	21 (6.3)
Discontinued study treatment during weeks 1 to 4, N (%)	63 (10.8)	115 (19.7)	45 (9.1)	183 (18.3)	12 (5.9)	113 (19.1)	12 (7.1)	74 (22.1)
Adverse event	13 (2.2)	57 (9.8)	18 (3.6)	128 (12.8)	4 (2.0)	89 (15.1)	8 (4.7)	58 (17.3)
mITT,[a] N (%)	536 (92.3)	538 (92.3)	474 (95.8)	943 (94.2)	NR	NR	166 (97.6)	321 (95.8)
Full analysis set,[b] N (%)	511 (88.0)	471 (80.8)	456 (92.1)	825 (82.4)	193 (95.5)	482 (81.6)	159 (93.5)	265 (79.1)
Week 56 completers analysis set,[c] N (%)	290 (49.9)	296 (50.8)	267 (53.9)	538 (53.7)	106 (52.5)	301 (50.9)	100 (58.8)	175 (52.2)
Week 28 completers analysis set,[c] N (%)	NA	NA	319 (64.4)	619 (61.8)	NA	NA	NA	NA
PP,[d] N (%)	251 (43.2)	267 (45.8)	248 (50.1)	483 (48.3)	92 (45.5)	245 (41.5)	102 (60.0)	149 (44.5)
Safety,[e] N (%)	569 (97.9)	573 (98.3)	492 (99.4)	992 (99.1)	200 (99.0)	584 (98.8)	169 (99.4)	333 (99.4)

	COR-I		COR-II		COR-BMOD		COR-DM	
Discontinuation phase safety, N (%)	284 (48.9)	292 (50.1)	NA	NA	NA	NA	NA	NA

mITT = modified intention to treat; NA = not applicable; NB = naltrexone and bupropion; NR = not reported; PL = placebo; PP = per protocol.

Note: All percentages are expressed as the percentage of randomized patients.

[a] The mITT analysis set included all randomized patients who had a baseline and at least one post-baseline body weight measurement during the defined treatment phase.

[b] The full analysis set included all randomized patients who had a baseline weight measurement, and at least one post-baseline weight measurement while on the study drug.

[c] Completers analysis set included all randomized patients who had a baseline measurement and a post-baseline measurement at week 56 (week 28 in the COR-II study) while on the study drug.

[d] The PP analysis set included all patients in the full analysis set who received the study drug for at least 28 weeks and were adherent to the drug (≥ 70% overall adherence).

[e] The safety analysis set included all randomized patients who received at least one tablet of the study drug and had at least one investigator-contact assessment at any time after the start of the study drug, regardless of whether or not they discontinued the study.

Source: Clinical Study Reports for the COR-I, COR-II, COR-BMOD, and COR-DM studies;[17-20] Greenway et al. (2010);[13] Apovian et al. (2013);[14] Hollander et al. (2013).[16]

Details of patient disposition based on the final data cut-off in the LIGHT study are provided in Table 12. Of the 10,514 patients randomized to the lead-in period, 1,490 discontinued the lead-in period and 105 completed the lead-in period but were not randomized to the treatment period. Patients who discontinued study treatment but still participated in study visits were encouraged to continue in the weight-management program. A MACE follow-up, if not refused, was conducted in patients who discontinued study treatment and study procedures.

Due to early termination of the LIGHT study, all patients discontinued treatment. Treatment discontinuations due to AEs were more common in the NB group than in the placebo group (30.5% versus 9.4%) and treatment discontinuations due to not meeting the week 16 continuation criterion were more common in the placebo group than in the NB group (40.6% versus 14.2%). Aside from these reasons, the most common reason for treatment discontinuation was patient decision to no longer receive study medication (22.2% to 25.4% of patients). There were no notable differences between treatment groups in discontinuation of study procedures (i.e., patients discontinued study visits and internet- or telephone-based contact). Vital status was not obtained for less than 1% of patients and MACE follow-up was not available for 11.6% of patients. Patients who discontinued study procedures and for whom MACE follow-up was not available were censored at the date of the last available assessment.

Table 12: Patient Disposition (LIGHT Study)

	LIGHT	
	PL	**NB**
Screened, N	13,192	
Randomized to lead-in period, N	10,514	
Discontinued lead-in period, N	1,490	
Completed lead-in period, but not randomized to treatment period, N	105	
Randomized to treatment period, N	4,454	4,456
ITT,[a] N (%)	4,450 (99.9)	4,455 (100)
PP,[b] N (%)	4,252 (95.5)	4,284 (96.1)
	ITT set	**ITT set**

	LIGHT	
Completed week 16 visit	3,787 (85.1)	3,745 (84.1)
Completed week 26 visit	3,321 (74.6)	3,425 (76.9)
Completed week 52 visit	2,886 (64.9)	3,025 (67.9)
Discontinued treatment, N (%)	4,450 (100)	4,455 (100)
Adverse event	419 (9.4)	1,358 (30.5)
Patient decision to no longer receive study medication	1,132 (25.4)	987 (22.2)
Protocol deviation	30 (0.7)	25 (0.6)
Lost to follow-up	225 (5.1)	251 (5.6)
Sponsor decision	681 (15.3)	1,022 (22.9)
Did not meet week 16 treatment continuation criterion (primary reason for discontinuing)	1,806 (40.6)	631 (14.2)
Other	157 (3.5)	180 (4.0)
Unknown	0	1 (< 0.1)
Discontinued study procedures (visits), N (%)		
Did not refuse MACE follow-up contact	2,202 (49.5)	2,055 (46.1)
Refused MACE follow-up contact, did not refuse contact through primary physician or designated contact	400 (9.0)	354 (7.9)
Refused MACE follow-up contact and contact through primary physician or designated contact	254 (5.7)	243 (5.5)
Vital status obtained	240 (5.4)	233 (5.2)
Vital status not obtained	14 (0.3)	10 (0.2)
Lost to follow-up to MACE contact and consent	283 (6.4)	251 (5.6)
Vital status obtained	271 (6.1)	241 (5.4)
Vital status not obtained	12 (0.3)	10 (0.2)

ITT = intention to treat; MACE = major adverse cardiovascular event; NB = naltrexone and bupropion; PL = placebo; PP = per protocol.

[a] The ITT analysis set included all patients randomized to the treatment period who were dispensed study medication.

[b] The PP analysis set included ITT patients who took at least one dose of study medication in the treatment period according to protocol and did not have major protocol deviations.

Source: Clinical Study Report for the LIGHT study.[27]

Protocol Deviations

The pivotal trials included no plans to discontinue study medication in patients with protocol deviations or to exclude them from the PP set (other than for lack of adherence). Commonly reported protocol deviations are provided in Table 13. The following deviations were consistently reported in 10% of patients or greater: visit outside of window (25.9% to 38.6%), patient did not follow correct dosing instructions (21.8% to 36.4%), patient missed an assessment visit (13.4% to 27.4%), lack of blood pressure evaluations (11.7% to 23.3%), and prohibited concomitant medication use (9.8% to 14.2%). In the COR-DM study, 18% of randomized patients did not meet study entry criteria compared with 4% to 7% of patients in the other pivotal trials. Visits outside the window and not following correct dosing instructions were reported in a notably greater percentage of patients in the placebo group (38.6% and 44.6%) compared with the NB group (29.4% and 36.4%) in the COR-BMOD study. The investigators did not consider the protocol deviations to have affected the study conclusions.

Table 13: Common Protocol Deviations (Pivotal Trials)

	COR-I randomized		COR-II randomized		COR-BMOD randomized		COR-DM randomized	
	PL N = 581	NB N = 583	PL N = 495	NB N = 1,001	PL N = 202	NB N = 591	PL N = 170	NB N = 335
Patients with common protocol deviation,[a] n (%)								
Visit outside window for weeks 4 to 56[b]	196 (33.7)	180 (30.9)	130 (26.3)	259 (25.9)	78 (38.6)	174 (29.4)	55 (32.4)	96 (28.7)
Patient did not follow correct dosing instructions	155 (26.7)	156 (26.8)	113 (22.8)	218 (21.8)	90 (44.6)	215 (36.4)	37 (21.8)	77 (23.0)
Patient missed an assessment visit	159 (27.4)	130 (22.3)	109 (22.0)	205 (20.5)	38 (18.8)	84 (14.2)	28 (16.5)	45 (13.4)
Evaluation of elevated blood pressure and/or pulse not done	68 (11.7)	90 (15.4)	109 (22.0)	233 (23.3)	NR	NR	26 (15.3)	45 (13.4)
Patient took prohibited concomitant medication	78 (13.4)	83 (14.2)	60 (12.1)	98 (9.8)	24 (11.9)	78 (13.2)	24 (14.1)	46 (13.7)
Study procedure/ assessment not done/taken	42 (7.2)	35 (6.0)	91 (18.6)	198 (19.8)	46 (22.8)	128 (21.7)	20 (11.8)	26 (7.8)
Did not meet entry criteria	32 (5.5)	39 (6.7)	20 (4.0)	62 (6.2)	5 (2.5)	33 (5.6)	30 (17.6)	60 (17.9)
Neurological exam outside window	57 (9.8)	61 (10.5)	23 (4.6)	56 (5.6)	27 (13.4)	68 (11.5)	26 (15.3)	35 (10.4)
ECG exam outside window	47 (8.1)	57 (9.8)	48 (9.7)	98 (9.8)	23 (11.4)	71 (12.0)	21 (12.4)	33 (9.9)
Protocol-required procedure not fully completed	5 (0.9)	4 (0.7)	31 (6.3)	65 (6.5)	19 (9.4)	64 (10.8)	19 (11.2)	26 (7.8)

ECG = electrocardiogram; NB = naltrexone and bupropion; NR = not reported; PL = placebo.

[a] Protocol deviation reported for at least 10% of patients in at least one treatment group.

[b] Or for week 58 in Study COR-I.

Source: Clinical Study Reports for the COR-I, COR-II, COR-BMOD, and COR-DM studies.[17-20]

Major protocol deviations in the LIGHT study were determined during a blinded review of the data prior to database lock and patients with major protocol deviations were excluded from the PP set. Major protocol deviations were reported in 9.9% and 9.8% of the placebo and NB groups, respectively, and the most common deviation was prohibited concomitant medication use (4.0% and 3.0% in the placebo and NB groups).

Table 14: Major Protocol Deviations (LIGHT Study)

	ITT set	
	PL N = 4,450	NB N = 4,455
Patients with major protocol deviation, n (%)	440 (9.9)	436 (9.8)
Lack of appropriate informed consent	162 (3.6)	205 (4.6)
Did not meet study entry criteria	55 (1.2)	52 (1.2)
Prohibited concomitant medication use	177 (4.0)	135 (3.0)
Weight-loss surgery during the study	31 (0.7)	23 (0.5)
Study medication not taken for > 4 consecutive weeks	29 (0.7)	40 (0.9)
Study medication overdose	2 (< 0.1)	1 (< 0.1)

ITT = intention to treat; NB = naltrexone and bupropion; PL = placebo.

Source: Clinical Study Report for the LIGHT study.[27]

Exposure to Study Treatments

Details of adherence to study medication and duration of exposure for the pivotal trials are provided in Table 15. The percentage of patients with at least 70% adherence measured from baseline to week 4 was lower in the NB group than in the placebo group in the pivotal trials (83.8% to 87.3% versus 93.9% to 96.3%). This was consistent with the higher percentage of patients in the NB compared with the placebo group with a treatment duration of 4 weeks or less. By week 52, the percentage of patients with at least 70% adherence was similar between treatment groups and was lower in the COR-BMOD study (88.7%) compared with the other three pivotal trials (95.9% to 100.0%).

Over the whole treatment period, the percentage of patients with at least 70% adherence was similar between the groups in the COR-I and COR-II studies and notably higher in the placebo group than in the NB group in the COR-BMOD (57.1% versus 51.6%) and COR-DM studies (75.3% versus 58.7%). In all pivotal trials, the percentage of patients on treatment for four weeks or less was higher in the NB group than in the placebo group (18.0% to 22.1% versus 5.0% to 10.4%).

Table 15: Exposure to Study Treatment (Pivotal Trials)

	COR-I randomized		COR-II randomized		COR-BMOD randomized		COR-DM randomized	
	PL N = 581	NB N = 583	PL N = 495	NB N = 1,001	PL N = 202	NB N = 591	PL N = 170	NB N = 335
Patients with ≥ 70% adherence, n (%)								
Overall DB treatment period	355 (65.9) N = 539	345 (63.1) N = 547	328 (68.8) N = 477	615 (64.8) N = 949	113 (57.1) N = 198	294 (51.6) N = 570	125 (75.3) N = 166	189 (58.7) N = 322
Baseline to week 4	475 (93.9) N = 506	452 (85.9) N = 526	424 (94.6) N = 448	795 (87.3) N = 911	190 (96.0) N = 198	482 (84.6) N = 570	156 (96.3) N = 162	263 (83.8) N = 314
Week 52	278 (95.9) N = 290	288 (97.3) N = 296	261 (97.8) N = 267	520 (97.0) N = 536	102 (88.7) N = 115	297 (88.7) N = 335	99 (100.0) N = 99	167 (96.5) N = 173

	COR-I randomized		COR-II randomized		COR-BMOD randomized		COR-DM randomized	
Patients that received ≥ 1 dose of study drug, n (%)	578 (99.5)	583 (100.0)	493 (99.6)	1,000 (99.9)	NR	NR	NR	NR
Category of duration of DB treatment, n (%)								
> 0 to 4 weeks	60 (10.4)	115 (19.7)	39 (7.9)	180 (18.0)	10 (5.0)	106 (18.2)	11 (6.5)	74 (22.1)
> 4 to 8 weeks	55 (9.5)	51 (8.7)	48 (9.7)	89 (8.9)	12 (6.0)	39 (6.7)	4 (2.4)	25 (7.5)
> 8 to 12 weeks	37 (6.4)	22 (3.8)	27 (5.5)	35 (3.5)	5 (2.5)	19 (3.3)	15 (8.9)	13 (3.9)
> 52 to 56 weeks	106 (18.3)	96 (16.5)	138 (28.0)	247 (24.7)	55 (27.5)	146 (25.0)	39 (23.1)	85 (25.4)
> 56 weeks	189 (32.7)	208 (35.7)	131 (26.6.)	298 (29.8)	67 (33.5)	202 (34.6)	63 (37.3)	92 (27.5)
Mean duration of DB treatment, weeks (SD)	36.1 (22.7)	35.5 (24.1)	38.3 (21.9)	36.4 (23.9)	42.6 (19.6)	38.6 (23.6)	41.7 (20.3)	35.1 (24.4)
Median duration on DB treatment, weeks (minimum, maximum)	56.0 (1, 60)	56.0 (1, 61)	56.0 (1, 60)	56.0 (1, 64)	56.0 (1, 59)	56.0 (1, 61)	56.0 (1, 62)	56.0 (1, 60)

DB = double-blind; NB = naltrexone and bupropion; NR = not reported; PL = placebo; SD = standard deviation.

Note: N represents the number of patients for whom adherence data were available at that time point.

Source: Clinical Study Reports for the COR-I, COR-II, COR-BMOD, and COR-DM studies.[17-20]

Table 16: Exposure to Study Treatment (LIGHT Study)

	ITT set	
	PL N = 4,450	**NB N = 4,455**
% of visits at which patient reported taking study medication regularly	N = 4,344	N = 4,343
Mean (SD)	90.8 (18.5)	85.6 (25.5)
Median (range)	100 (0 to 100)	100 (0 to 100)
Duration on study drug, weeks	N = 4,444	N = 4,450
Mean (SD)	41.7 (47.2)	53.1 (55.0)
Median (range)	16.3 (0.1 to 157.1)	18.4 (0.1 to 158.0)
Duration on study, weeks	N = 4,450	N = 4,455
Mean (SD)	130.5 (30.4)	131.4 (29.3)
Median (range)	139.0 (0.1 to 159.6)	139.1 (0.1 to 160.7)

ITT = intention to treat; NB = naltrexone and bupropion; PL = placebo; SD = standard deviation.

Source: Clinical Study Report for the LIGHT study.[27]

Efficacy

Only those efficacy outcomes identified in the review protocol (Table 3) are reported as follows.

Body Weight (Co-Primary End Points in the Pivotal Trials)

Detailed information on end points involving body weight in the pivotal trials is provided in Table 17. The co-primary end points were met in all four pivotal trials, demonstrating

superiority of NB over placebo for weight loss. Members of the NB group lost a greater percentage of their baseline weight compared with the placebo group, with least squares mean (LSM) differences in percentage change in body weight from baseline to week 56 (week 28 in the COR-II study) of –4.81% (95% CI, –5.63% to –3.99%) in the COR-I study, –4.56% (95% CI, –5.19% to –3.93%) in the COR-II study, –4.21% (95% CI, –5.56% to –2.86%) in the COR-BMOD study, and –3.28% (–4.34% to –2.22%) in the COR-DM study. Greater percentages of patients achieved at least 5% weight loss from baseline to week 56 (week 28 in the COR-II study) in the NB group compared with the placebo group, with odds ratios for the NB group versus the placebo group of 4.86 (95% CI, 3.60 to 6.57) in the COR-I study, 6.61 (95% CI, 4.95 to 8.84) in the COR-II study, 2.89 (95% CI, 2.02 to 4.13) in the COR-BMOD study, and 3.44 (95% CI, 2.15 to 5.50) in the COR-DM study.

Sensitivity analyses of the co-primary end points in the set of all randomized patients (or the full analysis set in the COR-BMOD study) with BOCF imputation and in the mITT set with LOCF imputation (not performed in the COR-BMOD study) yielded results consistent with the primary analyses, although the observed treatment effect in all four pivotal trials was consistently smaller for the co-primary end points in the sensitivity analysis compared with the primary analysis in the full analysis set using LOCF imputation (Table 17). Analyses in the PP set (patients in the full analysis set who received study drug for at least 28 weeks and had at least 70% overall adherence) using LOCF imputation also yielded results consistent with the primary analyses.

Subgroup analyses of the co-primary end points in the pivotal trials according to baseline BMI category (less than or at least the median baseline BMI) or the presence of hypertension or dyslipidemia did not demonstrate any notable differences between subgroups in treatment effect (Table 33 and Table 34 in Appendix 3).

The percentage of patients achieving at least 10% weight loss from baseline to week 56 (week 28 in the COR-II study) was evaluated as a secondary end point in the pivotal trials. The percentage of patients achieving at least 10% weight loss was greater in the NB group than in the placebo in the pivotal trials, with odds ratios for NB versus placebo of 4.19 (95% CI, 2.82 to 6.23) in the COR-I study, 5.36 (95% CI, 3.60 to 7.98) in the COR-II study, 2.89 (95% CI, 2.02 to 4.13) in the COR-BMOD study, and 3.44 (95% CI, 2.15 to 5.50) in the COR-DM study (Table 17). In the COR-I, COR-II, and COR-BMOD studies, testing of this secondary end point was controlled for type I error according to the closed testing procedure and statistical significance was demonstrated. In the COR-DM study, this secondary end point was below other end points in the testing hierarchy and the hypothesis testing ended at an end point further up in the hierarchy. The results should therefore be interpreted with consideration of the risk of type I error. Sensitivity analyses in the mITT set with LOCF imputation in the COR-I, COR-II, and COR-DM studies yielded results consistent with the primary analyses, but with smaller effect sizes (Table 17).

Body-weight outcomes in the LIGHT study were exploratory and not controlled for type I error. LOCF imputation using observations up to 30 days following treatment discontinuation in the ITT set was used for change in body weight from baseline to week 52 (Table 18). Compared to the placebo group, the NB group experienced greater weight loss (LSM difference in percentage change in weight of –2.87%; 95% CI, –3.07% to –2.67%), had a higher percentage of patients with at least 5% weight loss (odds ratio of 3.37; 95% CI, 3.01 to 3.76), and a higher percentage of patients with at least 10% weight loss (odds ratio of 4.16; 95% CI, 3.45 to 5.02). The results of PP analyses of percentage change in

body weight and percentage of patients with at least 5% weight loss were consistent with the ITT analysis results.

Patients in the LIGHT study took study medication for up to 208 weeks. Due to the large percentages of patients discontinuing treatment during the LIGHT study (Table 12). Most of the data in the ITT set at week 52 and later time points were imputed using LOCF rather than observed. Analysis in the PP set censored patients after three days following treatment discontinuation and therefore provided estimates of change in body weight for patients who remained on treatment. Although the sample size available for body-weight estimates decreased steadily over the course of the trial, a diminishing treatment effect over time was observed (Table 36 in Appendix 3).

Table 17: Key Efficacy Outcomes (Pivotal Trials)

	COR-I		COR-II (week 28 results)		COR-BMOD		COR-DM	
	PL	**NB**	**PL**	**NB**	**PL**	**NB**	**PL**	**NB**
Main analyses with LOCF imputation in the full analysis set	**N = 511**	**N = 471**	**N = 456**	**N = 825**	**N = 193**	**N = 482**	**N = 159**	**N = 265**
Co-primary end point: Mean body weight, kg								
Baseline (SD)	99.29 (14.33)	100.17 (16.26)	99.29 (15.97)	100.69 (16.65)	101.91 (15.04)	100.69 (15.43)	104.99 (17.13)	106.35 (19.11)
End point[a] (SD)	98.03 (15.21)	94.17 (17.40)	97.21 (16.18)	94.19 (17.61)	96.38 (17.07)	91.02 (17.13)	103.03 (17.33)	100.97 (19.67)
LSMD in % change, NB vs. PL (95% CI)	–4.81 (–5.63 to –3.99) **P < 0.001**		–4.56 (–5.19 to –3.93) **P < 0.001**		–4.21 (–5.56 to –2.86) **P < 0.001**		–3.28 (–4.34 to –2.22) **P < 0.001**	
Co-primary end point: patients with ≥ 5% decrease in body weight,[b] n (%)	84 (16.4)	226 (48.0)	80 (17.5)	459 (55.6)	82 (42.5)	320 (66.4)	30 (18.9)	118 (44.5)
Odds ratio, NB vs. PL (95% CI)	4.86 (3.60 to 6.57) **P < 0.001**		6.61 (4.95 to 8.84) **P < 0.001**		2.89 (2.02 to 4.13) **P < 0.001**		3.44 (2.15 to 5.50) **P < 0.001**	
patients with ≥ 10% decrease in body weight,[b] n (%)	38 (7.4)	116 (24.6)	32 (7.0)	225 (27.3)	39 (20.2)	200 (41.5)	9 (5.7)	49 (18.5)
Odds ratio, NB vs. PL (95% CI)	4.19 (2.82 to 6.23) **P < 0.001**		5.36 (3.60 to 7.98) **P < 0.001**		2.92 (1.95 to 4.37) **P < 0.001**		3.75 (1.79 to 7.88)	
Sensitivity analyses with LOCF imputation in the mITT set	**N = 536**	**N = 538**	**N = 474**	**N = 943**			**N = 166**	**N = 321**
Co-primary end point: Mean body weight, kg								
Baseline (SD)	99.50 (14.38)	99.75 (16.09)	99.36 (15.93)	100.38 (16.66)	NR	NR	105.28 (16.85)	104.22 (19.06)
End point[a] (SD)	98.25 (15.27)	94.48 (17.01)	97.33 (16.20)	94.63 (17.54)	NR	NR	103.41 (17.08)	100.27 (19.24)
LSMD in % change, NB vs. PL (95% CI)	–4.07 (–4.85 to –3.30) P < 0.001		–3.85 (–4.46 to –3.24) P < 0.001		NR		–2.00 (–2.98 to –1.01) P < 0.001	
Co-primary end point: patients with	93 (17.35)	226 (42.01)	81 (17.09)	461 (48.89)	NR	NR	30 (18.07)	115 (35.83)

	COR-I		COR-II (week 28 results)		COR-BMOD		COR-DM	
≥ 5% decrease in body weight[b], n (%)								
Odds ratio, NB vs. PL (95% CI)	3.59 (2.69 to 4.77) P < 0.001		5.10 (3.85 to 6.75) P < 0.001		NR		2.51 (1.59 to 3.97) P < 0.001	
Patients with ≥ 10% decrease in body weight[b], n (%)	37 (6.90)	114 (21.19)	35 (7.38)	225 (23.86)	NR	NR	9 (5.42)	49 (15.26)
Odds ratio, NB vs. PL (95% CI)	3.70 (2.49 to 5.49) P < 0.001		4.14 (2.83 to 6.07) P < 0.001		NR		3.10 (1.48 to 6.48)	
Sensitivity analyses with BOCF imputation in all randomized patients	**N = 581**	**N = 583**	**N = 495**	**N = 1,001**	**N = 202**	**N = 591**	**N = 170**	**N = 335**
Co-primary end point: Mean body weight, kg								
Baseline (SD)	99.45 (14.31)	99.70 (15.88)	99.21 (15.86)	100.31 (16.55)	101.88 (14.96)	100.16 (15.42)	105.08 (16.99)	104.22 (18.93)
End point[a] (SD)	98.59 (14.91)	95.77 (16.90)	97.57 (15.96)	95.50 (17.42)	97.50 (16.66)	93.90 (17.14)	103.60 (17.29)	100.91 (19.15)
LSMD in % change, NB vs. PL (95% CI)	–3.12 (–3.81 to –2.42) P < 0.001		–3.28 (–3.88 to –2.69) P < 0.001		–1.91 (–3.21 to –0.61) P = 0.004		–1.72 (–2.68 to –0.77) P < 0.001	
Co-primary end point: patients with ≥ 5% decrease in body weight[b], n (%)	67 (11.5)	180 (30.9)	69 (13.9)	421 (42.1)	64 (33.2) **FA set N = 193**	242 (50.2) **FA set N = 482**	24 (14.1)	94 (28.1)
Odds ratio, NB vs. PL (95% CI)	3.61 (2.63 to 4.94) P < 0.001		4.93 (3.68 to 6.62) P < 0.001		2.17 (1.51 to 3.11) P < 0.001		2.35 (1.44 to 3.86) P < 0.001	

BOCF = baseline observation carried forward; CI = confidence interval; FA = full analysis; LOCF = last observation carried forward; LSMD = least squares mean difference; mITT = modified intention to treat; NB = naltrexone and bupropion; NR = not reported; PL = placebo; SD = standard deviation; vs. = versus.

Note: The full analysis set included patients who were randomized, had a baseline weight measurement, and had at least one post-baseline weight measurement while on the study drug. The LOCF approach used observations made while on treatment (up to one day after the last confirmed dose of study medication). Continuous end points were analyzed using an analysis of covariance model. Categorical end points were analyzed using a logistic regression model. For the COR-I, COR-II, and COR-BMOD studies, the model adjusted for study centre and baseline body weight. For the COR-DM study, the model adjusted for the glycated hemoglobin category (≤ or > 8%), sulfonylurea use (with or without), and baseline body weight.

[a] Week 56 (week 28 in the COR-II study).

[b] From baseline to week 56 (week 28 in the COR-II study).

Source: Clinical Study Reports for the COR-I, COR-II, COR-BMOD, and COR-DM studies.[17-20]

Table 18: Body Weight (LIGHT Study)

	ITT set	
	PL N = 4,450	**NB N = 4,455**
Mean body weight, kg		
Baseline (SD)	106.29 (19.18) N = 4,443	105.64 (19.09) N = 4,450
Week 52 (SD)	105.07 (19.46) N = 4,372	101.37 (19.05) N = 4,376
LSMD in % change, NB vs. PL (95% CI)	–2.87 (–3.07 to –2.67) P < 0.0001	
≥ 5% decrease in body weight from baseline to week 52	N = 4,372	N = 4,376
Patients with ≥ 5% decrease in body weight from baseline to week 52, n (%)	545 (12.5)	1,414 (32.3)
Odds ratio (95% CI)	3.37 (3.01 to 3.76) P < 0.0001	
≥ 10% decrease in body weight from baseline to week 52	N = 4,372	N = 4,376
Patients with ≥ 10% decrease in body weight from baseline to week 52, n (%)	146 (3.3)	547 (12.5)
Odds ratio (95% CI)	4.16 (3.45 to 5.02) P < 0.0001	

CI = confidence interval; ITT = intention to treat; LSMD = least squares mean difference; NB = naltrexone and bupropion; PL = placebo; SD = standard deviation; vs. = versus.

Note: P values are provided for descriptive purposes only as the end points were exploratory. Missing data were imputed using the last observation carried forward approach for post-baseline observations made while on treatment (up to 30 days after treatment discontinuation). Responder analyses used a logistic regression model with cardiovascular risk group, race grouping (white or non-white), and sex as factors and age and baseline weight as covariates.

Source: Clinical Study Report for the LIGHT study.[27]

Mortality and Non-Fatal Cardiovascular Events

Time to MACE (Primary End Point in the LIGHT Study)

The primary end point in the LIGHT study was time to first occurrence of MACE (defined as cardiovascular death, non-fatal MI, or non-fatal stroke). In the main analysis using an unadjusted CPH model, the hazard ratio for NB versus placebo using the final data cut-off was 0.95 (99.7% CI, 0.65 to 1.38) with a P value of 0.0013 for ruling out a hazard ratio of 1.4 or greater and a P value of 0.6953 for demonstrating superiority (Table 19). The Kaplan-Meier plot of time to first occurrence of MACE is provided in Figure 3, Appendix 3. However, the LIGHT study was designed such that conclusions could not be made based on the interim analyses unless the trial was stopped due to an unfavourable safety profile or a favourable benefit-to-risk profile. Because the trial was terminated for a different reason, conclusions were not drawn by the investigators based on the analyses of the 50% and 64% datasets.

Sensitivity analyses in patients while they were within 365 days of their last dose (on-treatment, Table 19), and using the adjusted CPH model in the ITT set, were consistent with the main analysis. The PP analyses in both unadjusted and adjusted CPH models showed similar hazard ratios, but the hazard ratios had wider CIs that crossed 1.4, likely due to the smaller number of events contributing to the analyses.

Alternative definitions of MACE were evaluated as exploratory end points in the LIGHT study. Results for time to first occurrence of four-point expanded MACE (original MACE

definition plus non-fatal unstable angina requiring hospitalization) and five-point expanded MACE (four-point MACE plus coronary revascularization procedure) were similar to those for the primary end point (Table 19). The percentages of patients with each type of non-fatal cardiovascular event were also reported in the LIGHT study and there were no notable differences between treatment groups in occurrence of non-fatal MI, non-fatal stroke, non-fatal unstable angina requiring hospitalization, or coronary revascularization procedure (Table 20).

Cardiovascular events were not assessed in the pivotal trials.

Table 19: Key Efficacy Outcomes (LIGHT Study)

	ITT set	
	PL N = 4,450	**NB N = 4,455**
Primary end point: Time to first occurrence of MACE		
Patients with MACE (first occurrence), n (%)	124 (2.8)	119 (2.7)
CV death	37 (0.8)	25 (0.6)
Non-fatal MI	66 (1.5)	67 (1.5)
Non-fatal stroke	21 (0.5)	27 (0.6)
Unadjusted hazard ratio, NB vs. PL (99.7% CI[a])	0.95 (0.65 to 1.38)	
P value for noninferiority (hazard ratio ≥ 1.4 vs. 1-sided alternative)	**0.0013**	
P value for superiority (hazard ratio ≥ 1 vs. 2-sided alternative)	0.6953	
Time to first occurrence of MACE while on treatment (or within 365 days of last dose)		
Patients with MACE (first occurrence), n (%)	87 (2.0)	70 (1.6)
CV death	27 (0.6)	14 (0.3)
Non-fatal MI	47 (1.1)	42 (0.9)
Non-fatal stroke	13 (0.3)	14 (0.3)
Unadjusted hazard ratio, NB vs. PL (99.7% CI[a])	0.76 (0.47 to 1.22)	
P value for noninferiority (hazard ratio ≥ 1.4 vs. 1-sided alternative)	< 0.0001	
P value for superiority (hazard ratio ≥ 1 vs. 2-sided alternative)	0.0879	
Exploratory end points		
Time to first occurrence of 4-point expanded MACE		
Patients with expanded MACE (first occurrence), n (%)	171 (3.8)	164 (3.7)
CV death	36 (0.8)	24 (0.5)
Non-fatal MI	64 (1.4)	65 (1.5)
Non-fatal stroke	21 (0.5)	26 (0.6)
Non-fatal unstable angina requiring hospitalization	50 (1.1)	49 (1.1)
Unadjusted hazard ratio, NB vs. PL (99.7% CI)[a]	0.96 (0.69 to 1.31)	
P value for noninferiority (hazard ratio ≥ 1.4 vs. 1-sided alternative)	0.0002	
P value for superiority (hazard ratio ≥ 1 vs. 2-sided alternative)	0.6503	
Time to first occurrence of 5-point expanded MACE		
Patients with expanded MACE (first occurrence), n (%)	244 (5.5)	226 (5.1)
CV death	34 (0.8)	24 (0.5)
Non-fatal MI	63 (1.4)	61 (1.4)
Non-fatal stroke	19 (0.4)	26 (0.6)

	ITT set	
Non-fatal unstable angina requiring hospitalization	50 (1.1)	48 (1.1)
Coronary revascularization procedure	78 (1.8)	67 (1.5)
Unadjusted hazard ratio, NB vs. PL (99.7% CI)[a]	0.92 (0.70 to 1.20)	
P value for noninferiority (hazard ratio ≥ 1.4 vs. 1-sided alternative)	< 0.0001	
P value for superiority (hazard ratio ≥ 1 vs. 2-sided alternative)	0.3616	

CI = confidence interval; CV = cardiovascular; ITT = intention to treat; MACE = major adverse cardiovascular event; MI = myocardial infarction; NB = naltrexone and bupropion; PL = placebo; vs. = versus.

Note: P values other than for the primary end point are provided for descriptive purposes only.

[a] Using the same alpha level as for the 50% interim analysis.

Source: Clinical Study Report for the LIGHT study.[27]

Table 20: Individual Non-Fatal Cardiovascular Events (LIGHT Study)

	ITT set	
	PL N = 4,450	**NB N = 4,455**
Non-fatal CV events		
Patients with non-fatal MI, n (%)	66 (1.5)	68 (1.5)
Patients with non-fatal stroke, n (%)	21 (0.5)	28 (0.6)
Patients with non-fatal unstable angina requiring hospitalization, n (%)	50 (1.1)	51 (1.1)
Patients with coronary revascularization procedure, n (%)	170 (3.8)	152 (3.4)

CV = cardiovascular; ITT = intention to treat; MI = myocardial infarction; NB = naltrexone and bupropion; PL = placebo.

Note: All events were included, regardless of whether they were the first cardiovascular event to occur.

Source: Clinical Study Report for the LIGHT study.[27]

All-Cause Mortality

Time to death from any cause was an exploratory end point in the LIGHT study. The unadjusted hazard ratio was 0.91 (99.7% CI, 0.55 to 1.50) for NB versus placebo (Table 21).

See the Harms section for information on all-cause mortality in the pivotal trials.

Cardiovascular Mortality

Time to cardiovascular death was an exploratory end point in the LIGHT study. The unadjusted hazard ratio was 0.61 (99.7% CI, 0.30 to 1.27) for NB versus placebo (Table 21).

See Harms section for information on mortality in the pivotal trials.

Table 21: Mortality (LIGHT Study)

	ITT set	
	PL N = 4,450	**NB N = 4,455**
All-cause mortality		
Deaths, n (%)	71 (1.6)	65 (1.5)
Unadjusted hazard ratio, NB vs. PL (99.7% CI[a])	0.91 (0.55 to 1.50)	
P value for noninferiority (hazard ratio ≥ 1.4 vs. 1-sided alternative)	0.0057	
P value for superiority (hazard ratio ≥ 1 vs. 2-sided alternative)	0.5678	
CV mortality		
CV deaths, n (%)	42 (0.9)	26 (0.6)
Unadjusted hazard ratio, NB vs. PL (99.7% CI[a])	0.61 (0.30 to 1.27)	
P value for noninferiority (hazard ratio ≥ 1.4 vs. 1-sided alternative)	0.0005	
P value for superiority (hazard ratio ≥ 1 vs. 2-sided alternative)	0.0503	

CI = confidence interval; CV = cardiovascular; ITT = intention to treat; NB = naltrexone and bupropion; PL = placebo; vs. = versus.

Note: P values are provided for descriptive purposes only as all end points were exploratory.

[a] Using the same alpha level as the 50% interim analysis.

Source: Clinical Study Report for the LIGHT study.[27]

Other Efficacy Outcomes

Health-Related Quality of Life

Assessment of HRQoL was conducted in the pivotal trials but not in the LIGHT study.

IWQoL-Lite Total Score

The IWQoL-Lite instrument was used to assess HRQoL in the pivotal trials (Table 22). The IWQoL-Lite total score was in the statistical testing hierarchy of secondary end points in the pivotal trials. All treatment groups had an improvement in the IWQoL-Lite total score from baseline to week 56 (week 28 in the COR-II study), expressed as an improvement or increase in the transformed score (COR-I, COR-II, and COR-DM studies; possible range of 0 to 100) or as an improvement or decrease in the raw score (COR-BMOD study; possible range of 31 to 155). The improvement in total score was statistically significantly greater in the NB group than in the placebo group in COR-I (LSM difference of 4.14; 95% CI, 2.73 to 5.56), COR-II (LSM difference of 3.77; 95% CI, 2.46 to 5.09), and COR-BMOD (LSM difference in raw score of –3.89; 95% CI, –6.25 to –1.52). Statistical testing halted before the IWQoL-Lite total score end point was reached in the hierarchy for the COR-DM study (LSM difference of 1.37; 95% CI, –0.77 to 3.51). Although patients were encouraged to return for assessments originally planned for week 56 at an early termination visit if they discontinued treatment, data were missing for this outcome, most notably in the COR-II study (30% of the full analysis set was missing in the placebo group and 24% in the NB group). The LOCF method could only be used for patients with an available post-baseline assessment.

SF-36 MCS and PCS

The SF-36 questionnaire was used to assess HRQoL in the COR-II study (Table 22). Substantial amounts of data were missing for these exploratory end points. The mean SF-36 MCS score decreased in both groups from baseline to week 28 and the LSM

difference in change for NB versus placebo was 0.64 (95% CI, –0.05 to 1.33). The mean SF-36 PCS score increased in both groups and the LSM difference in change for NB versus placebo was 1.04 (95% CI, 0.35 to 1.73) in favour of NB.

Table 22: Health-Related Quality of Life (Pivotal Trials)

	COR-I full analysis set		COR-II full analysis set		COR-BMOD full analysis set		COR-DM full analysis set	
	PL N = 511	**NB N = 471**	**PL N = 456**	**NB N = 825**	**PL N = 193**	**NB N = 482**	**PL N = 159**	**NB N = 265**
Mean IWQoL-Lite total score[a]	N = 468	N = 417	N = 317	N = 628	N = 178	N = 448	N = 153	N = 241
Baseline (SD)	71.8 (17.2)	70.3 (16.5)	72.9 (15.7)	72.0 (17.4)	63.5 (19.4)	65.8 (19.1)	73.5 (16.9)	73.2 (17.2)
Week 28 (SD)	NA	NA	79.0 (14.6)	82.2 (14.3)	NA	NA	NA	NA
Week 56 (SD)	80.1 (15.5)	83.3 (14.7)	NA	NA	51.4 (18.5)	48.8 (17.4)	81.4 (15.4)	82.5 (15.9)
LSMD in change, NB vs. PL (95% CI)	4.14 (2.73 to 5.56) **P < 0.001**		1.77 (2.46 to 5.09) **P < 0.001**		–3.89 (–6.25 to –1.52) **P = 0.001**		1.37 (–0.77 to 3.51)	
Mean SF-36 MCS score			N = 319	N = 628				
Baseline (SD)	NR	NR	49.5 (5.6)	49.0 (5.8)	NR	NR	NR	NR
Week 28 (SD)	NR	NR	48.4 (6.2)	48.8 (5.4)	NR	NR	NR	NR
LSMD in change, NB vs. PL (95% CI)	NR		0.64 (–0.05 to 1.33) P = 0.070[b]		NR		NR	
Mean SF-36 PCS score			N = 319	N = 626				
Baseline (SD)	NR	NR	48.7 (7.6)	48.8 (7.7)	NR	NR	NR	NR
Week 28 (SD)	NR	NR	50.3 (6.8)	51.5 (6.2)	NR	NR	NR	NR
LSMD in change, NB vs. PL (95% CI)	NR		1.04 (0.35 to 1.73) P = 0.003[b]		NR		NR	

CI = confidence interval; IWQoL-Lite = Impact of Weight on Quality of Life – Lite; LSMD = least squares mean difference; MCS = mental component summary; NA = not applicable; NB = naltrexone and bupropion; PCS = physical component summary; PL = placebo; SD = standard deviation; SF-36 = Short-Form (36) Health Survey; vs. = versus.

Note: Boldface P values are those for which type I error was controlled using a sequential hierarchical closed testing procedure for the secondary end points. P values are not provided for end points that could not be tested due to failure at a higher point in the hierarchy. The full analysis set included patients who were randomized, had a baseline weight measurement, and had at least one post-baseline weight measurement while on study drug. Analysis of covariance models were used and missing data were imputed using the last observation carried forward approach. For the COR-I, COR-II, and COR-BMOD studies, the model adjusted for study centre and baseline value. For the COR-DM study, the model adjusted for glycated hemoglobin category (≤ or > 8%), sulfonylurea use (with or without), and baseline value.

[a] IWQoL total scores were reported as raw scores in the COR-BMOD study (lower scores indicate better quality of life; range is from 31 to 155) and transformed scores in the other pivotal trials (higher scores indicate better quality of life; range is from 0 to 100).

[b] P value is provided for descriptive purposes as this was an exploratory outcome.

Source: Clinical Study Reports for the COR-I, COR-II, COR-BMOD, and COR-DM studies.[17-20]

Severity of Depression

Severity of depression was assessed in the pivotal trials and not in the LIGHT study.

IDS-SR Total Score

Changes in IDS-SR total score from baseline to week 56 (week 28 in the COR-II study) were similar between treatment groups in the pivotal studies (Table 23). The LSM difference in change was 0.46 (95% CI, −0.09 to 1.00) in the COR-I study, 0.06 (95% CI, −0.49 to 0.60) in the COR-II study, 0.09 (95% CI, −0.70 to 0.87) in the COR-BMOD study, and 1.62 (95% CI, 0.59 to 2.65) in the COR-DM study. Because the IDS-SR was assessed at every study visit, post-baseline values for LOCF imputation were available for almost all patients. While the IDS-SR total score was part of the statistical testing hierarchy, statistical testing halted at an end point further up the hierarchy for all four pivotal trials.

Table 23: Severity of Depression (Pivotal Trials)

	COR-I Full analysis set		COR-II Full analysis set		COR-BMOD Full analysis set		COR-DM Full analysis set	
	PL N = 511	**NB N = 471**	**PL N = 456**	**NB N = 825**	**PL N = 193**	**NB N = 482**	**PL N = 159**	**NB N = 265**
Mean IDS-SR total score	N = 511	N = 470	N = 455	N = 825	N = 193	N = 482	N = 159	N = 265
Baseline (SD)	6.21 (5.02)	6.72 (5.45)	6.89 (5.32)	7.15 (5.97)	6.09 (5.32)	5.78 (4.77)	7.77 (5.73)	8.16 (5.86)
Week 28 (SD)	NA	NA	6.78 (6.39)	6.94 (5.25)	NA	NA	NA	NA
Week 56 (SD)	5.58 (4.88)	6.36 (5.13)	NA	NA	6.03 (6.03)	5.97 (5.00)	6.36 (5.52)	8.26 (6.58)
LSMD in change, NB vs. PL (95% CI)	0.46 (−0.09 to 1.00)		0.06 (−0.49 to 0.60)		0.09 (−0.70 to 0.87)		1.62 (0.59 to 2.65)	

CI = confidence interval; IDS-SR = Inventory of Depressive Symptomology – Subject-Rated; LSMD = least squares mean difference; NA = not applicable; NB = naltrexone and bupropion; PL = placebo; SD = standard deviation; vs. = versus.

Note: P values are not provided as the end points could not be tested due to failure at a higher point in the sequential testing hierarchy. The full analysis set included patients who were randomized, had a baseline weight measurement, and had at least one post-baseline weight measurement while on study drug. Analysis of covariance models were used and missing data were imputed using the last observation carried forward approach. For the COR-I, COR-II, and COR-BMOD studies, the model adjusted for study centre and baseline value. For the COR-DM study, the model adjusted for the glycated hemoglobin category (≤ or > 8%), sulfonylurea use (with or without), and baseline value.

Source: Clinical Study Reports for the COR-I, COR-II, COR-BMOD, and COR-DM studies.[17-20]

Food Craving

Food craving was assessed in the pivotal trials and not in the LIGHT study.

COE Questionnaire Item 19

The score for item 19 (“Generally, how difficult has it been to control your eating?”; 0 = Not at all difficult; 100 = Extremely difficult) in the 21-item COE questionnaire was in the statistical testing hierarchy of secondary end points in the pivotal trials. Results for this end point are provided in Table 24. The score decreased from baseline to week 56 (week 28 in the COR-II study) in all treatment groups and the LSM difference in change for NB versus placebo was −5.84 (95% CI, −8.71 to −2.98) in the COR-I study, −7.23 (95% CI, −9.93 to −4.54) in the COR-II study, −5.29 (95% CI, −9.16 to –1.42) in the COR-BMOD study, and −4.98 (95% Ci, −9.22 to −0.74) in the COR-DM study. The difference was statistically

significant in the COR-I study while statistical testing halted at an end point further up the hierarchy in the other pivotal trials.

FCI Sweets and Carbohydrates Subscale Scores

The FCI sweets and carbohydrates subscale scores were in the statistical testing hierarchy of secondary end points in the pivotal trials (Table 24). Changes in the subscale scores from baseline to week 56 (week 28 in the COR-II study) were similar between treatment groups in each trial. For change in the sweets subscale score (which can range from 8 to 40), the LSM difference for NB versus placebo was 0.15 (95% CI, –0.40 to 0.69) in the COR-I study, –0.02 (95% CI, –0.56 to 0.52) in the COR-II study, –0.11 (95% CI, –0.85 to 0.63) in the COR-BMOD study, and 0.43 (95% CI, –0.42 to 1.27) in the COR-DM study. For change in the carbohydrates subscale score (which can range from 9 to 45), the LSM difference for NB versus placebo was –0.27 (95% CI, –0.80 to 0.27) in the COR-I study, –0.48 (95% CI, –0.98 to 0.02) in the COR-II study, –0.09 (95% CI, –0.78 to 0.60) in the COR-BMOD study, and 0.04 (95% CI, –0.76 to 0.85) in the COR-DM study. Statistical testing halted at an end point further up the hierarchy in all the pivotal trials.

Table 24: Food Craving (Pivotal Trials)

	COR-I full analysis set		COR-II full analysis set		COR-BMOD full analysis set		COR-DM full analysis set	
	PL N = 511	**NB N = 471**	**PL N = 456**	**NB N = 825**	**PL N = 193**	**NB N = 482**	**PL N = 159**	**NB N = 265**
Mean COE Item-19 score	N = 453	N = 409	N = 409	N = 731	N = 178	N = 436	N = 146	N = 225
Baseline (SD)	57.6 (25.5)	58.4 (25.3)	62.0 (23.5)	61.9 (24.1)	58.7 (23.1)	60.2 (23.2)	55.6 (23.5)	58.0 (22.4)
Week 28 (SD)	NA	NA	51.1 (24.3)	43.9 (24.0)	NA	NA	NA	NA
Week 56 (SD)	50.1 (23.0)	44.4 (23.6)	NA	NA	50.7 (23.6)	46.0 (23.4)	49.5 (21.7)	45.5 (22.5)
LSMD in change, NB vs. PL (95% CI)	–5.84 (–8.71 to –2.98) **P < 0.001**[a]		–7.23 (–9.92 to –4.54)		–5.29 (–9.16 to –1.42)		–4.98 (–9.22 to –0.74)	
Mean FCI sweets subscale score	N = 470	N = 418	N = 418	N = 753	N = 180	N = 448	N = 155	N = 241
Baseline (SD)	20.4 (6.0)	20.3 (6.3)	21.1 (6.0)	20.8 (6.2)	21.0 (6.4)	20.9 (6.1)	20.1 (5.7)	20.2 (5.8)
Week 28 (SD)	NA	NA	18.0 (5.4)	17.7 (5.8)	NA	NA	NA	NA
Week 56 (SD)	17.8 (5.3)	17.8 (5.2)	NA	NA	18.4 (5.6)	18.3 (5.4)	17.8 (5.6)	18.3 (5.6)
LSMD in change, NB vs. PL (95% CI)	0.15 (–0.40 to 0.69)		–0.02 (–0.56 to 0.52)		–0.11 (–0.85 to 0.63)		0.43 (–0.42 to 1.27)	
Mean FCI carbohydrates subscale score	N = 469	N = 418	N = 418	N = 754	N = 180	N = 448	N = 155	N = 241
Baseline (SD)	19.5 (5.5)	19.1 (5.5)	19.4 (5.9)	19.4 (5.7)	19.2 (6.0)	19.1 (5.7)	19.9 (4.9)	20.0 (5.3)
Week 28 (SD)	NA	NA	17.3 (5.5)	16.8 (5.2)	NA	NA	NA	NA

	COR-I full analysis set		COR-II full analysis set		COR-BMOD full analysis set		COR-DM full analysis set	
Week 56 (SD)	17.6 (5.2)	17.1 (4.9)	NA	NA	17.0 (5.1)	16.8 (5.1)	18.4 (4.9)	18.6 (5.3)
LSMD in change, NB vs. PL (95% CI)	–0.27 (–0 to 0.27)		–0.48 (–0.98 to 0.02)		–0.09 (–0.78 to 0.60)		0.04 (–0.76 to0.85)	

CI = confidence interval; COE = Control of Eating; FCI = Food Craving Inventory; LSMD = least squares mean difference; NA = not applicable; NB = naltrexone and bupropion; PL = placebo; SD = standard deviation.

Note: Except for the COE item-19 score in the COR-1 study (highlighted in boldface), the end points could not be tested due to failure at a higher point in the sequential testing hierarchy. The full analysis set included patients who were randomized, had a baseline weight measurement, and had at least one post-baseline weight measurement while on study drug. Analysis of covariance models were used and missing data were imputed using the last observation carried forward approach. For the COR-I, COR-II, and COR-BMOD studies, the model adjusted for study centre and baseline value. For the COR-DM study, the model adjusted for the glycated hemoglobin category (≤ or > 8%), sulfonylurea use (with or without), and baseline value.

[a] Type I error was controlled using a sequential hierarchical closed testing procedure for the secondary end points.

Source: Clinical Study Reports for the COR-I, COR-II, COR-BMOD, and COR-DM studies.[17-20]

Dose Reduction or Complete Withdrawal of Concomitant Medications for Weight-Related Comorbidities

Dose reduction or complete withdrawal of concomitant medications for weight-related comorbidities was assessed in the COR-DM study only.

Dose Reduction in Oral Hypoglycemic Medication and Need for Rescue Antidiabetic Medication

Changes in antidiabetic medication dose were recorded in the COR-DM study (Table 25). The percentage of patients with a dose reduction in oral hypoglycemic medication was 1.3% versus 1.9% in the placebo versus NB groups, with an odds ratio of 1.43 (95% CI, 0.27 to 7.57) for NB versus placebo. The percentage of patients requiring rescue antidiabetic medication (dose increase in antidiabetic medication or initiation of a new antidiabetic medication) was 35.2% versus 22.3% in the placebo versus NB groups, with an odds ratio of 0.55 (95% CI, 0.35 to 0.86) for NB versus placebo. Although both end points were included in the statistical hierarchy of secondary end points, statistical testing halted at an end point further up the hierarchy.

Table 25: Dose Change in Antidiabetic Medication (COR-DM Study)

	Full analysis set	
	PL N = 159	NB N = 265
Dose reduction in oral hypoglycemic medication		
Patients with dose reduction in oral hypoglycemic medication, n (%)	2 (1.26)	5 (1.89)
Odds ratio, NB vs. PL (95% CI)	1.43 (0.27 to 7.57)	
Need for rescue antidiabetic medication		
Patients with dose increase in or initiation of new antidiabetic medication, n (%)	56 (35.22)	59 (22.26)
Odds ratio, NB vs. PL (95% CI)	0.55 (0.35 to 0.86)	

CI = confidence interval; NB = naltrexone and bupropion; PL = placebo; vs. = versus.

Note: P values are not provided as the end points could not be tested due to failure at a higher point in the sequential testing hierarchy.

Source: Clinical Study Report for the COR-DM study.[17]

Harms

Only those harms identified in the review protocol (Table 3) are reported.

Adverse Events

In the pivotal trials, AEs were more common in the NB group than in the placebo group (Table 26). The percentage of patients with at least one AE in the NB versus placebo group was 83.1% versus 68.5% in the COR-I study, 85.9% versus 75.2% in the COR-II study, 93.7% versus 88.0% in the COR-BMOD study, and 90.4% versus 85.2% in the COR-DM study. The AEs that consistently occurred more commonly in the NB group versus the placebo group were constipation (15.7% to 24.1% versus 5.6% to 14.0%), dry mouth (6.3% to 9.1% versus 1.0% to 3.0%), nausea (29.2% to 42.3% versus 5.3% to 10.5%), vomiting (8.5% to 18.3% versus 2.0% to 6.5%), dizziness (6.9% to 14.6% versus 2.6% to 5.3%), headache (13.8% to 23.8% versus 8.7% to 17.5%), and insomnia (7.5% to 11.1% versus 5.1% to 6.7%). Gastrointestinal disorders and insomnia were identified as notable harms in the CADTH review protocol.

In the LIGHT study, AEs were not reported unless they led to treatment discontinuation or were serious.

Serious Adverse Events

In the pivotal trials, SAEs were reported in 1.6% versus 1.4% of the NB versus placebo groups in the COR-I study, 2.1% versus 1.4% in the COR-II study, 3.8% versus 0.5% in the COR-BMOD study, and 3.9% versus 4.7% in the COR-DM study (Table 26). SAEs reported in more than 1% of a treatment group were angina pectoris and atrial fibrillation, each occurring in two patients in the COR-DM study placebo group.

In the LIGHT study, 9.7% of patients in the placebo group and 10.4% in the NB group reported an SAE (Table 27). No SAEs were reported in at least 1% of either treatment group.

Withdrawals Due to Adverse Events

In the pivotal trials, WDAEs were more common in the NB group than in the placebo group (Table 26). The percentage of WDAEs in the NB versus placebo group was 19.5% versus 9.8% in the COR-I study, 24.3% versus 13.8% in the COR-II study, 25.7% versus 12.5% in the COR-BMOD study, and 29.4% versus 15.4% in the COR-DM study. Reasons for WDAE reported by at least 1% in at least one treatment group were nausea, dizziness, headache, anxiety, disturbance in attention, vomiting, and urticaria. Withdrawal due to nausea was more common in the NB group than in the placebo group for all the pivotal trials (4.6% to 15.0% versus 0% to 1.8%).

In the LIGHT study, the percentage of patients with an AE leading to treatment discontinuation was 9.0% in the placebo group and 29.0% in the NB group (Table 27). AEs leading to treatment discontinuation in at least 1% of at least one treatment group were nausea (7.8% versus 0.5% for NB versus placebo), constipation (2.9% versus 0.3%), vomiting (2.0% versus < 0.1%), tremor (1.8% versus 0%), dizziness (1.5% versus 0.2%), and headache (1.1% versus 0.3%).

Mortality

One patient in the NB group in the COR-I study died from a myocardial infarction (Table 26). There were no other deaths in the pivotal trials. Deaths in the LIGHT study are reported in the Efficacy section (Table 21).

Table 26: Harms (Pivotal Trials)

	COR-I safety set		COR-II safety set		COR-BMOD safety set		COR-DM safety set	
	Placebo N = 569	**NB N = 573**	**Placebo N = 492**	**NB N = 992**	**Placebo N = 200**	**NB N = 584**	**Placebo N = 169**	**NB N = 333**
Patients with > 0 AEs, n (%)	390 (68.5)	476 (83.1)	370 (75.2)	852 (85.9)	176 (88.0)	547 (93.7)	144 (85.2)	301 (90.4)
Most common AEs[a]								
Gastrointestinal disorders[b]	136 (23.9)	292 (51.0)	131 (26.6)	532 (53.6)	78 (39.0)	380 (65.1)	53 (31.4)	215 (64.6)
Abdominal pain upper	7 (1.2)	10 (1.7)	7 (1.4)	29 (2.9)	3 (1.5)	32 (5.5)	3 (1.8)	17 (5.1)
Constipation	32 (5.6)	90 (15.7)	35 (7.1)	189 (19.1)	28 (14.0)	141 (24.1)	12 (7.1)	59 (17.7)
Diarrhea	28 (4.9)	26 (4.5)	18 (3.7)	55 (5.5)	15 (7.5)	43 (7.4)	16 (9.5)	52 (15.6)
Dry mouth	11 (1.9)	43 (7.5)	13 (2.6)	90 (9.1)	6 (3.0)	47 (8.0)	5 (3.0)	21 (6.3)
Nausea	30 (5.3)	171 (29.8)	34 (6.9)	290 (29.2)	21 (10.5)	199 (34.1)	12 (7.1)	141 (42.3)
Vomiting	14 (2.5)	56 (9.8)	10 (2.0)	84 (8.5)	13 (6.5)	64 (11.0)	6 (3.6)	61 (18.3)
Nasopharyngitis	31 (5.4)	29 (5.1)	40 (8.1)	82 (8.3)	15 (7.5)	36 (6.2)	23 (13.6)	28 (8.4)
Sinusitis	34 (6.0)	30 (5.2)	35 (7.1)	51 (5.1)	6 (3.0)	16 (2.7)	14 (8.3)	16 (4.8)
Upper respiratory tract infection	64 (11.2)	57 (9.9)	55 (11.2)	86 (8.7)	18 (9.0)	38 (6.5)	16 (9.5)	26 (7.8)
Nervous system disorders								
Dizziness	15 (2.6)	54 (9.4)	18 (3.7)	68 (6.9)	9 (4.5)	85 (14.6)	9 (5.3)	39 (11.7)
Headache	53 (9.3)	79 (13.8)	43 (8.7)	174 (17.5)	35 (17.5)	139 (23.8)	15 (8.9)	46 (13.8)
Tremor	1 (0.2)	12 (2.1)	3 (0.6)	35 (3.5)	2 (1.0)	34 (5.8)	4 (2.4)	22 (6.6)
Psychiatric disorders[b]	62 (10.9)	85 (14.8)	75 (15.2)	205 (20.7)	45 (22.5)	145 (24.8)	20 (11.8)	75 (22.5)
Anxiety[b]	12 (2.1)	9 (1.6)	21 (4.3)	48 (4.8)	7 (3.5)	30 (5.1)	2 (1.2)	18 (5.4)
Insomnia[b]	29 (5.1)	43 (7.5)	33 (6.7)	97 (9.8)	12 (6.0)	51 (8.7)	9 (5.3)	37 (11.1)
Vascular disorders								
Hot flush	7 (1.2)	30 (5.2)	6 (1.2)	42 (4.2)	1 (0.5)	28 (4.8)	4 (2.4)	7 (2.1)
Hypertension	14 (2.5)	17 (3.0)	8 (1.6)	19 (1.9)	4 (2.0)	14 (2.4)	7 (4.1)	33 (9.9)
Musculoskeletal and connective tissue disorders								
Arthralgia	22 (3.9)	13 (2.3)	28 (5.7)	38 (3.8)	8 (4.0)	20 (3.4)	6 (3.6)	13 (3.9)
Back pain	24 (4.2)	23 (4.0)	21 (4.3)	39 (3.9)	12 (6.0)	28 (4.8)	9 (5.3)	9 (2.7)
General disorders and administration site conditions								

	COR-I safety set		COR-II safety set		COR-BMOD safety set		COR-DM safety set	
Edema peripheral	6 (1.1)	6 (1.0)	3 (0.6)	3 (0.3)	1 (0.5)	3 (0.5)	10 (5.9)	2 (0.6)
Fatigue	11 (1.0)	20 (3.5)	18 (3.7)	35 (3.5)	13 (6.5)	31 (5.3)	7 (4.1)	16 (4.8)
Respiratory, thoracic and mediastinal disorders								
Pharyngolaryngeal pain	14 (2.5)	13 (2.3)	11 (2.2)	25 (2.5)	17 (8.5)	29 (5.0)	5 (3.0)	6 (1.8)
Cough	16 (2.8)	13 (2.3)	9 (1.8)	15 (1.5)	15 (7.5)	28 (4.8)	7 (4.1)	14 (4.2)
Nasal congestion	7 (1.2)	5 (0.9)	8 (1.6)	12 (1.2)	10 (5.0)	20 (3.4)	1 (0.6)	3 (0.9)
Sinus congestion	24 (4.2)	18 (3.1)	14 (2.8)	25 (2.5)	13 (6.5)	18 (3.1)	8 (4.7)	9 (2.7)
Metabolism and nutrition disorders								
Hypoglycemia[b]	0	0	0	2 (0.2)	1 (0.5)	0	12 (7.1)	25 (7.5)
Worsening of diabetes mellitus	0	0	1 (0.2)	0	2 (1.0)	0	15 (8.9)	15 (4.5)
Ear and labyrinth disorders								
Tinnitus	6 (1.1)	15 (2.6)	1 (0.2)	29 (2.9)	1 (0.5)	31 (5.3)	1 (0.6)	8 (2.4)
Other notable AEs[b]								
Agitation	1 (0.2)	0	0	3 (0.3)	0	2 (0.3)	0	0
Aggression	0	0	0	0	0	1 (0.2)	0	0
Akathisia	0	0	1 (0.2)	0	0	0	0	0
Anger	0	0	2 (0.4)	1 (0.1)	2 (1.0)	1 (0.2)	0	0
Angle closure glaucoma	0	0	0	0	0	1 (0.2)	0	0
Blood pressure diastolic increased	1 (0.2)	0	0	1 (0.1)	1 (0.5)	0	0	0
Blood pressure increased	5 (0.9)	12 (2.1)	7 (1.4)	17 (1.7)	6 (3.0)	26 (4.5)	4 (2.4)	6 (1.8)
Blood pressure systolic increased	1 (0.2)	0	0	1 (0.1)	0	0	0	0
Convulsion	0	0	0	1 (0.1)	0	0	0	0
Depression	6 (1.1)	3 (0.5)	8 (1.6)	13 (1.3)	5 (2.5)	2 (0.3)	4 (2.4)	5 (1.5)
Depressive symptom	0	0	2 (0.4)	1 (0.1)	0	0	0	0
Dissociation	0	1 (0.2)	0	3 (0.3)	0	6 (1.0)	0	0
Drug hypersensitivity	0	0	3 (0.6)	2 (0.2)	0	0	1 (0.6)	0
Elevated mood	0	0	0	0	0	2 (0.3)	0	0
Euphoric mood	0	2 (0.3)	0	1 (0.1)	0	1 (0.2)	0	0
Generalized anxiety disorder	0	0	0	0	1 (0.5)	0	0	0
Glaucoma	0	0	1 (0.2)	0	0	0	0	0
Grand mal convulsion	0	0	0	0	0	0	0	1 (0.3)
Heart rate increased	9 (1.6)	6 (1.0)	6 (1.2)	15 (1.5)	2 (1.0)	20 (3.4)	0	0
Hypersensitivity	2 (0.4)	1 (0.2)	0	2 (0.2)	0	2 (0.3)	1 (0.6)	1 (0.3)

	COR-I safety set		COR-II safety set		COR-BMOD safety set		COR-DM safety set	
Hypertension	14 (2.5)	17 (3.0)	8 (1.6)	19 (1.9)	4 (2.0)	14 (2.4)	7 (4.1)	33 (9.9)
Initial insomnia	0	1 (0.2)	1 (0.2)	3 (0.3)	1 (0.5)	2 (0.3)	2 (1.2)	0
Intraocular pressure increased	1 (0.2)	0	1 (0.2)	0	0	0	0	0
Major depression	0	0	0	0	0	0	0	0
Middle insomnia	1 (0.2)	3 (0.5)	0	7 (0.7)	2 (1.0)	6 (1.0)	0	0
Myocardial infarction	0	1 (0.2)	0	1 (0.1)	0	0	0	1 (0.3)
Restlessness	2 (0.4)	0	1 (0.2)	1 (0.1)	0	3 (0.5)	0	0
Suicidal ideation	0	0	0	1 (0.1)	2 (1.0)	0	0	0
Patients with > 0 SAEs, n (%)	8 (1.4)	9 (1.6)	7 (1.4)	21 (2.1)	1 (0.5)	22 (3.8)	8 (4.7)	13 (3.9)
Most common SAEs[c]								
Angina pectoris	0	0	0	0	0	0	2 (1.2)	0
Atrial fibrillation	0	0	0	0	0	0	2 (1.2)	0
Notable SAEs[b]								
Anxiety	0	0	0	1 (0.1)	0	0	0	0
Anaphylactic reaction	0	0	0	0	0	0	1 (0.6)	0
Convulsion	0	0	0	1 (0.1)	0	0	0	0
Grand mal convulsion	0	0	0	0	0	0	0	1 (0.3)
Acute myocardial infarction	0	1	0	0	0	0	0	0
Myocardial infarction	0	1 (0.2)	0	1 (0.1)	0	0	0	1 (0.3)
WDAEs, n (%)	56 (9.8)	112 (19.5)	68 (13.8)	241 (24.3)	25 (12.5)	150 (25.7)	26 (15.4)	98 (29.4)
Most common reasons for WDAE[c]								
Nausea	2 (0.4)	36 (6.3)	1 (0.2)	60 (6.0)	0	27 (4.6)	3 (1.8)	50 (15.0)
Dizziness	3 (0.5)	7 (1.2)	1 (0.2)	10 (1.0)	0	4 (0.7)	1 (0.6)	2 (0.6)
Headache	4 (0.7)	5 (0.9)	4 (0.8)	26 (2.6)	1 (0.5)	5 (0.9)	0	6 (1.8)
Anxiety	2 (0.4)	2 (0.3)	5 (1.0)	6 (0.6)	3 (1.5)	7 (1.2)	0	3 (0.9)
Disturbance in attention	0	1 (0.2)	1 (0.2)	3 (0.3)	0	6 (1.0)	0	1 (0.3)
Vomiting	1 (0.2)	5 (0.9)	0	8 (0.8)	0	4 (0.7)	0	10 (3.0)
Urticaria	0	0	1 (0.2)	4 (0.4)	1 (0.5)	10 (1.7)	1 (0.6)	0
Deaths, n (%)	0	1[d]	0	0	0	0	0	0

AE = adverse event; NB = naltrexone and bupropion; SAE = serious adverse event; WDAE = withdrawal due to adverse event.

Note: AEs and SAEs were reported if they occurred up to seven days (30 days in the COR-BMOD study) following study drug discontinuation.

[a] Frequency 5% or greater in at least one treatment group.

[b] Identified as a notable harm in the review protocol.

[c] Frequency 1% or greater in at least one treatment group.

[d] Cause of death was severe myocardial infarction, which was considered unlikely to be related to the study drug.

Source: Clinical Study Reports for the COR-I, COR-II, COR-BMOD, and COR-DM studies.[17-20]

Table 27: Harms (LIGHT Study)

	ITT set	
	PL N = 4,450	**NB N = 4,455**
Patients with > 0 AEs leading to treatment discontinuation, n (%)	400 (9.0)	1,292 (29.0)
Most common reasons[a]		
Gastrointestinal disorders[b]	86 (1.9)	660 (14.8)
Nausea	21 (0.5)	346 (7.8)
Constipation	15 (0.3)	129 (2.9)
Vomiting	1 (< 0.1)	89 (2.0)
Nervous system disorders	53 (1.2)	236 (5.3)
Tremor	0	80 (1.8)
Dizziness	8 (0.2)	65 (1.5)
Headache	15 (0.3)	51 (1.1)
Notable AEs leading to treatment discontinuation, n (%)		
Psychiatric disorders (system organ class)	40 (0.9)	142 (3.2)
Agitation	1 (< 0.1)	1 (< 0.1)
Anger	1 (< 0.1)	1 (< 0.1)
Anxiety	8 (0.2)	26 (0.6)
Bipolar disorder	0	1 (< 0.1)
Depression	10 (0.2)	5 (0.1)
Insomnia	16 (0.4)	38 (0.9)
Major depression	0	2 (< 0.1)
Middle insomnia	0	2 (< 0.1)
Restlessness	0	1 (< 0.1)
Suicidal ideation	0	1 (< 0.1)
Acute coronary syndrome	1 (< 0.1)	1 (< 0.1)
Acute myocardial infarction	3 (0.1)	1 (< 0.1)
Angina unstable	2 (< 0.1)	4 (0.1)
Blood pressure increased	14 (0.3)	21 (0.5)
Blood pressure systolic increased	0	1 (< 0.1)
Cardiac arrest	0	1 (< 0.1)
Drug hypersensitivity	0	1 (< 0.1)
Heart rate increased	1 (< 0.1)	2 (< 0.1)
Hypersensitivity	1 (< 0.1)	0
Hypertension	11 (0.2)	25 (0.6)
Hypoglycemia	2 (< 0.1)	3 (0.1)
Myocardial infarction	5 (0.1)	20 (0.4)
Patients with > 0 SAEs, n (%)	386 (8.7)	463 (10.4)
Notable SAEs		
Acute coronary syndrome	3 (0.1)	4 (0.1)
Acute myocardial infarction	7 (0.2)	11 (0.2)
Anaphylactic reaction	1 (< 0.1)	0

	ITT set	
Angina unstable	15 (0.3)	22 (0.5)
Bipolar disorder	0	1 (< 0.1)
Blood pressure increased	0	2 (< 0.1)
Cardiac arrest	1 (< 0.1)	2 (< 0.1)
Convulsion	0	2 (< 0.1)
Death	2 (< 0.1)	4 (0.1)
Depression	1 (< 0.1)	0
Gastrointestinal disorders (system organ class)	28 (0.6)	47 (1.1)
Hallucination	0	1 (< 0.1)
Hypersensitivity	0	1 (< 0.1)
Hypoglycemia	1 (< 0.1)	5 (0.1)
Ischemic stroke	0	2 (< 0.1)
Major depression	0	3 (0.1)
Myocardial infarction	13 (0.3)	14 (0.3)
Psychiatric disorders (system organ class)	2 (< 0.1)	9 (0.2)
Sudden cardiac death	1 (< 0.1)	0
Suicidal ideation	1 (< 0.1)	0

AE = adverse event; ITT = intention to treat; SAE = serious adverse event.

Note: AEs leading to treatment discontinuation and SAEs were reported if they occurred up to 30 days following treatment discontinuation or up to study discontinuation (the earlier of the two).

[a] Frequency 1% or greater in at least one treatment group.

[b] Identified as a notable harm in the review protocol.

Source: Clinical Study Report for the LIGHT study.[27]

Notable Harms

Notable AEs

In the pivotal trials, gastrointestinal disorders (23.9% to 39.0% for placebo and 51.0% to 65.1% for NB) and psychiatric disorders (10.9% to 22.5% for placebo and 14.8% to 24.8% for NB) were reported as AEs more commonly in the NB group than in the placebo group (Table 26). Aside from gastrointestinal disorders, the most common notable AEs (expressed as ranges for NB and placebo, respectively) included anxiety (1.6% to 5.4% and 1.2% to 4.3%), increased blood pressure (1.7% to 4.5% and 0.9% to 3.0%), increased heart rate (0% to 3.4% and 0% to 1.6%), and hypertension (1.9% to 9.9% and 1.6% to 4.1%). Other notable AEs reported in 1% or more in at least one treatment group were hypoglycemia (7.5% and 7.1% for NB and placebo in the COR-DM study), anger, depression, initial insomnia, middle insomnia, and suicidal ideation. Notable SAEs that were reported were anxiety, anaphylactic reaction, convulsion, grand mal convulsion, acute myocardial infarction, and myocardial infarction.

In the LIGHT study, gastrointestinal disorders (14.8% and 1.9% for NB and placebo) and psychiatric disorders (3.2% and 0.9%) were reported as AEs leading to treatment discontinuation more commonly in the NB group than in the placebo group (Table 27). The most commonly reported notable AEs leading to treatment discontinuation (expressed as values for NB and placebo, respectively) were anxiety (0.6% and 0.2%), insomnia (0.9% and 0.4%), blood pressure increased (0.5% and 0.3%), hypertension (0.6% and 0.2%), and myocardial infarction (0.4% and 0.1%).The most common SAEs (values for NB and

placebo, respectively) included unstable angina (0.5% and 0.3%), myocardial infarction (0.3% in both groups), and acute myocardial infarction (0.2% in both groups). Gastrointestinal disorder SAEs were reported in 1.1% of the NB group and 0.6% of the placebo group.

Increase in Pulse Rate and Blood Pressure

In the pivotal trials, increases above pre-specified thresholds in pulse rate, systolic blood pressure, and diastolic blood pressure with respect to baseline values recorded for at least two consecutive study visits (or at least one if it was the last assessment) or occurring at least once were reported (Table 28). In the LIGHT study, increases recorded for at least two consecutive study visits were reported (Table 29). Study visits occurred every four weeks in the pivotal trials and every 26 weeks (following visits as weeks 2, 8, 16, and 26) in the LIGHT study.

In the pivotal trials (Table 28), increases in pulse rate of at least five beats per minute (bpm) or 10 bpm for at least two consecutive visits were consistently reported in higher percentages of the NB group than in the placebo group (49.5% to 61.6% in the NB group and 42.9% to 47.2% in the placebo group for five bpm and 23.3% to 30.9% and 16.6% to 23.3% for 10 bpm). Similar trends were observed for increases of at least 10 bpm occurring at least once, while increases of at least 20 bpm occurred in similar percentages in each group (and increases of 50 bpm were not observed). In the LIGHT study, the percentage of patients with at least two consecutive increases of at least 10 bpm was 18.0% in the NB group and 16.9% in the placebo group (Table 29).

Consecutive increases above baseline of at least 10 mm Hg and 15 mm Hg in systolic blood pressure were consistently more common in the NB group in the COR-I, COR-II, and COR-BMOD studies (23.2% to 26.1% in the NB group and 14.5% to 17.9% in the placebo group for 10 mm Hg and 9.8% to 11.8% and 4.7% to 8.2% for 15 mm Hg; see Table 28). Similar trends were observed in all the pivotal trials for any increases of at least 10 mm Hg and 15 mm Hg (and 20 mm Hg in the COR-BMOD study). In the LIGHT study, the percentage of patients with at least two consecutive increases of at least 10 mm Hg was 30.2% in the NB group and 26.0% in the placebo group (Table 29).

Consecutive increases above baseline of at least 10 mm Hg and 15 mm Hg in diastolic blood pressure were consistently more common in the NB group in the pivotal trials (36.5% to 37.9% in the NB group and 23.8% to 32.3% in the placebo group for 10 mm Hg and 12.4% to 14.7% and 7.8% to 11.2% for 15 mm Hg; see Table 28). Similar trends were observed for any increases of at least 10 mm Hg, while any increases of at least 20 mm Hg occurred in similar percentages between the NB and placebo group. In the LIGHT study, the percentage of patients with at least two consecutive increases of at least 10 mm Hg was 18.3% in the NB group and 15.0% in the placebo group (Table 29).

Table 28: Increase in Pulse Rate and Blood Pressure (Pivotal Trials)

	COR-I Safety set		COR-II Safety set		COR-BMOD Safety set		COR-DM Safety set	
	Placebo N = 569	**NB N = 573**	**Placebo N = 492**	**NB N = 992**	**Placebo N = 200**	**NB N = 584**	**Placebo N = 169**	**NB N = 333**
Pulse rate	N = 518	N = 491	N = 464	N = 874	N = 193	N = 482	N = 161	N = 293
Patients with ≥ 2 consecutive values above baseline (≥ 1 if last value), n (%)								
By ≥ 5 bpm	222 (42.9)	243 (49.5)	203 (43.8)	451 (51.6)	83 (43.0)	297 (61.6)	76 (47.2)	146 (50.2)
By ≥ 10 bpm	86 (16.6)	127 (25.9)	89 (19.2)	219 (25.1)	45 (23.3)	149 (30.9)	35 (21.7)	68 (23.2)
Patients with ≥ 1 value above baseline, n (%)								
By ≥ 10 bpm	187 (36.1)	218 (44.4)	176 (37.9)	396 (45.3)	86 (44.6)	272 (56.4)	64 (39.8)	122 (41.6)
By ≥ 20 bpm	39 (7.5)	46 (9.4)	36 (7.8)	98 (11.2)	25 (13.0)	59 (12.2)	15 (9.3)	23 (7.8)
By ≥ 50 bpm	0	0	0	0	0	0	0	0
Systolic BP	N = 518	N = 491	N = 464	N = 874	N = 193	N = 482	N = 161	N = 293
Patients with ≥ 2 consecutive values above baseline (≥ 1 if last value), n (%)								
By ≥ 10 mm Hg	87 (16.8)	126 (25.7)	83 (17.9)	203 (23.2)	28 (14.5)	126 (26.1)	42 (26.1)	85 (29.0)
By ≥ 15 mm Hg	33 (6.4)	49 (10.0)	38 (8.2)	86 (9.8)	9 (4.7)	57 (11.8)	21 (13.0)	38 (13.0)
Patients with ≥ 1 value above baseline, n (%)								
By ≥ 10 mm Hg	174 (33.6)	222 (45.2)	165 (35.6)	349 (39.9)	60 (31.1)	222 (46.1)	80 (49.7)	151 (51.5)
By ≥ 15 mm Hg	82 (15.8)	113 (23.0)	83 (17.9)	178 (20.4)	28 (14.5)	123 (25.5)	45 (28.0)	91 (31.1)
By ≥ 20 mm Hg	NR	NR	NR	NR	13 (6.7)	55 (11.4)	NR	NR
Diastolic BP	N = 518	N = 491	N = 464	N = 874	N = 193	N = 482	N = 161	N = 293
Patients with ≥ 2 consecutive values above baseline (≥ 1 if last value), n (%)								
By ≥ 5 mm Hg	138 (26.6)	183 (37.3)	148 (31.9)	331 (37.9)	46 (23.8)	176 (36.5)	52 (32.3)	109 (37.2)
By ≥ 10 mm Hg	47 (9.1)	64 (13.0)	48 (10.3)	117 (13.4)	15 (7.8)	60 (12.4)	18 (11.2)	43 (14.7)
Patients with ≥ 1 value above baseline, n (%)								
By ≥ 10 mm Hg	89 (17.2)	137 (27.9)	97 (20.9)	231 (26.4)	32 (16.6)	132 (27.4)	43 (26.7)	89 (30.4)
By ≥ 20 mm Hg	15 (2.9)	14 (2.9)	14 (3.0)	22 (2.5)	3 (1.6)	16 (3.3)	2 (1.2)	13 (4.4)

BP = blood pressure; bpm = beats per minute; NB = naltrexone and bupropion; NR = not reported.

Note: Values were those observed while on treatment (up to seven days [one day for the COR-BMOD study] of last confirmed dose of study medication). Denominator was based on the number of patients with at least one post-baseline measurement.

Source: Clinical Study Reports for the COR-I, COR-II, COR-BMOD, and COR-DM studies.[17-20]

Table 29: Increase in Pulse Rate and Blood Pressure (LIGHT Study)

	ITT set	
	PL N = 4,450	**NB N = 4,455**
Pulse Rate		
Patients with ≥ 2 consecutive values ≥ 10 bpm above baseline, n (%)	754 (16.9)	802 (18.0)
Systolic BP		
Patients with ≥ 2 consecutive values ≥ 10 mm Hg above baseline, n (%)	1,161 (26.0)	1,347 (30.2)
Diastolic BP		
Patients with ≥ 2 consecutive values ≥ 10 mm Hg above baseline, n (%)	666 (15.0)	813 (18.3)

BP = blood pressure; bpm = beats per minute; ITT = intention to treat; NB = naltrexone and bupropion; PL = placebo.

Source: Clinical Study Report for the LIGHT study.[27]

Critical Appraisal

Internal Validity: Pivotal Trials

Randomization, Allocation, and Blinding

Appropriate methods for randomization, treatment allocation, and maintenance of blinding to treatment assignment were used in the pivotal trials and in the LIGHT study. A centralized voice or web response system was used to administer a computer-generated randomization schedule and patients, investigators, and study personnel were blinded to treatment assignment using matching placebo tablets. There were no notable imbalances in baseline characteristics between treatment groups in any of the trials. Given the notable imbalance in study discontinuations due to AEs, it is possible that unblinding could have occurred in patients experiencing an AE commonly associated with naltrexone or bupropion use (e.g., nausea). Unblinding also could have occurred due to weight loss, as patients may not have expected to lose weight if they were receiving placebo.

Treatment Discontinuations and Data Imputation

The main limitation common to all the trials was the large proportion of treatment and study discontinuations. Additionally, rates of discontinuation due to AEs and due to lack of efficacy were imbalanced between treatment groups in each trial. Discontinuation due to an AE was more common in the NB groups and discontinuation due to lack of efficacy (including those who did not achieve at least 2% weight loss in the LIGHT study by week 16) was more common in the placebo groups. Although the numbers of patients who discontinued and returned for the final study visit at week 56 were not reported, the numbers of efficacy observations at week 56 for the sensitivity analyses (visit-wise observed cases and repeated measures) indicated that most did not return for this visit. Therefore, data for most patients who discontinued were imputed. The FDA draft guidance[29] and EMA guideline[30] on products for weight management encourage follow-up in all patients for the entire trial, regardless of whether they adhere to study treatment.

The primary analyses in the pivotal trials were in the full analysis set (all randomized patients with a baseline weight measurement and at least one post-baseline weight measurement while on the study drug), using the LOCF method to impute missing data. The FDA draft guidance on weight management products[29] states that analysis should be performed in the mITT population of patients who receive at least one dose of the study drug and have at least one post-baseline measurement (regardless of whether they were

on the study drug for this measurement). The use of the full analysis set rather than all randomized patients or the FDA-defined mITT set required exclusion of any patients who discontinued treatment before the week 4 visit. As detailed in Table 11, the percentage of patients discontinuing study treatment during the first four weeks was significant and imbalanced between treatment groups, ranging from 5.9% to 10.8% in the placebo groups and 18.3% to 22.1% in the NB groups. Because patients were not missing at random, using the full analysis set instead of the set of all randomized patients likely biased the results in favour of NB, as patients who discontinued in the first four weeks were less likely than the rest of the patients to receive treatment benefit. The mITT set of patients who received at least one dose of the study drug is likely an appropriate representation of the population of patients who would receive the drug under review.

Using LOCF to impute missing data may not have been appropriate given the chronic nature of the condition. While the LOCF approach is recommended for analysis in the FDA draft guidance, the FDA also recommends sensitivity analyses using other imputation approaches to assess the effect of study discontinuations on the results.[29] According to the clinical expert consulted for this review, patients who discontinue treatment are generally expected to return to their baseline weight. The clinical expert also noted that there is no evidence for an overall benefit from temporary weight loss. Patients who discontinued early in the study were likely close to baseline weight and would have been appropriately recorded as non-responders for the 5% weight loss outcome using LOCF imputation. However, patients who discontinued treatment after losing at least 5% of their weight would have been recorded as responders under LOCF imputation, although they would have been expected to return to baseline weight following discontinuation. Two methods of imputing missing data were used to address weight changes following discontinuation. In the weight-regain imputation method, weight regain at a rate of 0.3 kg per month (until baseline weight was reached) was assumed, and in the BOCF method, baseline weight was imputed as the end-of-study value. The BOCF method was more conservative than the weight-regain method and assigned no overall benefit in weight loss to patients who discontinued treatment. Consistent with this approach, the EMA guideline for weight management states that patients who discontinue prior to the end of the study should be considered non-responders.[30] In contrast, the weight-regain method assigned a benefit to temporary weight loss, following treatment discontinuation, which is inappropriate for the responder analysis (i.e., percentage of patients who achieved at least 5% weight loss). In terms of measuring mean difference in weight change at week 56, it is unclear which imputation method would have yielded the most accurate estimate, and the true effect size likely lies between the estimates produced using the LOCF and BOCF approaches in the mITT set and randomized patients set, respectively.

Because LOCF imputation in the full analysis set was used for the secondary end points, those analyses are also subject to the same potential biases as the weight-loss end points due to missing data. In addition, the imputation of missing data for individual assessments using the IWQoL-Lite, COE, IDS-SR, and FCI when less than 20% to 25% of item scores were missing is another potential source of bias in these end points; however, the direction of the bias on study results is uncertain.

PP analysis can yield complementary information, typically by estimating treatment effects in patients who adhere to treatment and have no major protocol deviations. However, the PP sets in the pivotal trials did not exclude patients based on protocol deviations and some patients who took prohibited concomitant medications or did not meet study entry criteria

were included in the PP analyses. The risk of bias from the presence of these protocol deviations is unknown.

Multiplicity of Outcomes and Subgroup Analyses

While type I error was controlled in the pivotal studies using a closed testing procedure for the secondary efficacy end points, there were additional exploratory end points for which type I error was not controlled. Interpretation of the results of subgroup analyses (including those for baseline hypertension status, dyslipidemia status, BMI category, and cardiovascular risk category) is limited by the lack of stratification of randomization by subgroup and the lack of sample size considerations based on subgroups (i.e., lack of study power within subgroups). Statistically significant differences between treatment groups were therefore unlikely to be observed.

Outcomes

While there is evidence to support the validity of some of the instruments used in the pivotal trials, MIDs in patients with obesity were not found for any of the patient-reported efficacy outcomes, aside from the IWQoL-Lite questionnaire. Also, the validity of using a single item from the COE questionnaire as an outcome is unclear, information on the validity and reliability of the IDS-SR in patients with obesity was not found, and the version of the FCI used in the pivotal trials differs from the validated 28-item version. The FCI may also be subject to inaccuracy as it relies on a recall period of a month without the use of a diary. No rationale was given for selecting the FCI sweets and carbohydrate subscale scores as outcomes.

Internal Validity: LIGHT Study

The NI margin of 1.4 in the LIGHT study was agreed upon by the FDA in its post-marketing requirements for Contrave,[28] and the LIGHT study Clinical Study Report[27] indicated that the trial was conducted under an agreed FDA Special Protocol Assessment. In the LIGHT study, ITT analysis was performed for the main analysis of the primary end point. However, the large proportions of patients discontinuing treatment early may have biased the results toward the null (which is problematic in an NI study), as the risk of cardiovascular events could be positively associated with the duration of treatment exposure and/or negatively associated with time since treatment discontinuation. Patients reported taking study medication regularly at a mean of 85.6% of visits, and a lack of adherence could have also biased the results toward the null. An on-treatment sensitivity analysis in the ITT set in which patients were censored 365 days after treatment discontinuation may have mitigated some of the potential bias. The PP analysis censored patients at 30 days after treatment discontinuation, but would not have been sufficiently powered due to the significantly smaller sample sizes.

The expanded MACE outcomes in the LIGHT study are more challenging to interpret than the primary outcome as events that are likely to be less consequential to patients (non-fatal hospitalization for unstable angina and coronary revascularization) were added to the composite outcome. There was also no control for multiplicity of outcomes in the LIGHT study and results for end points other than the primary end point should be interpreted with this in mind. Also, the subgroup analyses in the LIGHT study had the same limitations as for those in the pivotal trials.

The run-in period in the LIGHT study and subsequent dropout of patients prior to randomization to the treatment period may have enriched the ITT population with patients

more likely to adhere to treatment. This may have led to underestimation of the percentage of patients discontinuing due to AEs and overestimation of treatment adherence, as well as bias in favour of NB for both of these parameters.

The major limitation in the LIGHT study was its early termination and the inability to draw conclusions based on the 50% interim analysis or the final data cut-off analysis. Because it was not terminated due to an unfavourable safety profile or a favourable benefit-to-risk profile, a final analysis of 100% of the expected events was required to make a conclusion on cardiovascular safety.

External Validity: Pivotal Trials and LIGHT Study

Population

The populations in the pivotal trials may not represent the entire indication for NB: adults with an initial BMI of 30 kg/m^2 or greater (obese) or 27 kg/m^2 or greater (overweight) in the presence of at least one weight-related comorbidity. While the clinical expert consulted for this review indicated that the study populations were generally similar to the population seen in clinical practice in Canada, 3.1% or less of patients in each treatment group in the COR-I, COR-II, and COR-BMOD studies had a BMI of less than 30 kg/m^2 (compared with 5.4% to 6.5% of patients in the COR-DM study). Other than controlled hypertension and dyslipidemia, depression, and anxiety (and type 2 diabetes in the COR-DM study), weight-related comorbidities were not reported. There is therefore insufficient information to assess whether the pivotal trial populations represent the full spectrum of weight-related comorbidities.

Interventions

The clinical expert consulted by CADTH considered the dietary and physical activity co-interventions in the COR-I, COR-II, and COR-DM studies to be similar to the nonpharmacologic interventions patients in Canada would receive and considered the co-interventions in the COR-BMOD study to be much more intensive than typical co-interventions in Canada (particularly the closed-group sessions and the food diary).

Despite the inclusion of a titration period, patients in the trials may have been more likely to discontinue treatment due to AEs than in the real world, as clinicians typically reassure their patients that the adverse effects will improve over time and encourage their patients to stay on the drug.

Outcomes

The clinical expert considered the responder analyses (percentage of patients with at least 5% or 10% weight loss) to be the most important weight-loss outcomes. While a decrease in weight of 5% may be of clinical benefit and was a co-primary end point, the clinical expert indicated that patients generally require weight loss in the range of at least 10% to 15% to be satisfied with efficacy and continue on treatment. Therefore, some patients in the trials who were considered responders for the co-primary end point would have been more likely to discontinue outside of a clinical trial setting due to perceived lack of efficacy and experience weight regain, and therefore receive minimal overall benefit.

According to the clinical expert consulted for this review, maintenance of weight following weight loss is a key challenge for patients with obesity and patients are expected to continue pharmacotherapy for weight management indefinitely. The pivotal trials did not provide efficacy results beyond one year of treatment and most patients in the LIGHT study

discontinued treatment after less than one year. Evidence for the long-term efficacy of NB past one year of treatment is therefore limited.

Improvement in weight-related comorbidities was identified in the patient input submissions as an outcome that is important to patients with obesity, but it was not assessed comprehensively in the studies. While dose changes in antidiabetic medications were assessed in the COR-DM study, changes in medications for hypertension or dyslipidemia were not assessed in the trials. Depressive symptoms were assessed using the IDS-SR, but its validity in this patient population is unclear.

Indirect Evidence

Objectives and Methods for the Summary of Indirect Evidence

No direct comparisons of NB versus any of the relevant active comparators in the CADTH Common Drug Review CDR systematic review protocol were identified. As a result, CDR conducted a targeted literature search for indirect evidence with respect to the comparative efficacy and safety of NB. The results of the literature search detailed in Appendix 1 (which was not limited by study design) were screened by one reviewer for indirect comparisons of naltrexone hydrochloride 8 mg and bupropion hydrochloride 90 mg in extended-release tablets with any of the relevant comparators in the CDR systematic review protocol. Two potentially relevant published NMAs were identified;[39,40] however, one NMA[40] was excluded due to the lack of relevant outcomes.

Description of the Indirect Comparison

One relevant NMA,[39] by Khera et al. and published in 2016, was included in the review. The NMA compared weight loss and AEs between five FDA-approved weight-loss drugs (orlistat, lorcaserin, NB, phentermine-topiramate [PT], and liraglutide) for long-term use in obese (BMI of at least 30 kg/m^2) or overweight (BMI of at least 27 kg/m^2) patients with at least one weight-related comorbidity.

Methods of the Indirect Comparison

Study Selection Methods

The protocol for the systematic review was pre-specified and registered online. Several RCTs comparing one of the five FDA-approved drugs (orlistat, lorcaserin, NB, PT, and liraglutide) with placebo or another FDA-approved drug were included. The treatment had to be administered at the most effective recommended dosage for at least one year. Eligible patient populations were obese (BMI of at least 30 kg/m^2) or overweight (BMI of at least 27 kg/m^2) with at least one weight-related comorbidity. To be included, RCTs had to include as an outcome either difference in mean weight loss between treatment groups or the proportion of patients achieving at least 5% weight loss. Any RCTs comparing individual components of NB or PT and RCTs in special populations (e.g., patients with non-alcoholic fatty liver disease or polycystic ovary syndrome) were excluded.

Multiple databases (Ovid MEDLINE, Embase, Scopus, Web of Science, and the Cochrane Central Register of Controlled Trials) were searched from inception to March 23, 2016. Clinical trial registries, conference proceedings, and published systematic reviews were also screened. Study screening was performed independently by two reviewers, and conflicts in study selection were resolved by consensus in consultation with a third reviewer. The Cochrane Risk of Bias tool was used to assess study quality in the primary RCTs,

although it was not clear whether this was performed in duplicate. Risk of bias was assessed for the primary efficacy outcome alone. Using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) method[41] for rating quality of evidence in an NMA, levels of quality of evidence (high, moderate, low, or very low) were assigned in a stepwise manner, starting with direct comparisons, then indirect comparisons, and lastly the combination of direct and indirect estimates for each pairwise comparison. There were no plans to exclude studies based on quality.

Data extraction using a standardized form was performed by two pairs of authors independently, with discrepancies resolved by consensus in consultation with a separate reviewer. In trials with differences in dosages of a particular medication, the treatment group with the most effective FDA-approved dosage (120 mg three times daily for orlistat, 10 mg twice daily for lorcaserin, 32 mg/360 mg twice daily for NB, 15 mg/92 mg once daily for PT, and 3 mg daily subcutaneous injection for liraglutide) was included and other dosages were excluded. Data pertaining to primary study characteristics, baseline patient characteristics, treatment characteristics, co-interventions, efficacy end points, and AEs were extracted. Baseline patient characteristics were reported for the enrolled population and efficacy data were reported for the mITT population (patients who received at least one dose of study drug and had at least one post-baseline weight assessment), with missing values imputed using the LOCF approach.

ITC Analysis Methods

Random-effects Bayesian NMAs with Markov chain Monte Carlo methods were used according to the methods described by Dias et al.[42,43] The dichotomous outcomes (proportion of patients with at least 5% weight loss and at least 10% weight loss, and rate of discontinuation due to AEs) were entered into the model as log-odds ratios for each comparison, and a binomial likelihood and a logit link function were used. In analyses involving the three-arm RCT comparing orlistat, liraglutide, and placebo, between-arm correlations were adjusted for using a conditional univariate distribution. Mean weight loss in excess of placebo, a continuous outcome, was entered into the model as a mean difference and standard error for each comparison and a normal likelihood and an identity link function were used. Random effects were modelled for both types of outcomes by assuming a single heterogeneity value per pairwise comparison. A summary of the analysis methods used for the NMA is provided in Table 30.

Assessments of clinical heterogeneity among RCTs for each direct comparison were not described. Similarly, clinical heterogeneity of RCTs among the different pairwise comparisons was not assessed. Publication bias was assessed by examining the funnel plot and using the Egger regression test.

Table 30: Indirect Treatment Comparison Analysis Methods

	Khera et al. (2016)
ITC methods	Random-effects Bayesian network meta-analysis using Markov chain Monte Carlo methods (100,000 iterations following a burn-in of 10,000 iterations) Post hoc sensitivity analysis: Frequentist approach by White et al. (2011)[44] that did not assume consistency between direct and indirect estimates and included a trial design covariate to distinguish between the two types of estimate
Priors	Non-informative priors (defined as "made no assumption about the efficacy of the drugs") Post hoc sensitivity analyses: Vague priors (uniform, normal, and gamma distributions) with different means and variances
Assessment of model fit	Total residual deviance
Assessment of consistency	Node-splitting method in the closed loop formed by placebo, orlistat, and liraglutide
Assessment of convergence	Trace plots, Monte Carlo error, and the Brooks-Gelman-Rubin statistic
Outcomes	Primary: Proportion of patients with at least 5% weight loss relative to baseline weight Other: Proportion of patients with at least 10% weight loss relative to baseline weight, change in weight in kilograms relative to baseline weight in excess of placebo, rate of discontinuation of treatment due to adverse event
Follow-up timepoints	52 weeks (± 4 weeks)
Construction of nodes	Each node represents a single drug; for each drug, only the results for the treatment arm with the most effective FDA-approved dosage are included
Pre-planned sensitivity analyses	• Include only RCTs of non-diabetic patients • Include results for the standard dosage of phentermine-topiramate (7.5 mg/46 mg daily) instead of the higher dosage of 15 mg/92 mg daily
Additional post hoc sensitivity analyses	• Worst-case scenario analysis: All randomized patients not assessed at the end of the study were classified as treatment failures • Complete-case analysis: Only patients who completed the entire study and were assessed at the end were included. It was not specified whether patients still had to be on study treatment at the end of the study • Exclude the COR-BMOD study
Methods for pairwise meta-analysis	Random-effects direct meta-analysis using the DerSimonian and Laird method Post hoc sensitivity analysis: Random-effects direct meta-analysis using the Hartung-Knapp method to address possible type I error with the DerSimonian and Laird method

RCT = randomized controlled trial.

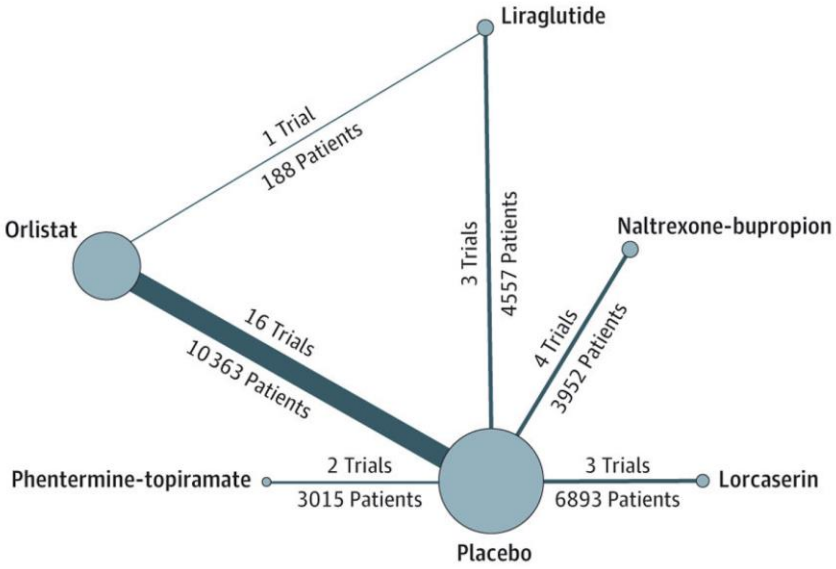
Source: Khera et al. (2016).[39]

Results of the Indirect Comparison

Summary of Included Studies

A total of 28 relevant RCTs were included. There were 16 RCTs of orlistat versus placebo, two of liraglutide versus placebo, four of NB versus placebo, three of lorcaserin versus placebo, two of PT versus placebo, and one three-armed trial comparing orlistat and liraglutide with placebo. The evidence network for the primary end point is shown in Figure 2. In addition to the four NB RCTs, 17 additional RCTs[13-16,45-61] were surveyed by CADTH reviewers for study characteristics not reported in the NMA publication.

Figure 2: Evidence Network for the Primary Efficacy Outcome



Note: The size of the nodes and the thickness of the edges are weighted according to the number of studies evaluating each treatment and direct comparison, respectively.[39]

Source: Reproduced with permission from JAMA. 2016 June 14; 315(22): 2424–2434. doi:10.1001/jama.2016.7602. Copyright © 2016 American Medical Association. All rights reserved.[39]

Patient Populations

While mean weight (95.3 kg to 115.8 kg) was similar among the RCTs, there were notable variations in mean age (ranging from 40 years to 60 years) and proportion of female patients (45% to 92%). The presence of diabetes, hypertension, and dyslipidemia at baseline also varied among the primary RCTs. Of the 28 RCTs, eight were in diabetic populations being treated with pharmacological therapy and 16 were in patients without diabetes or with diet-controlled diabetes. Diabetes status was not reported in four RCTs. The proportion of patients with hypertension at baseline ranged from 2% to 100% in 13 RCTs and was not reported in 15 RCTs. The proportion of patients with dyslipidemia at baseline ranged from 2% to 84% in 15 RCTs and was not reported in 13 RCTs.

Interventions

The dosages of the study medications used in the main analyses were as follows: 120 mg three times a day for orlistat, 10 mg twice a day for lorcaserin, 16 mg naltrexone and 180 mg bupropion twice daily for NB (aside from re-randomization in the COR-II study), 15 mg and 92 mg daily for PT, and 3.0 mg daily subcutaneously for liraglutide. All RCTs compared one active intervention with placebo (some with more than one dosage of active intervention), with the exception of one trial comparing various dosages of liraglutide with orlistat and placebo. Data were extracted for the first 52 or 56 weeks of treatment. A variety of dietary and physical activity co-interventions were administered in the RCTs and are described in Table 31.

Titration phases and run-in phases and follow-up for patients who discontinued treatment were not described in the NMA publication and were surveyed by CADTH reviewers in 21 RCTs. Of the nine placebo-controlled orlistat RCTs surveyed, none planned to follow up

with patients who discontinued treatment early. In contrast, most of the other RCTs surveyed encouraged patients who discontinued treatment early to continue with study assessment or to return for end-of-study assessment. The presence of titration and run-in phases in the 21 RCTs are summarized in Table 31.

Comparators

The two relevant pharmacological comparators identified in the systematic review protocol, orlistat and liraglutide (Table 3), were included in an NMA at the Health Canada–approved dosages. While NB, orlistat, and liraglutide are indicated in Canada as adjuncts to a reduced-calorie diet and increased physical activity for chronic weight management, not all of the RCTs in the NMA reported a physical activity co-intervention.

Non-pharmacological comparators were not included; therefore, no indirect comparisons were available for NB versus bariatric surgery or intensive behaviour or lifestyle modification. Lorcaserin and PT were also included in the NMA, but these therapies are not currently marketed in Canada.

Outcomes

The primary efficacy outcome for the NMA was the proportion of patients with at least 5% weight loss at one year (52 weeks ± four weeks) of follow-up, relative to baseline weight. Other assessed efficacy outcomes were the proportion of patients with at least 10% weight loss and a change in weight (in kilograms) relative to baseline weight in excess of placebo after one year of follow-up. The only assessed harms outcome was the proportion of patients discontinuing treatment due to AEs. Overall AEs and SAEs were not evaluated. Efficacy outcomes related to weight-related comorbidities or HRQoL were not included in the NMA.

Quality Assessment

According to the NMA authors' quality assessment, the RCTs were at high risk of bias due to attrition rates ranging from 30% to 45%. There was a high risk of bias in random sequence generation for one RCT and in allocation concealment and blinding of outcome assessment for another RCT. There was also a low risk of bias other than an unclear risk of bias in random sequence generation for several RCTs. The GRADE quality of evidence for the primary outcome, taking both direct and indirect evidence into account, was moderate for all comparisons, aside from three comparisons with a low quality of evidence: lorcaserin versus orlistat, lorcaserin versus NB, and liraglutide versus NB.

Homogeneity Assessment

Assessment of clinical homogeneity among the RCTs was not described in the NMA and measures of heterogeneity for each direct comparison were not provided. The results of the CDR review team's assessment of clinical homogeneity are provided in Table 31.

Table 31: Assessment of Homogeneity

	Description and handling of potential effect modifiers
Diabetes status at baseline	Among the RCTs, 8 were in diabetic populations being treated with pharmacological therapy and 16 were in patients without diabetes or with diet-controlled diabetes. Handling: A pre-planned sensitivity analysis was performed in RCTs with non-diabetic patients only.
Age at baseline	Mean age at baseline ranged from 40 years to 60 years.
Sex	The proportion of female patients ranged from 45% to 92%.
Dietary co-intervention	• The NB (4 RCTs), PT (2 RCTs), liraglutide RCTs (2 RCTs) and the multi-arm RCT instructed patients to follow a 500 kcal/day deficit • The lorcaserin RCTs (3 RCTs) instructed patients to follow a 600 kcal/day deficit • The orlistat RCTs instructed patients to: reduce fat intake (1 RCT), follow a 600 kcal/day deficit (11 RCTs), follow an 800 kcal/day deficit (1 RCT), reduce energy intake by 20% (1 RCT), or follow an energy-deficient diet with 30% energy from fat (2 RCTs)
Physical activity co-intervention	• Most RCTs instructed patients to perform moderate exercise or walking (or brisk walking) for 20 to 30 minutes a day (every day or 3 to 5 times a week) • 4 RCTs among the orlistat and PT RCTs instructed patients to “increase exercise” • No exercise interventions were reported in 7 orlistat RCTs and 1 PT RCT • 1 NB RCT, the COR-BMOD study, had a structured intensive behavioural-modification program (diet and physical activity) Handling: A post hoc sensitivity assessment was performed that excluded the COR-BMOD study
Analysis population	In 21 surveyed RCTs, efficacy results were reported for: • The full analysis set (randomized patients who received at least one dose of study drug and with at least one post-baseline assessment while on study drug) in the 4 NB RCTs • The mITT set (randomized patients who received at least one dose of study drug and with at least one post-baseline assessment) in 16 RCTs • The ITT set (all randomized patients) in 1 RCT
Run-in phase	In 21 surveyed RCTs: • 7 orlistat RCTs (including the multi-arm RCT) had a 2- or 4- week run-in period and 3 had no run-in period. In some RCTs patients had to meet a minimum treatment-adherence requirement to remain in the study • None of the other RCTs reported having a run-in period
Titration phase	In 21 surveyed RCTs: • Titration periods were used in the PT (2 RCTs) and NB (4 RCTs) RCTs, multi-arm RCT, and 1 of 2 liraglutide RCTs • None the orlistat (9 RCTs) and lorcaserin (3 RCTs) RCTs reported a titration period
End-of-study assessment for patients who discontinued	Most or all of the orlistat RCTs did not perform end-of-study assessments in patients who discontinued treatment early. Most of the non-orlistat RCTs encouraged patients who discontinued treatment early to continue with study assessments or return for the end-of-study assessment. Study discontinuation rates ranged from 30% to 45%.

NB = naltrexone and bupropion; PT = phentermine-topiramate; RCT = randomized controlled trial.

Source: Khera et al. (2016);[39] publications for surveyed RCTs.[13-16,45-61]

Evidence Network

The evidence network for the primary efficacy outcome (proportion of patients with at least 5% weight loss), which was identical to the evidence network for discontinuation of treatment due AE, is provided in Figure 2. The RCT comparing orlistat, liraglutide, and placebo contributed to three different direct comparisons in the evidence network. The evidence network for the other efficacy outcomes (proportion of patients with at least 10% weight loss and mean change in weight in excess of placebo) were similar, except that they

each had 14 rather than 16 trials informing the comparison between orlistat and placebo, and the network for change in weight had two rather than four trials for the comparison between NB and placebo.

Efficacy Results

In the main analyses of the three efficacy outcomes, the 95% credible intervals (CrIs) excluded values of 1 for odds ratios and 0 for mean differences for the comparisons of NB versus placebo and NB versus orlistat (and not for the comparison of NB versus liraglutide).

For the primary outcome, proportion of patients with at least 5% weight loss, the odds ratios were:

- 0.71 (95% CrI, 0.46 to 1.04) for NB versus liraglutide
- 1.47 (95% CrI, 1.09 to 1.96) for NB versus orlistat
- 3.96 (95% CrI, 3.03 to 5.11) for NB versus placebo.

For the proportion of patients with at least 10% weight loss, the odds ratios were:

- 0.83 (95% CrI, 0.50 to 1.30) for NB versus liraglutide
- 1.74 (95% CrI, 1.22 to 2.47) for NB versus orlistat
- 4.19 (95% CrI, 3.08 to 5.72) for NB versus placebo.

For the mean change in weight in excess of placebo (in kilograms), the mean differences were:

- 0.32 (95% CrI, –0.92 to 1.59) for NB versus liraglutide
- −2.36 (95% CrI, –3.43 to –1.28) for NB versus orlistat
- −4.95 (95% CrI, –5.94 to –3.96) for NB versus placebo.

Safety Results

For percentage of patients discontinuing due to AE, the odds ratios were:

- 0.90 (95% CrI, 0.58 to 1.35) for NB versus liraglutide
- 1.44 (95% CrI, 1.07 to 1.95) for NB versus orlistat
- 2.64 (95% CrI, 2.1 to 3.35) for NB versus placebo.

Direct Meta-Analyses

The results of the direct meta-analyses with both methods (the DerSimonian and Laird and the Hartung-Knapp methods) were similar compared with the results of the NMA for the efficacy outcomes. The report noted that significant heterogeneity was present for most pairwise direct comparisons. Using the DerSimonian and Laird method, I^2 values of 50% to 68% were observed for orlistat, lorcaserin, and NB versus placebo for the primary outcome (and I^2 values were less than 25% for the other comparisons). The I^2 value was 64% for NB versus placebo, between 25% and 50% for orlistat and lorcaserin versus placebo, and 0% for PT and liraglutide versus placebo for the 10% weight-loss outcome. The I^2 value was 59% for lorcaserin versus placebo, 83% for liraglutide versus placebo, 26% for orlistat versus placebo, and 0% for NB versus placebo for the weight-loss (in kilograms) outcome. The direction of treatment effect for the efficacy outcomes was consistent within each pairwise direct comparison using the DerSimonian and Laird method (forest plots were not provided for the Hartung-Knapp method). For the safety results, substantial heterogeneity was evident in the orlistat versus placebo comparison (I^2 = 65%), although I^2 was 0% for

the other comparisons and the direction of the treatment effect was generally consistent within each pairwise direct comparison.

Consistency Between Direct and Indirect Comparisons

No significant differences between the direct and indirect estimates in the closed loop formed by placebo, orlistat, and liraglutide were found for any of the outcomes.

Sensitivity Analyses

The results from the sensitivity analyses for the primary outcome in non-diabetic patients only and excluding the COR-BMOD study were consistent with the results from the main analyses. The results for the sensitivity analysis for the primary outcome using the standard dosage of PT (7.5 mg/46 mg daily) were also consistent with those for the main analysis using the high dosage of PT, although the 95% CrI for the comparison of PT versus NB no longer excluded an odds ratio of 1. The results for the sensitivity analyses using the frequentist approach for combining direct and indirect evidence were similar to the results for the main analyses for all outcomes. Results from using different prior distributions were not reported.

The results from the worst-case scenario sensitivity analyses for the primary and 10% weight-loss outcomes were largely consistent with the main results, although the treatment-effect estimates were smaller for each comparator versus placebo. The treatment effects for each comparator versus orlistat were also smaller in the worst-case scenario sensitivity analyses and the 95% CrI for NB versus orlistat no longer excluded an odds ratio of 1 for both outcomes.

The results from the complete-case sensitivity analyses for the primary outcome, the 10% weight-loss outcome, and the change in weight in kilograms were largely consistent with the main results, although the treatment-effect estimates were greater for each comparator versus placebo and for each comparator versus orlistat (aside from orlistat versus placebo and liraglutide versus placebo). For change in weight in kilograms, the 95% CrI for NB versus orlistat no longer excluded a value of 0.

Critical Appraisal of the Indirect Comparison

Overall, the systematic review methods proved appropriate for identifying relevant studies, extracting data, and assessing study quality. The evidence network contained all relevant drug comparators identified in CADTH's systematic review protocol.

With regards to the meta-analyses, the statistical methods and sensitivity analyses were appropriate and well-reported.

The following limitations were identified in the NMA:

- For the primary outcome, the NMA comparisons of NB with relevant comparators were of moderate quality (and of low quality for NB versus liraglutide) according to the GRADE level of evidence. Studies were not excluded based on quality, and attrition was substantial in all the RCTs, contributing to a high risk of attrition bias in the efficacy outcomes.
- While key trial characteristics were reported, the authors did not provide an assessment of clinical heterogeneity or the appropriateness of pooling trial results.
- Substantial statistical heterogeneity was identified in many of the pairwise comparisons. For example, I^2 was 67% for NB versus placebo for the primary outcome and 64% for the

10% weight-loss outcome. Heterogeneity could not be assessed for NB versus orlistat or liraglutide as there were no direct comparisons. While random-effects models were used, statistical heterogeneity may have limited the precision of the treatment-effect estimates and may also have reflected underlying clinical heterogeneity.

- There was bias in favour of NB due to the use of the full analysis set rather than the mITT set (which was the pre-specified analysis set for the NMA) in the four placebo-controlled NB RCTs. In the clinical study reports for the NB RCTs, the full analysis set results were more favourable for NB compared with the mITT set results. Therefore, there was bias in the NMA in favour of NB versus the other comparators for the efficacy outcomes. Because the proportions of patients who discontinued due to AEs were greater in the NB versus the placebo groups and these patients were not counted in the denominator when the NMA authors calculated this outcome, the imbalance was erroneously amplified and there was a bias in the NMA against NB for the safety outcome.
- The week 56 results from the COR-II study were from the weighted LOCF analysis, which was not considered appropriate for the purposes of the current review due to methodological concerns.
- Dietary co-interventions varied between RCTs. While they were similar among the NB, PT, liraglutide, and multi-armed RCTs, they varied among the orlistat RCTs: 600 kcal/day deficit, 800 kcal/day deficit, 20% reduction in energy intake, reduction in energy intake with 30% energy from fat, and reduction in fat intake. This variation in dietary interventions may have contributed to the substantial statistical heterogeneity observed in the orlistat versus placebo results for all outcomes.
- Baseline age and proportion of female patients varied between RCTs. According to the clinical expert consulted for this review, both older patients and female patients may experience greater difficulty in losing weight. Heterogeneity in these characteristics may have contributed to heterogeneity within the pairwise comparisons and it is unclear if the assumption of clinical similarity between pairwise comparisons was affected.
- Study discontinuation rates ranged from 30% to 45% in the RCTs and analyses using different approaches for handling missing data did not yield consistent results for the comparison of NB versus orlistat. All three efficacy outcomes favoured NB versus orlistat in the main analyses and the sensitivity analyses. While the 95% CrIs excluded odds ratios of 1 and mean differences of 0 in the main analyses of the three efficacy outcomes, this was not the case in the worst-case scenario and complete-case sensitivity analyses.
- The following potential effect modifiers may have undermined the assumption of clinical similarity between pairwise comparisons. Certain study design characteristics tended to be different in the orlistat RCTs versus the other RCTs (see Table 31 for more details). Because consistency could be assessed only in one closed loop (formed by orlistat, liraglutide, and placebo), the impact on consistency throughout the network could not be assessed. The potential directions of bias are conflicting or unclear, and it is not possible to predict overall trends in bias from these effect modifiers.
  - Run-in phase: A run-in placebo treatment phase was more common in the orlistat versus placebo RCTs than in the RCTs of other comparators versus placebo. As a run-in phase can enrich the trial population with patients more likely to adhere to treatment, the results for any of the outcomes may have been biased in favour of orlistat relative to the other comparators.
  - Titration phase: A two- or four-week titration phase was more common in the RCTs with PT, NB, and liraglutide than in the RCTs with orlistat and lorcaserin. If a titration phase made it more likely that participants would tolerate a treatment, then the lack of

a titration phase in the orlistat and lorcaserin RCTs could have introduced bias against orlistat and lorcaserin for discontinuations due to AE.

- End-of-study assessment for patients who discontinued: The encouragement of patients to continue with study assessment or return for the end-of-study assessment following treatment discontinuation was more common in the non-orlistat RCTs than in the orlistat RCTs. The potential direction of bias from this source of heterogeneity is unclear.
- Systematic review protocol for the current report: Not all relevant comparators (particularly non-pharmacological comparators) were included in the scope of the NMA, and important efficacy outcomes, including mortality, weight-related comorbidities, and HRQoL, were not assessed in the NMA. As well, long-term efficacy beyond one year of treatment was not assessed.

Summary

One relevant indirect treatment comparison, an NMA by Khera et al. published in 2016, was identified in the literature search. The NMA compared weight-loss outcomes and discontinuations due to AEs between weight-loss drugs approved by the FDA for long-term use in patients with obesity (BMI of at least 30 kg/m^2) or overweight (BMI of at least 27 kg/m^2) with at least one weight-related comorbidity. The evidence network contained the relevant comparators identified in the CADTH systematic review protocol and patients in all included primary RCTs received dietary and physical activity co-interventions. Major limitations of the NMA included the substantial amounts of missing data across all the primary RCTs (study discontinuation rates of 30% to 45%) and heterogeneity in baseline age, sex, study design characteristics, and analysis populations that may have undermined the assumption of similarity between the various pairwise comparisons.

The results appeared to confirm the pivotal NB trial results, with NB being more effective than placebo in terms of patients achieving at least 5% and 10% weight loss and in terms of difference in weight loss after one year of treatment. While NB was also consistently favoured over orlistat for weight loss in the efficacy analyses, the treatment-effect estimates were reduced in the worst-case scenario sensitivity analyses (performed for the 5% and 10% weight-loss outcomes), with the 95% CrIs for the odds ratios no longer excluding 1, compared with the main analyses using LOCF for missing-data imputation. This inconsistency, coupled with bias in favour of NB due to the use of the full analysis population as well as uncertainty in the validity of the assumption of similarity between pairwise comparisons, meant that superior efficacy of NB over orlistat could not be concluded. NB was associated with a higher proportion of patients discontinuing due to AE than placebo and orlistat, although potential sources of bias working in the opposite direction (inflated proportions of patients discontinuing because of AEs in NB groups due to use of the full analysis population in the NB trials and lack of titration periods in the orlistat RCTs) meant that superiority of orlistat over NB for this outcome could not be concluded. There was no evidence for a difference in weight-loss efficacy or treatment discontinuation due to AE between NB and liraglutide.

Other Relevant Studies

No other relevant studies were identified for this review.

Discussion

Summary of Available Evidence

Four pivotal RCTs (COR-I, COR-II, COR-BMOD, and COR-DM) and one long-term cardiovascular-outcomes RCT (LIGHT) were included in the systematic review. All RCTs were double-blind, placebo-controlled, parallel-group trials that were sponsored by the sponsor. In addition, one relevant published network NMA was identified in a literature search.

Interpretation of Results

Efficacy

A benefit of NB over placebo in terms of weight loss was demonstrated in patients who were overweight (with controlled hypertension and/or dyslipidemia) or obese after 52 weeks of treatment at the maintenance dosage. The co-primary end points were met in the four pivotal trials for the primary analysis as well as the conservative BOCF sensitivity analysis, which assigned no benefit to patients who discontinued treatment early. Similarly, the percentage of patients who reported losing at least 10% of their weight, likely a more relevant outcome, was statistically significantly greater with NB versus placebo in the COR-I, COR-II, and COR-BMOD studies.

Higher percentages of patients lost at least 5% of their weight in both groups of the COR-BMOD study compared with the other studies in the primary analyses (the only analysis comparable across the four trials), which likely reflects the higher intensity of the co-interventions in the COR-BMOD study. The effect size was also smaller in the COR-BMOD study, and the clinical expert indicated that any additional weight loss superimposed on weight loss from an intensive behavioural-modification program is expected to be more difficult.

The results for weight loss from the COR-I and COR-II studies may best represent the non-diabetic subgroup of the target population in Canada and the results for the COR-DM study may best represent the subgroup of the target population with type 2 diabetes. While the week 56 results in the COR-II study were at risk of bias and not included in the present review, the week 28 results support the results from the COR-1 study. In the BOCF sensitivity analyses, the percentage of patients with at least 5% weight loss at week 56 in the COR-I and COR-DM studies were similar (11.5% to 14.1% for patients on placebo and 28.1% to 30.9% for patients on NB). However, the clinical expert consulted for this review indicated that patients in the real world are likely to discontinue treatment within three months of initiation if they do not experience at least 10% or 15% weight loss, particularly given the AEs associated with drugs for weight management. For the 10% weight-loss outcome, the percentages of responders were lower in the COR-I and COR-DM studies than for the 5% weight-loss outcome: 5.4% to 6.9% for patients on placebo and 15.26% to 21.19% for patients on NB. While patients receiving NB were more likely than patients receiving placebo to reach 5% or 10% weight loss in the trials, it is likely that only a small proportion of patients in clinical practice would remain on NB in the long-term and receive this benefit, based on the clinical expert input regarding patient satisfaction with amount of weight loss. There is no evidence for markers, prior to initiation of treatment, to predict treatment response or to identify patients who would benefit.

The clinical expert consulted for this review expected weight loss to be more difficult in patients with diabetes, as insulin and sulfonylureas tend to promote weight gain, and patients who lose weight may become more prone to hypoglycemia and therefore increase their caloric intake. However, there were no consistent or notable differences in weight loss between trials in non-diabetic patients (COR-I and COR-II) and in the COR-DM study and the LIGHT study (in which most patients had type 2 diabetes).

According to the clinical expert, patients who receive pharmacotherapy for weight management are expected to remain on treatment indefinitely. Due to the progressive nature of obesity, patients already on pharmacotherapy for weight management may eventually require dose escalation or add-on therapy to prevent weight gain. The pivotal trials do not provide evidence for efficacy of NB past one year of treatment. The LIGHT study was of longer duration, but high proportions of patients discontinuing treatment and imbalances between treatment groups in the reasons for discontinuation biased the results, and sensitivity analyses for missing data were not performed.

There was no evidence of clinically meaningful improvement in, or prevention of, weight-related comorbidities in the trials. Only selected weight-related comorbidities (controlled hypertension, dyslipidemia, depression, anxiety, and type 2 diabetes) were reported in the pivotal trials at baseline. Conclusions could not be drawn regarding severity of depression as the IDS-SR outcome was not statistically tested and its validity in patients with obesity is uncertain. Blood pressure and lipid parameters were not included in the present systematic review because changes in these parameters in the trials would have had uncertain impacts on cardiovascular outcomes. While cardiovascular outcomes were assessed in the LIGHT study, conclusions could not be drawn due to an early termination that was unrelated to superiority or an unfavourable safety profile. A decrease in medications for weight-related comorbidities would have been clinically meaningful, but dose reductions in antidiabetic medications were rare in the COR-DM study. The percentage of patients requiring a dose increase in or initiation of a new antidiabetic medication was numerically lower for patients on NB. However, outcomes related to adjustments in antidiabetic medications were not statistically tested, in accordance with the closed testing procedure, and conclusions could not be drawn. Adjustments in medications for other weight-related comorbidities were not assessed.

Patient input submissions emphasized the importance of improving quality of life, which was assessed in the pivotal trials with the IWQoL-Lite. There was statistically significantly greater improvement in HRQoL in the NB group versus the placebo group in the COR-I, COR-II, and COR-BMOD studies, but the between-group differences did not meet the lower bound of the range of MIDs identified for the instrument. This was also the case in the COR-II study for the SF-36 PCS score, which was an exploratory end point. The clinical expert agreed that no clinically meaningful improvement was observed, although the results provide reassurance that patients did not experience a worsening in HRQoL due to AEs.

Improvement in food craving was also identified as an important outcome in the patient input. However, the only between-group difference found for food craving was for the COE item-19 scores and there were issues identified concerning the validity of a single-item COE score and the FCI subscale scores. Other outcomes important to patients (fatigue, pain, productivity, sleep, and mobility) were not assessed in the trials.

One published NMA assessed weight-loss outcomes for NB and other drugs approved by the FDA for long-term use. There were comparisons of NB versus liraglutide and orlistat, the other two approved drugs for chronic weight management in Canada. Although the

main NMA analyses favoured NB over orlistat for weight loss, worst-case scenario sensitivity analyses were not consistent with the main analyses for this comparison and several limitations were identified by CADTH reviewers. These limitations included bias in favour of NB due to the use of the full analysis population in the pivotal trials (compared with the use of the mITT population in other RCTs) as well as uncertainty in the validity of the assumption of similarity between pairwise comparisons. Therefore, superior efficacy of NB over orlistat could not be concluded. There was also no evidence for a difference between NB and liraglutide for weight loss.

Intensive behavioural or lifestyle modification programs and bariatric surgery were considered relevant comparators in the present systematic review, but comparisons of NB with these interventions were not found. However, according to the clinical expert, access to interdisciplinary behavioural intervention programs and bariatric surgery (even for eligible patients) is limited in Canada. Orlistat and liraglutide are therefore likely the most appropriate comparators for NB. The clinical expert noted the importance of a range of pharmacologic options, given that patients may experience success with one drug but not another. Notably, the purported mechanisms of action differ among NB, orlistat, and liraglutide.

Harms

Patients receiving NB reported more AEs compared with patients receiving placebo in the pivotal trials, with the following consistently occurring in greater proportions of patients receiving NB: nausea, constipation, headache, vomiting, dizziness, insomnia, and dry mouth. The most common reasons for WDAEs were similar: nausea, dizziness, headache, and anxiety. The clinical expert consulted for this review considered these AEs to be manageable and often transient. SAEs occurred in less than 5% of patients in the pivotal trials and individual SAEs occurred in 1.2% or less of patients in a given treatment group. In the LIGHT study, AEs leading to treatment discontinuation were similar to those in the pivotal trials and the only SAE that was notably more common in the NB group was the system organ class of gastrointestinal disorders.

Individual AEs classified as psychiatric disorders were rare, although as a group of AEs they were consistently more common in the NB group across all trials. While the pivotal trials excluded patients with a recent psychiatric illness requiring treatment, the LIGHT study selection criteria were less stringent. The clinical expert expressed no concerns with identifying patients who can safely receive NB and noted that some patients in the target population already receive bupropion for depression.

In all the pivotal trials, increases from baseline at two consecutive visits in pulse rate (of at least 5 bpm or 10 bpm), systolic blood pressure (of at least 10 mm Hg or 15 mm Hg), and diastolic blood pressure (of at least 5 mm Hg or 10 mm Hg) were more common in patients receiving NB than in patients receiving placebo. While the clinical significance of these observed increases is unclear, exploratory analyses of the pooled pivotal trial data by the FDA showed a trend in patients who experienced at least 5% weight loss during the treatment period (and completed the treatment period) of less-beneficial mean changes in pulse rate, systolic blood pressure, and diastolic blood pressure in the NB group than in the placebo group.[23] Concerns over higher pulse rate and blood pressure in NB-treated patients versus placebo-treated patients in the pivotal trials, as well as greater proportions of NB-treated patients who reported hypertension as an AE, led to the FDA requiring the sponsor to conduct the LIGHT study to demonstrate that the risk of cardiovascular events does not adversely affect the risk-benefit profile of NB.[22] Because the LIGHT study was

terminated early and conclusions about relative cardiovascular risk with NB treatment could not be drawn, the results of the new cardiovascular-outcomes trial (to be completed in 2021) will be important for excluding an increased risk of cardiovascular events in patients receiving NB.

The NMA compared proportions of patients discontinuing treatment due to AE between NB, orlistat, and liraglutide. No evidence for a difference between NB and either comparator was reported for this outcome.

Conclusions

The pivotal trials demonstrated that NB results in greater weight loss versus placebo in adult patients who have obesity (BMI of at least 30 kg/m^2) or overweight (BMI of at least 27 kg/m^2) in the presence of at least one weight-related comorbidity. Whether this greater weight loss, measured as percent change in weight and percentage of patients who achieve at least 5% weight loss, translates to a clinically meaningful benefit is unclear, given that improvement in, or prevention of, weight-related comorbidities was either not assessed in the trials or could not be statistically tested. No evidence was found for clinically meaningful benefits from NB over placebo in HRQoL or food craving, and other outcomes important to patients were not assessed.

Treatment discontinuation was common in the pivotal trials, often due to AEs. A limited subgroup of patients of the indicated population may achieve weight loss that they find satisfactory with NB when balanced against AEs, but there are no predictive markers for identifying these patients prior to initiating treatment. There was insufficient evidence to demonstrate maintenance of weight loss with NB past one year of treatment, which is a major limitation considering the progressive nature of the disease and the expectation that patients will remain on the treatment indefinitely.

The most common AEs associated with NB in the pivotal trials were gastrointestinal and nervous disorders that are generally considered manageable. The LIGHT study was designed to rule out the possibility of increased risk of major adverse cardiovascular outcomes with NB treatment based on higher pulse rate and blood pressure associated with NB in the pivotal trials, but conclusions could not be drawn due to its early termination. Until results are available from a planned second cardiovascular-outcomes study, the potential cardiovascular harms associated with NB remain uncertain.

The one available NMA found no evidence for a difference in weight loss or discontinuations due to AE between NB and orlistat and liraglutide, the other available pharmacotherapies for weight management.

Appendix 1: Literature Search Strategy

OVERVIEW	
Interface:	Ovid
Databases:	MEDLINE All (1946–present) Embase (1974–present) **Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	May 30, 2019
Alerts:	Biweekly search updates until project completion
Study Types:	No publication type filters were applied.
Limits:	Publication date limit: none Language limit: none Conference abstracts: excluded

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical Subject Heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
.ti	Title
.ab	Abstract
.hw	Heading word; usually includes subject headings and controlled vocabulary
.kf	Author keyword heading word (MEDLINE)
.kw	Author keyword (Embase)
.pt	Publication type
.ot	Original title (MEDLINE)
.rn	Registry number
.dq	Candidate term word (Embase)
medall	Ovid database code: MEDLINE All, 1946 to present, updated daily
oemezd	Ovid database code; Embase, 1974 to present, updated daily

MULTI-DATABASE STRATEGY	
Line #	**Search Strategy**
1	(Contrave or Mysimba*).ti,ab,kf,ot,hw,rn,nm.
2	Bupropion/
3	(bupropion* or amfebutamon* or bupropin* or buproprion* or budeprion* or buprion* or buproban* or wellbutrin* or wellbatrin* or aplenzin* or zyban* or buxon* or odranal* or quomen* or forfivo* or elontril* or prexaton* or voxra* or BW 323* or BW323* or NSC 315851 or NSC315851 or BRN 2101062 or BRN2101062 or ZG7E5POY8O or 01ZG3TPX31).ti,ab,kf,ot,hw,rn,nm.
4	or/2-3
5	Naltrexone/
6	(Depade* or naltrexon* or nalerona* or nalorex* or naltrel* or ReVia* or re via or antaxon* or celupan* or nemexin* or nodict* or nutrexon* or phaltrexia* or regental* or revez or trexan* or vivitrex* or vivitrol* or adepend* or narcoral* or BRN 3596648 or BRN3596648 or EN 1639 A or EN 1639A or EN1639A or NIH 8503 or NIH8503 or PTI 901 or PTI901 or UM 792 or UM792 or Z6375YW9SF or 5S6W795CQM).ti,ab,kf,ot,hw,rn,nm.
7	or/5-6
8	4 and 7
9	1 or 8
10	9 use medall
11	*amfebutamone plus naltrexone/
12	(Contrave or Mysimba*).ti,ab,kw,dq.
13	or/11-12
14	*amfebutamone/
15	(bupropion* or amfebutamon* or bupropin* or buproprion* or budeprion* or buprion* or buproban* or wellbutrin* or wellbatrin* or aplenzin* or zyban* or buxon* or odranal* or quomen* or forfivo* or elontril* or prexaton* or voxra* or BW 323* or BW323* or NSC 315851 or NSC315851 or BRN 2101062 or BRN2101062).ti,ab,kw,dq.
16	or/14-15
17	*naltrexone/
18	(Depade* or naltrexon* or nalerona* or nalorex* or naltrel* or ReVia* or re via or antaxon* or celupan* or nemexin* or nodict* or nutrexon* or phaltrexia* or regental* or revez or trexan* or vivitrex* or vivitrol* or adepend* or narcoral* or BRN 3596648 or BRN3596648 or EN 1639 A or EN 1639A or EN1639A or NIH 8503 or NIH8503 or PTI 901 or PTI901 or UM 792 or UM792).ti,ab,kw,dq.
19	or/17-18
20	16 and 19
21	13 or 20
22	21 use oemezd
23	22 not conference abstract.pt.
24	10 or 23
25	remove duplicates from 24

CLINICAL TRIAL REGISTRIES	
ClinicalTrials.gov	Produced by the US National Library of Medicine. Targeted search used to capture registered clinical trials. [Search -- Studies with results | contrave OR Mysimba OR (Naltrexone and Bupropion)]
WHO ICTRP	International Clinical Trials Registry Platform, produced by the World Health Organization. Targeted search used to capture registered clinical trials. [Search terms – contrave OR Mysimba OR (Naltrexone and Bupropion)]

OTHER DATABASES	
PubMed	Searched to capture records not found in MEDLINE. Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used.

Grey Literature

Dates for Search:	May 20, 2019 to May 27, 2019
Keywords:	[Contrave, Mysimba, (Naltrexone and Bupropion), obesity, and weight]
Limits:	Publication years: all years

Relevant websites from the following sections of the CADTH grey literature checklist, *Grey matters: a practical tool for evidence-based searching* (http://www.cadth.ca/en/resources/finding-evidence-is/grey-matters) were searched:

- Health Technology Assessment Agencies
- Health Economics
- Clinical Practice Guidelines
- Drug and Device Regulatory Approvals
- Advisories and Warnings
- Drug Class Reviews
- Clinical Trial Registries
- Databases (free)
- Health Statistics
- Internet Search
- UpToDate.

Appendix 2: Excluded Studies

Table 32: Excluded Studies

Reference	Reason for exclusion
Dalton M, Finlayson G, Walsh B, Halseth AE, Duarte C, Blundell JE. Early improvement in food cravings are associated with long-term weight loss success in a large clinical sample. Int J Obes. 2017;41(8):1232-1236.	Irrelevant study design (pooled analysis)
Fujioka K, Plodkowski R, O'Neil PM, Gilder K, Walsh B, Greenway FL. The relationship between early weight loss and weight loss at 1 year with naltrexone ER/bupropion ER combination therapy. Int J Obes. 2016;40(9):1369-1375.	Irrelevant study design (pooled analysis)
Halseth A, Shan K, Gilder K, Malone M, Acevedo L, Fujioka K. Quality of life, binge eating and sexual function in participants treated for obesity with sustained release naltrexone/bupropion. Obes. 2018;4(2):141-152.	Irrelevant comparator
Halseth A, Shan K, Walsh B, Gilder K, Fujioka K. Method-of-use study of naltrexone sustained release (SR)/bupropion SR on body weight in individuals with obesity. Obesity (Silver Spring). 2017;25(2):338-345.	Irrelevant comparator
Hong K, Herrmann K, Dybala C, Halseth AE, Lam H, Foreyt JP. Naltrexone/Bupropion extended release-induced weight loss is independent of nausea in subjects without diabetes. Clin. 2016;6(5):305-312.	Irrelevant study design (pooled analysis)
Kolotkin RL, Chen S, Klassen P, Gilder K, Greenway FL. Patient-reported quality of life in a randomized placebo-controlled trial of naltrexone/bupropion for obesity. Clin. 2015;5(5):237-244.	Irrelevant study design (pooled analysis)

Appendix 3: Detailed Outcome Data

Table 33: Subgroup Analyses for Mean Body Weight, kg (Co-Primary End Point in Pivotal Trials)

	COR-I Full analysis set		COR-II Full analysis set		COR-BMOD Full analysis set		COR-DM Full analysis set	
	PL	NB	PL	NB	PL	NB	PL	NB
BMI SUBGROUPS								
< MEDIAN BMI	N = 244	N = 228	N = 223	N = 412	N =83	N = 221	N = 67	N = 114
Baseline (SD)	90.76 (10.58)	89.88 (10.61)	88.74 (10.80)	89.79 (10.71)	90.66 (8.38)	90.25 (10.62)	93.31 (11.70)	94.10 (13.43)
Week 28 (SD)			86.93 (11.08)	83.50 (12.32)				
Week 56 (SD)	89.52 (11.62)	84.01 (12.22)			84.90 (10.10)	81.22 (12.37)	91.87 (11.80)	89.59 (14.16)
LSM % change (SE)	–1.38 (0.43)	–6.55 (0.45)	–1.96 (0.39)	–7.15 (0.29)	–6.25 (0.90)	–10.06 (0.55)	–1.48 (0.63)	–4.85 (0.48)
LSM difference in % change, NB vs. PL (95% CI)	–5.16 (–6.38 to –3.95) P < 0.001		–5.19 (–6.15 to –4.23) P < 0.001		–3.81 (–5.89 to –1.73) P < 0.001		–3.38 (–4.94 to –1.82) P < 0.001	
≥ MEDIAN BMI	N = 267	N = 243	N = 233	N = 413	N = 110	N = 261	N = 92	N = 151
Baseline (SD)	107.09 (12.79)	109.81 (14.65)	109.39 (13.38)	111.55 (14.26)	110.39 (13.30)	109.54 (13.18)	113.49 (15.39)	115.61 (17.51)
Week 28 (SD)			107.05 (14.04)	104.86 (15.49)				
Week 56 (SD)	105.82 (13.88)	103.71 (16.10)			105.05 (16.14)	99.32 (16.21)	111.15 (16.18)	109.56 (18.89)
LSM % change (SE)	–1.14 (0.39)	–5.63 (0.41)	–2.10 (0.35)	–6.11 (0.26)	–5.00 (0.79)	–9.44 (0.52)	–2.05 (0.57)	–5.38 (0.45)
LSM difference in % change, NB vs. PL (95% CI)	–4.49 (–5.61 to –3.37) P < 0.001		–4.00 (–4.86 to –3.15) P < 0.001		–4.43 (–6.30 to –2.57) P < 0.001		–3.33 (–4.77 to –1.89) P < 0.001	
Treatment-by-subgroup interaction	P = 0.673		P = 0.074		P = 0.641		P = 0.941	
HYPERTENSION SUBGROUPS								
PRESENT	N = 101	N = 110	N = 98	N = 178	N = 37	N = 76	N = 97	N = 166
Baseline (SD)	100.34 (15.17)	105.76 (17.89)	100.62 (17.87)	103.98 (18.79)	99.19 (19.31)	102.37 (17.52)	105.41 (16.75)	108.00 (19.19)
Week 28 (SD)			98.11 (17.59)	97.56 (19.34)				
Week 56 (SD)	97.92 (16.64)	98.97 (18.18)			92.76 (19.89)	92.32 (20.08)	103.20 (17.01)	102.78 (19.61)
LSM % change (SE)	–2.45 (0.62)	–6.43 (0.59)	–2.38 (0.52)	–6.33 (0.39)	–6.14 (1.26)	–10.43 (0.88)	–2.06 (0.54)	–4.90 (0.41)
LSM difference in % change, NB vs. PL (95% CI)	–3.98 (–5.68 to –2.29) P < 0.001		–3.95 (–5.23 to –2.68) P < 0.001		–4.29 (–7.34 to –1.25) P = 0.006		–2.84 (–4.19 to –1.50) P < 0.001	
ABSENT	N = 410	N = 361	N = 358	N = 647	N = 156	N = 406	N = 62	N = 99
Baseline (SD)	99.03 (14.12)	98.46 (15.36)	98.93 (15.42)	99.78 (15.91)	102.55 (13.84)	100.38 (15.01)	104.32 (17.82)	103.60 (18.76)
Week 28 (SD)			96.96 (15.79)	93.26 (17.00)				

	COR-I Full analysis set		COR-II Full analysis set		COR-BMOD Full analysis set		COR-DM Full analysis set	
Week 56 (SD)	98.06 (14.85)	92.71 (16.91)			97.24 (16.29)	90.78 (16.54)	102.76 (17.96)	97.94 (19.48)
LSM % change (SE)	–0.96 (0.33)	–5.96 (0.35)	–1.96 (0.30)	–6.70 (0.22)	–5.37 (0.67)	–9.60 (0.42)	–1.47 (0.69)	–5.54 (0.54)
LSM difference in % change, NB vs. PL (95% CI)	–4.99 (–5.93 to –4.05) P < 0.001		–4.75 (–5.48 to –4.01) P < 0.001		–4.23 (–5.78 to –2.67) P < 0.001		–4.07 (–5.80 to –2.33) P < 0.001	
Treatment-by-subgroup interaction	P = 0.395		P = 0.355		P = 0.981		P = 0.270	
DYSLIPIDEMIA SUBGROUPS								
PRESENT	N = 253	N = 244	N = 244	N = 460	N = 77	N = 234	N = 136	N = 219
Baseline (SD)	100.04 (15.07)	100.71 (16.75)	100.00 (17.04)	101.40 (17.59)	101.99 (16.00)	101.24 (16.82)	103.83 (16.10)	107.28 (19.02)
Week 28 (SD)			97.76 (17.37)	94.85 (18.40)				
Week 56 (SD)	98.14 (15.99)	94.22 (17.37)			95.18 (18.35)	90.74 (18.01)	101.77 (16.20)	101.80 (19.58)
LSM % change (SE)	–1.94 (0.39)	–6.46 (0.40)	–2.20 (0.35)	–6.65 (0.26)	–6.82 (0.96)	–10.49 (0.55)	–1.91 (0.45)	–5.20 (0.36)
LSM difference in % change, NB vs. PL (95% CI)	–4.52 (–5.61 to –3.43) P < 0.001		–4.45 (–5.31 to –3.59) P < 0.001		–3.66 (–5.84 to –1.49) P = 0.001		–3.29 (–4.42 to –2.16) P < 0.001	
ABSENT	N = 258	N = 227	N = 212	N = 365	N = 116	N = 248	N = 23	N = 46
Baseline (SD)	98.55 (13.54)	99.58 (15.74)	98.49 (14.64)	99.79 (15.37)	101.85 (14.44)	100.17 (14.01)	111.83 (21.45)	101.96 (19.12)
Week 28 (SD)			96.58 (14.71)	93.36 (16.54)				
Week 56 (SD)	97.93 (14.43)	94.12 (17.46)			97.18 (16.20)	91.29 (16.30)	110.43 (21.88)	97.00 (19.81)
LSM % change (SE)	–1.94 (0.39)	–6.46 (0.40)	–1.86 (0.39)	–6.59 (0.30)	–4.73 (0.75)	–8.98 (0.51)	–1.39 (1.27)	–4.86 (0.89)
LSM difference in % change, NB vs. PL (95% CI)	–5.11 (–6.34 to –3.87) P < 0.001		–4.73 (–5.70 to –3.77) P < 0.001		–4.25 (–6.05 to –2.46) P < 0.001		–3.48 (–6.61 to –0.34) P = 0.030	
Treatment-by-subgroup interaction	P = 0.124		P = 0.644		P = 0.667		P = 0.887	

BMI = body mass index; CI = confidence interval; LSM = least squares mean; NA = not applicable; NB = naltrexone and bupropion; PL = placebo; SD = standard deviation; SE = standard error; vs. = versus.

Note: The full analysis set included patients who were randomized, had a baseline weight measurement, and had at least one post-baseline weight measurement while on study drug. The last observation carried forward approach used observations made while on treatment (up to one day after last confirmed dose of study medication). An analysis of covariance model was used that included treatment, baseline weight, subgroup, and treatment-by-subgroup interaction.

Source: Clinical Study Reports for the COR-I, COR-II, COR-BMOD, and COR-DM studies.[17-20]

Table 34: Subgroup Analyses for Percentage of Patients With a ≥ 5% Decrease in Body Weight From Baseline to End Point (Co-Primary End Point in Pivotal Trials)

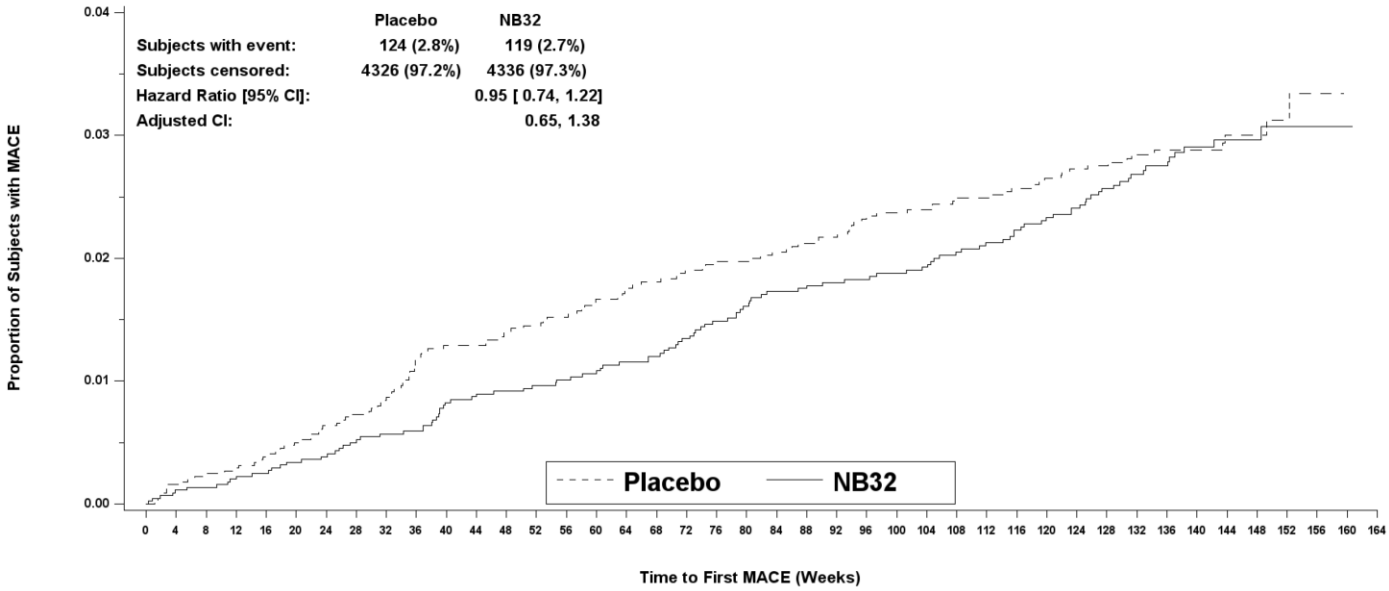
	COR-I Full analysis set		COR-II Full analysis set		COR-BMOD Full analysis set		COR-DM Full analysis set	
	PL	**NB**	**PL**	**NB**	**PL**	**NB**	**PL**	**NB**
BMI subgroups							N = 67	N = 114
< median BMI	N = 244	N = 228	N = 223	N = 412	N = 83	N = 221		
Patients, n (%)	37 (15.2)	117 (51.3)	38 (17.0)	232 (56.3)	39 (47.0)	149 (67.4)	9 (13.4)	48 (42.1)
Odds ratio, NB vs. PL (95% CI)	5.87 (3.79 to 9.08) P < 0.001		6.44 (4.31 to 9.63) P < 0.001		2.35 (1.41 to 3.94) P = 0.001		4.70 (2.12 to 10.41) P < 0.001	
≥ median BMI	N = 267	N = 243	N = 233	N = 413	N = 110	N = 261	N = 92	N = 151
Patients, n (%)	47 (17.6)	109 (44.9)	42 (18.0)	227 (55.0)	43 (39.1)	171 (65.5)	21 (22.8)	70 (46.4)
Odds ratio, NB vs. PL (95% CI)	3.86 (2.57 to 5.79) P < 0.001		5.78 (3.91 to 8.54) P < 0.001		2.95 (1.86 to 4.68) P < 0.001		3.07 (1.70 to 5.54) P < 0.001	
Treatment-by-subgroup interaction	P = 0.370		P = 0.716		P = 0.503		P = 0.369	
Hypertension subgroups								
Present	N = 101	N = 110	N = 98	N = 178	N = 37	N = 76	N = 97	N = 166
Patients, n (%)	25 (24.8)	57 (51.8)	17 (17.4)	99 (55.6)	14 (37.8)	54 (71.1)	15 (15.5)	74 (44.6)
Odds ratio, NB vs. PL (95% CI)	3.43 (1.89 to 6.21) P < 0.001		6.39 (3.47 to 11.77) P < 0.001		4.32 (1.85 to 10.1) P < 0.001		4.44 (2.36 to 8.36) P < 0.001	
Absent	N = 410	N = 361	N = 358	N = 647	N = 156	N = 406	N = 62	N = 99
Patients, n (%)	59 (14.4)	169 (46.8)	63 (17.6)	360 (55.6)	68 (43.6)	266 (65.5)	15 (24.2)	44 (44.4)
Odds ratio, NB vs. PL (95% CI)	5.23 (3.70 to 7.38) P < 0.001		5.93 (4.33 to 8.12) P < 0.001		2.44 (1.67 to 3.56) P < 0.001		2.50 (1.24 to 5.06) P = 0.011	
Treatment-by-subgroup interaction	P = 0.165		P = 0.907		P = 0.254		P = 0.276	
Dyslipidemia subgroups								
Present	N = 253	N = 244	N = 244	N = 460	N = 77	N = 234	N = 136	N = 219
Patients, n (%)	43 (17.0)	127 (52.1)	43 (17.6)	265 (57.6)	36 (46.8)	165 (70.5)	27 (19.9)	102 (46.6)
Odds ratio, NB vs. PL (95% CI)	5.34 (3.53 to 8.07) P < 0.001		6.55 (4.48 to 9.59) P < 0.001		2.72 (1.60 to 4.62) P < 0.001		3.61 (2.19 to 5.96) P < 0.001	
Absent	N = 258	N = 227	N = 212	N = 365	N = 116	N = 248	N = 23	N = 46
Patients, n (%)	41 (15.9)	99 (43.6)	37 (17.5)	194 (53.2)	46 (39.7)	155 (62.5)	3 (13.0)	16 (34.8)
Odds ratio, NB vs. PL (95% CI)	4.13 (2.70 to 6.32) P < 0.001		5.40 (3.58 to 8.15) P < 0.001		2.52 (1.60 to 3.97) P < 0.001		3.66 (0.91 to 14.68) P = 0.067	
Treatment-by-subgroup interaction	P = 0.498		P = 0.544		P = 0.826		P = 0.983	

BMI = body mass index; CI = confidence interval; NB = naltrexone and bupropion; PL = placebo; vs. = versus.

Note: The full analysis set included patients who were randomized, had a baseline weight measurement, and had at least one post-baseline weight measurement while on study drug. The last observation carried forward approach used observations made while on treatment (up to one day after last confirmed dose of study medication). The end point was week 56 for the COR-I, COR-BMOD, and COR-DM studies and week 28 for the COR-BMOD study. A logistic regression model was used that included treatment, subgroup, baseline body weight, and treatment-subgroup interaction.

Source: Clinical Study Reports for the COR-I, COR-II, COR-BMOD, and COR-DM studies.[17-20]

Figure 3: Kaplan-Meier Plot of Time to First Occurrence of MACE (Primary End Point in LIGHT Study)



CI = confidence interval; MACE = major adverse cardiovascular event; NB32 = naltrexone 32 mg/bupropion 360 mg daily.

Source: Clinical Study Report for the LIGHT study.[27]

Table 35: Subgroup Analyses for Time to First Occurrence of MACE (Primary End Point in LIGHT Study)

	ITT set	
	PL N = 4,450	**NB N = 4,455**
CV risk subgroups		
CV disease without type 2 diabetes	N = 646	N = 670
Patients with MACE (first occurrence), n (%)	32 (5.0)	27 (4.0)
Adjusted hazard ratio, NB vs. PL (95% CI)	0.80 (0.48 to 1.34)	
CV disease with type 2 diabetes	N = 801	N = 745
Patients with MACE (first occurrence), n (%)	53 (6.6)	42 (5.6)
Adjusted hazard ratio, NB vs. PL (95% CI)	0.81 (0.54 to 1.22)	
Type 2 diabetes without CV disease	N = 3,001	N = 3,039
Patients with MACE (first occurrence), n (%)	39 (1.3)	50 (1.6)
Adjusted hazard ratio, NB vs. PL (95% CI)	1.27 (0.83 to 1.93)	
Treatment-by-subgroup interaction	P = 0.2416	
BMI subgroups		
< 35 kg/m^2	N = 1,719	N = 1,692
Patients with MACE (first occurrence), n (%)	46 (2.7)	43 (2.5)

	ITT set	
Adjusted hazard ratio, NB vs. PL (95% CI)	0.96 (0.63 to 1.46)	
≥ 35 kg/m² to < 40 kg/m²	N = 1,383	N = 1,476
Patients with MACE (first occurrence), n (%)	33 (2.4)	35 (2.4)
Adjusted hazard ratio, NB vs. PL (95% CI)	0.94 (0.58 to 1.51)	
≥ 40 kg/m²	N = 1,348	N = 1,284
Patients with MACE (first occurrence), n (%)	45 (3.3)	41 (3.2)
Adjusted hazard ratio, NB vs. PL (95% CI)	0.99 (0.65 to 1.51)	
Treatment-by-subgroup interaction	P = 0.9869	

BMI = body mass index; CI = confidence interval; CV = cardiovascular; DM = diabetes mellitus; ITT = intention to treat; MACE = major adverse cardiovascular event; NB = naltrexone and bupropion; PL = placebo; vs. = versus.

Note: The Cox proportional hazards model included treatment, race grouping (white or non-white), sex, subgroup, and treatment-by-subgroup interaction as factors and age as a covariate. For the BMI subgroup analyses, CV risk group was also included as a factor. P values are provided for descriptive purposes only and are based on the likelihood ratio test for the model with and without the treatment-by-subgroup interaction term.

Source: Clinical Study Report for the LIGHT study.[27]

Table 36: Long-Term Change From Baseline in Body Weight Using PP Analysis (LIGHT Study)

	PP set	
	PL N = 4,253	**NB N = 4,286**
Mean body weight, kg		
Week 52	N = 1,119	N = 1,599
LSM % change (SE)	–3.85 (0.232)	–7.25 (0.216)
LSM difference in % change, NB vs. PL (95% CI)	–3.40 (–3.84 to –2.95)	
Week 78	N = 900	N = 1,332
LSM % change (SE)	–3.48 (0.279)	–6.75 (0.256)
LSM difference in % change, NB vs. PL (95% CI)	–3.27 (–3.80 to –2.73)	
Week 104	N = 741	N = 1,137
LSM % change (SE)	–3.50 (0.363)	–6.32 (0.332)
LSM difference in % change, NB vs. PL (95% CI)	–2.81 (–3.51 to –2.12)	
Week 130	N = 122	N = 195
LSM % change (SE)	–4.19 (0.894)	–6.26 (0.797)
LSM difference in % change, NB vs. PL (95% CI)	–2.08 (–3.78 to –0.37)	

CI = confidence interval; LSM = least squares mean; NB = naltrexone and bupropion; PL = placebo; PP = per protocol; SE = standard error; vs. = versus.

Note: The PP set included randomized patients who took at least one dose of study medication in the treatment period and did not have notable protocol deviations. Patients were censored after 30 days following treatment discontinuation.

Source: Clinical Study Report for the LIGHT study.[27]

Appendix 4: Description and Appraisal of Outcome Measures

Aim

To describe the following outcome measures in Table 37 and review their measurement properties (validity, reliability, responsiveness to change), and MID.

Table 37: Outcome Measures Included in Each Study

Outcome measure	COR-I NB-301	COR-II NB-303	COR-BMOD NB-302	COR-DM NB-304
Percent change in weight from baseline	Co-primary	Co-primary	Co-primary	Co-primary
IWQoL-Lite total score	Secondary	Secondary	Secondary	Secondary
21-item Control of Eating questionnaire item 19 (each of the 21 items for the COR-BMOD study)	Secondary	Secondary	Secondary	Secondary
Inventory of Depressive Symptomatology–Self-Report total score	Secondary	Secondary	Secondary	Secondary
Food Craving Inventory sweets subscale and carbohydrates/starches subscale scores	Secondary	Secondary	Secondary	Secondary
SF-36 MCS and PCS scores, individual item scores		Secondary		

IWQoL-Lite = Impact of Weight on Quality of Life – Lite; MCS = mental component summary; NB = naltrexone and bupropion; PCS = physical component summary; SF-36 = Short-Form (36) Health Survey.

Findings

Table 38: Summary of Outcome Measures and Their Measurement Properties

Outcome measure	Type	Conclusions about measurement properties	MID
Percent change in weight from baseline	Body weight was obtained at each study visit	Not identified	Not identified
Impact of Weight on Quality of Life – Lite version total score	Disease-specific measure of HRQoL 31-item self-administered 5-point Likert scale	Acceptable internal consistency has been demonstrated in adults who have overweight or obesity seeking treatment and with diabetes, as well as individuals in the community. Acceptable test-retest reliability has been demonstrated in the community population. There is evidence of convergent validity of total score and the physical function and work subscale scores with BMI and other quality of life scales. There is acceptable evidence of responsiveness to change. A range of MIDs was established in patients participating in weight loss trials.	MID for improvement ranges from 7.7 to 12, depending on baseline score
21-item Control of Eating questionnaire item 19: “Generally, how difficult has it been to	Disease-specific measure of HRQoL	For adults who are overweight or obese in the community, there is some evidence of acceptable internal consistency for two of the four subscales, and some evidence of	Not identified

Outcome measure	Type	Conclusions about measurement properties	MID
control your eating?”	Single item of a 21-item questionnaire Visual Analogue Scale	construct validity. No evidence for an MID or responsiveness to change was found. The validity administering a single question of the COEQ as a study end point is unclear.	
Inventory of Depressive Symptomatology – Subject-Rated total score	Severity of symptoms of depression 30-item self-administered 3-point Likert scale	The IDS-SR has been validated in numerous studies and has been shown to measure depression in a manner consistent with the most widely used assessments, including the commonly used depression-rating scales. For adults who are overweight or obese, no information about the psychometric properties of the IDS-SR was found. No evidence for an MID was found.	Not identified.
Food Craving Inventory sweets subscale and carbohydrates/starches subscale scores	Severity of food craving 28 item self-administered 5-point Likert scale	For adults who are overweight or obese in the community, there is evidence of acceptable internal consistency, and evidence of content validity and convergent validity. For individuals with binge-eating disorder seeking treatment, there is evidence for acceptable internal consistency. No evidence for an MID or responsiveness to change was found. The impact of the additional items to the original 28-item FCI on the on the psychometric properties of the FCI are unclear.	Not identified.
Short-Form (36) Health Survey	Generic measure of HRQoL	For adults who are overweight or obese in the community, there is some evidence of validity, for the PCS and MCS; however, the validity of the subscales in this population has not been confirmed.	General (non–disease-specific) MID: 2 points in PCS; 3 points in MCS; 2 to 4 points for individual dimensions. An MID was not identified for adults who have overweight or obesity.

BMI = body mass index; HRQoL = health-related quality of life; IDS-SR – Inventory of Depressive Symptoms – Subject-Rated; MCS = mental component summary; MID = minimal important difference; PCS = physical component summary.

Percent Change in Weight

The four pivotal phase III trials for NB have end points that all describe weight loss (percent body weight loss, percentage of patients with greater than 5% and greater than 10% weight loss). As these measures are all related, the validity of these outcomes will be discussed together.

The FDA and the EMA require a primary end point of reduction in body weight, both as absolute and relative weight loss for regulatory approval for a weight management product.[29,30] Both agencies consider a 5% or greater loss of body weight (placebo-adjusted

and statistically significant) after one year of treatment to be an appropriate criterion that supports an indication for weight management.[29,30]

Weight loss is a surrogate for other expected clinical benefits, such as morbidity and mortality. Loss of excess body fat is expected to cause biochemical changes, such as improved blood pressure, lipid profile, and glycemic indices, which in turn would be expected to reduce morbidity and mortality.[29]

However, metabolic risk factors, such as blood pressure, lipid profile, and glycemic indices are themselves surrogate end points for the morbidity and mortality outcomes that are of greater interest. This assessment of the benefit of weight loss focuses on mortality, cardiovascular morbidity, prevention of type 2 diabetes, and HRQoL.

A summary of a literature search for systematic reviews of RCTs for non-surgical interventions for weight loss and reporting mortality, cardiovascular morbidity, HRQoL and onset of type 2 diabetes is presented. Systematic reviews of RCTs of surgical interventions were excluded due to the highly selected patient population, poor generalizability to the Canadian adult population with excess weight or obesity, and magnitude of weight loss. Epidemiologic studies were excluded due to risk of bias.

Weight Loss, Mortality, and Cardiovascular Morbidity

A 2019 systematic review and meta-analysis of studies assessed the impact of pharmacologic weight loss on cardiovascular morbidity and mortality in adults who have overweight or obesity.[62] Included studies for screening were published in peer-reviewed journals, were prospective or retrospective studies, and had quantitative data on the end points listed; however, all non-RCTs were excluded. Medications included orlistat, lorcaserin, NB, PT, and liraglutide, and controls included placebo alone, hypocaloric diet alone, hypocaloric diet with moderate exercise, placebo plus a hypocaloric diet, placebo plus maintenance diet, and placebo with an internet-based program including diet and exercise.[62] There was no requirement for study length. The systematic review found seven trials (N = 18,598; with 8,685 in intervention groups and 9,913 in control groups) that included outcomes of cardiovascular risk factors, cardiovascular morbidity, and mortality, and allowed for meta-analysis.[62] When RCTs compared pharmacologic weight-loss interventions to controls, there was a statistically significant reduction in percentage of weight lost (Hedges' g of 0.43; 95% CI, –0.48 to –0.39; P < 0.001); however, the duration of studies and time frame of end-point assessment were not reported. The percentage of weight lost by intervention and control groups was not reported.[62] The meta-analysis found no significant difference in all-cause mortality between patients receiving pharmacologic weight-loss interventions and patients in control groups.[62] There was a statistically significant reduction in cardiovascular mortality on meta-analysis.[62] There were 17 and 36 cardiovascular deaths in the pharmacologic weight-loss intervention and control groups, respectively, with a pooled odds ratio of 0.50 (95% CI, 0.28 to 0.87; P = 0.015).[62] A major limitation in the interpretation of the effect size is the extremely low event rates for cardiovascular mortality observed in the trials.

A US Preventive Services Task Force systematic review and meta-analysis was published in 2018 of RCTs of the effects of weight loss or weight maintenance on morbidity, mortality, HRQoL, weight loss, and AEs.[63] Included RCTs were of primary care-relevant interventions (behaviour-based interventions or pharmacologic interventions, including orlistat, lorcaserin, NB, PT, and liraglutide).[63] Controls in behaviour-based interventions had no intervention, minimal intervention (usual care, quarterly counselling, or generic brochures) or were

attention controls with different content to intervention.[63] Controls in pharmacologic trials were all placebos with the same behaviour-based intervention.[63] All included RCTs had weight end points measured after at least 12 months of intervention. The systematic review excluded trials with patient populations with chronic diseases such as known cardiovascular disease or diabetes, for which weight loss is part of management.[63] With respect to RCTs of behavioural interventions, 38 (N = 12,231) were included in a meta-analysis that found that participants in behavioural intervention groups were more likely to achieve 5% weight loss from baseline at 12 to 18 months than controls (pooled risk ratio of 1.94; 95% CI, 1.70 to 2.22; I^2 = 67.2%).[63] For RCTs of pharmacologic interventions, 31 found that participants in pharmacologic intervention groups were more likely to have 5% weight loss from baseline compared with controls over a planned follow-up period of 12 to 48 months; however, pooled outcome data were not presented for each drug or overall. The percentage of weight lost by intervention and control groups was not reported for behaviour or pharmacologic RCTs.[63] Data for health outcomes had a limited number of contributing studies and variability in outcomes, which did not allow for meta-analysis. Four trials (N = 4,442) reported mortality; however, no trial found a significant difference between intervention and control groups over a follow-up of two to 16 years.[64-71] Two RCTs assessed the impact of weight loss on cardiovascular events (N = 2,666); however, neither trial found a significant difference between intervention and control groups over a follow-up period of three or 10 years.[65,66,69,70]

A 2017 systematic review and meta-analysis of RCTs assessed the impact of dietary interventions with or without exercise with a follow-up of at least one year in adults who have overweight or obesity.[72] Included RCTs were of diet with or without advice for activity and/or provision of a physical activity program to attend compared to a control and reported data on all-cause, cardiovascular, and cancer mortality, cardiovascular disease, cancer, and body weight.[72] The review included 54 RCTs (N = 30,206) in total, with a follow-up range from 12 to 152 months.[72] The percentage of weight lost by intervention and control groups was not reported.[72] For all-cause mortality, there were 34 trials (N = 11,266 intervention and 10,433 controls, with a follow-up range from 12 to 152 months) (rated with GRADE as high-quality evidence), with 311 and 374 all-cause mortality events in the intervention and control groups, respectively (risk ratio of 0.82; 95% CI, 0.71 to 0.95; I^2 = 0%).[72] The LOOK AHEAD trial[73] accounted for more than 50% of the weighting in the meta-analysis; however, a significant effect on all-cause mortality was maintained without this trial in the analysis.[72] There were no statistically significant differences between intervention and control groups for cardiovascular mortality, cancer mortality (moderate quality evidence), new cardiovascular events (high-quality evidence) or new cancers (low-quality evidence).[72]

A 2016 systematic review and meta-analysis of RCTs assessed the impact of intentional weight loss through lifestyle interventions on all-cause mortality.[74] Included RCTs that randomized patients to lifestyle interventions (weight loss versus non-weight loss, weight loss plus co-intervention such as exercise, or weight-stable co-intervention such as exercise alone) had a duration of at least 18 months and reported all-cause mortality by study arm.[74] The percentage of weight lost by intervention and control groups was not reported.[74] Deaths were reported as outcomes in three trials, and as AEs in the remaining trials.[74] The meta-analysis for mortality included 12 RCTs (N = 17,186; length of intervention ranged from six to 48 months and follow-up ranged from 18 to 152 months) with 264 and 310 deaths in the intervention and control groups, respectively (relative risk of 0.85; 95% CI, 0.73 to 1.00; I^2 = 0%).[74] The LOOK AHEAD trial contributed to 65.5% of the

total deaths;[73] without this data the summary estimate for relative risk was not statistically significant.[74]

Weight Loss and Diabetes Prevention

The US Preventive Services Task Force systematic review (methods described in the previous section) found nine RCTs (N= 3,140, with a planned follow-up duration ranging from 12 to 108 months) that assessed the impact of weight loss on prevention of type 2 diabetes in patients over follow-up from one to nine years. The percentage of weight lost by intervention and control groups was not reported. The meta-analysis found the risk ratio for type 2 diabetes onset in the intervention group versus the control group was 0.67 (95% CI, 0.51 to 0.89; I^2 = 49.2%). The majority of these trials included patients with impaired fasting glucose.[63]

Weight Loss and Quality of Life

The US Preventive Services Task Force systematic review found 17 behaviour-based weight-loss and weight-maintenance trials that reported HRQoL (N = 7,120) with planned follow-up from 12 to 38 months.[63] Data heterogeneity did not allow for meta-analysis. However, 14 of these 17 trials found no statistical difference on any HRQoL measure.[63] Of the three trials that did find a difference between groups on HRQoL, the observed differences were only for some components of HRQoL measures, and were generally of small magnitude.[63] The systematic review found 10 trials (N = 13,145, with planned follow-up of 12 to 36 months) of medications for weight loss that reported weight-related HRQoL; most of the trials observed improvements in HRQoL compared to placebo.[63] However, the magnitude of the differences was generally small and challenging to interpret given high dropout rates in the RCTs.[63]

A systematic review of reviews to assess the impact of weight loss on HRQoL published in 2017 found four meta-analyses and systematic reviews that assessed HRQoL after non-surgical weight loss (two from RCTs and two from varied intervention or study design).[75] These studies found that HRQoL improved after weight loss, but the relationship was inconsistent.[75] The most recent meta-analyses of RCTs, published in 2014, assessed the effect of weight loss on HRQoL in 53 RCTs of any non-surgical weight-loss intervention with 20 HRQoL instruments and study durations from eight weeks to three years.[76] Seventeen studies reported statistically significant weight loss and HRQoL improvement; however, no statistically significant relationship between weight loss and improvement in HRQoL were found (using contingency tables).[76] Poor reporting limited data pooling, but trials that included SF-36 data found statistically significant improvement in physical health (n = 6 trials) and physical functioning (n = 7 trials), but not mental health.[76]

In addition to the RCT evidence summarized above, results from one epidemiology study are included in this section as the results are specific to the Canadian context and relate to clinically meaningful changes in HRQoL, an outcome identified in the patient input as important to patients with excess weight or obesity. A Canadian study of 500 obese patients (BMI of 47.9 of kg/m^2) receiving medical treatment, waiting for surgery, or having experienced weight loss surgery followed for a two-year period sought to assess weight loss and HRQoL.[77] The study evaluated the SF-12 PCS using a MID of 5 and MCS, EuroQol 5-Dimensions (EQ-5D) index (MID = 0.03) VAS (MID = 10), and Impact of Weight on Quality of Life – Lite (IWQoL-Lite) total score (MID = 12) to estimate the amount of weight loss required to achieve the HRQoL MIDs.[77] After a two-year follow-up, a total of 17%, 32%, and 75% of patients in the wait-listed, medically managed, and surgically

treated groups, respectively, lost at least 5% of their initial body weight.[77] Similarly, 9%, 17%, and 63% lost at least 10% of their initial body weight in the wait-listed, medically managed, and surgically treated groups, respectively (P < 0.001 for all).[77] In the wait-listed, medically managed, and surgically treated groups, the MID for the SF-36 PCS score was reached in 23%, 46%, and 54% of patients, and the MID for the SF-12 MCS score was reached for 28%, 42%, and 30%, respectively.[77] The MID for the EQ-5D VAS was reached for 37%, 50%, and 56% of the wait-listed, medically managed, and surgically treated groups.[77] Finally, the MID for the IWQoL-Lite total score was reached for 21%, 49%, and 76% of the wait-listed, medically managed, and surgically treated groups.[77] The study performed instrument-specific multivariable linear regression models (adjusted for age, sex, study arm, baseline BMI, and HRQoL score) to determine the association between two-year change in weight and HRQoL score; a weight-change model coefficient was used to calculate the weight loss required to achieve HRQoL MIDs. The estimated amounts of weight loss required to achieve the HRQoL MIDs for each instrument were 23% for the SF-12 PCS, 25% for the MCS, 9% for the EQ-5D, 23% for the EQ-5D VAS, and 17% for the IWQoL-Lite total score, and no MIDs were met with 5% weight loss.[77] The authors concluded that weight loss of 5% to 10% is insufficient to achieve clinically meaningful change in HRQoL.[77]

Summary

Although studies report that weight-loss interventions can result in weight loss, few meta-analyses report the proportion of patients achieving the percentage of the weight that was actually lost. Few studies have assessed the long-term impact of interventions for weight loss on all-cause and cardiovascular mortality or cardiovascular morbidity. Meta-analyses of RCTs of behavioural and pharmacologic interventions for weight loss did not find a significant reduction in all-cause mortality with weight-loss interventions; however, data for health outcomes had a limited number of contributing studies and variability in outcomes, which did not allow for meta-analysis.[63] One meta-analysis of pharmacologic interventions for weight loss did not find a significant reduction in all-cause mortality, but did observe a statistically significant reduction in cardiovascular mortality.[62] However, the number of events was small and few studies included long-term follow-up.[62] Two meta-analyses suggested that lifestyle weight-loss interventions may reduce all-cause mortality; although the results were driven by a single trial.[72,74] Several RCTs described a reduction in new type 2 diabetes with weight loss in patients with impaired glucose tolerance and obesity.[63] The changes in HRQoL associated with weight loss may not be clinically meaningful.[75,76]

Limitations to the 5% and 10% weight-loss outcome measures include the possibility that the physiological effects of lifestyle interventions such as exercise and diet may be responsible for the observed beneficial effects on physiological parameters. Weight loss of more than 10% is likely required to achieve clinically significant improvement in HRQoL.[77] These benefits may not be related to weight loss. In addition, it should not be assumed that weight-management drugs will have similar benefits unless demonstrated in clinical trials.

Impact of Weight on Quality of Life – Lite Questionnaire

The IWQoL-Lite questionnaire was a secondary end point in all four pivotal phase III RCTs for NB. It is a disease-specific questionnaire designed to assess the effect of obesity on quality of life.[31]

The IWQoL-Lite is the shorter version of the full 74-item Impact of Weight on Quality of Life questionnaire.[78,79] The full questionnaire measures areas of quality of life identified by

adults with moderate-to-severe obesity as those of greatest concern to them (health, social/interpersonal, work, mobility, self-esteem, sexual life, activities of daily living and comfort with food).[78,79] The IWQoL-Lite includes 31 self-administered items with five scales: self-esteem (seven items), sexual life (four items), physical function (11 items), public distress (five items), and work (four items).31 The items of the IWQoL-Lite begin with "Because of my weight…"; for example, "Because of my weight, I experience ridicule, teasing, or unwanted attention."[31] Five response options are provided for each item, ranging from "always true" (score of 5) to "never true" (score of 1).[31] The scale score is the sum of all the item scores, and all scale scores are added to create the total score. Total scores and scale scores on the IWQoL-Lite are transformed to a range from 0 to 100; with 100 being the best and a 0 being the poorest quality of life.[31] There is no specific recall period.[31] A literature search found one development and cross-validation study of the IWQoL-Lite in patients with obesity,[31] and four other publications that describe the psychometric properties of the scale in patients with obesity.[80-83]

In the development and cross-validation of the IWQoL-Lite, there was a total sample of 1,987 patients (mean BMI of 37 kg/m^2, 69% female).[31] Patients had participated in a variety of weight-loss interventions involving drugs (211 patients in an open-label trial of phentermine-fenfluramine), behaviour (834 patients with obesity from a day-treatment program and 668 patients from weight-reduction studies or programs), and surgery (51 patients who were undergoing gastric-bypass surgery for obesity); there were also 223 community participants without obesity.[31] Within the total sample, a group of patients or participants completed questionnaires; these data were used to create the IWQoL-Lite and a separate cross-validation sample of 991 patients.[31] In the development sample, the correlation between the full questionnaire and IWQoL-Lite scores was 0.97.[31] In the cross-validation sample, internal consistency, as measured by Cronbach's alpha, was acceptable (0.70 or higher[84]) for the subscale scores and the total score.[31]

In the same study, baseline BMI was moderately correlated85 with the scores for work (Pearson correlation coefficient R = 0.35), sexual life (R = 0.30), and self-esteem subscale (R = 0.34), and strongly correlated[85] with the physical functioning (R = 0.61) and public distress (R = 0.68) subscale scores, as well as the total score (R = 0.59).[31] Changes in the total IWQoL-Lite score and subscale scores, aside from the public distress score, were significantly correlated with change in the Rosenberg self-esteem scale.[31] Mean effect size for adjacent BMI categories (each spanning a range of ± 5 kg/m^2) ranged from 0.25 to 0.44 for the subscale score and total scores on the IWQoL-Lite.[31] Effect size between the extreme BMI categories (less than 25 kg/m^2 and greater than 40 kg/m^2) ranged from 0.97 to 1.76 for the subscale scores and total score.[31]

In another study that assessed the psychometric properties of the IWQoL-Lite questionnaire, a community-based sample of 492 individuals with overweight or obesity (mean BMI of 27.4 kg/m$^{2)}$ who were not undergoing weight-loss treatment completed the IWQoL-Lite.80 Convergent validity of the total score and subscale scores was assessed in individuals with a BMI of at least 25 kg/m^2 using BMI, the SF-36 (including the mental and physical component summary scores and each subscale score), the Rosenberg self-esteem scale, the Marlowe-Crowne social desirability scale, and ad hoc sexual-life and public-distress scales using items from the obesity quality of life instrument (OBQoL).[80] The IWQoL-Lite total score demonstrated strong correlations (R with a magnitude of over 0.50[85]) in the expected direction with BMI, the general health, vitality, and PCS scores of the SF-36, as well as the Rosenberg self-esteem score and the OBQoL-based measures.[80] The IWQoL-Lite total score was weakly correlated with the Marlowe-Crowne social

desirability score (magnitude of R between 0.10 and 0.30) and SF-36 role emotional score and moderately correlated with the rest of the measures (magnitude of R between 0.30 and 0.50).[80] The IWQoL-Lite physical function score was strongly correlated with the SF-36 physical functioning, role physical, bodily pain, general health, and PCS scores, moderately correlated with the SF-36 vitality and social functioning scores and OBQoL-based measures, and weakly correlated with the SF-36 mental MCS and role emotional scores.[80] The IWQoL-Lite work score was weakly correlated with the SF-36 role emotional score and the Marlowe-Crowne score and moderately correlated with the rest of the measures.[80] Internal consistency, as assessed with Cronbach's alpha, was acceptable for the IWQoL-Lite subscale and total scores. Test-retest reliability was evaluated an average of 14 days apart (SD of 0.7 days) in 112 individuals. Intraclass correlation coefficients for test-retest reliability ranged from 0.81 (public distress) to 0.88 (physical function) for the subscale scores, and 0.94 for the total score.[80] These measures of reliability are acceptable relative to the generally accepted threshold of 0.70 or higher.[84]

The content validity of the IWQoL-Lite was assessed through a study that compared it to the International Classification of Functioning, Disability and Health using the Delphi technique with 21 raters. This study found that content was compatible and had good content validity in English and French.[81]

In another validation study, IWQoL-Lite data were collected from 1,197 individuals with obesity (225 with type 2 diabetes) who were seeking weight-loss treatment and gastric-bypass surgery in a clinical trial to determine the impact of weight on quality of life and the psychometric properties of the IWQoL-Lite instrument.[82] This study found that internal consistency was acceptable[84] for the IWQoL-Lite total score and subscale scores in patients with and without diabetes.[82] To test the scale structure and construct validity, a confirmatory factor analysis was performed as part of the same study.[82] These results found that there was comparable factor structure for patients with and without diabetes.[82] Moderate-to-strong correlations[85] were found between BMI and IWQoL-Lite for both patients with and without diabetes; suggesting construct validity.[82] The correlation coefficient ranged from –0.545 (sexual life) to –0.737 (public distress) for IWQoL-Lite subscale scores and BMI, and was 0.705 for IWQoL-Lite total score and BMI among patients with diabetes.[82] The correlation coefficient ranged from −0.458 (sexual life) to −0.749 (public distress) for IWQoL-Lite subscale scores and BMI, and was 0.683 for IWQoL-Lite total score and BMI among patients without diabetes.[82]

An MID range was estimated for the IWQoL-Lite total score in patients with obesity.[83] Both anchor- and distribution-based methods were used to study 1,476 patients in weight-loss trials, and IWQoL-Lite total scores were compared at baseline and six months.[83] Patients were categorized according to baseline IWQoL-Lite total scores using a normative mean (calculated from a sample of 534 individuals with a BMI of 18 kg/m^2 to 29.9 kg/m^2 not enrolled in any weight-loss treatment program) for comparison.[83] The categories of baseline impairment were: none (less than one SD below the normative mean), mild (greater than or equal to one but less than two SDs from the normative mean), moderate (greater than or equal to two but less than three SDs from the normative mean), and severe (greater than three SDs from normative mean).[83] Standard error of measurement corrected for regression to the mean was used to evaluate the precision of the IWQoL-Lite using the Edwards-Nunnally approach to the distribution-based method.[83] The anchor-based method considered a 5% to 9.9% decrease in weight to represent improvement, and anything below this cut-off represented no change.[83] Discrepancies in the change in IWQoL-Lite score corresponding to improvement between the distribution-based and anchor-based methods

were resolved by selecting the greater of the two cut-offs for a given category of baseline impairment.[83] Greater quality-of-life change was observed with greater weight loss and more severe baseline quality-of-life impairments.[83] The MIDs for improvement were 7.7 to 7.8 for patients with no impairment at baseline (depending on exact baseline score), 7.9 to 8.1 for patients with mild impairment, 8.1 to 8.4 for patients with moderate impairment, and 12.0 for patients with severe impairment.[83] The MIDs for deterioration determined using the distribution-based method ranged from −7.8 to −4.4, depending on baseline severity of impairment.[83]

Food Craving Inventory

The FCI is a 28-item, self-administered questionnaire designed to assess specific food cravings.[37] A craving is defined as an intense desire to consume a particular food (or food type) that was difficult to resist.[37] This definition of craving specifically acknowledges the cognitive nature of craving and is distinct from hunger. The 28-item FCI is organized into four subscales (high fats, sweets, carbohydrates or starches, and fast-food fats).[37] Subjects rate the frequency of craving for each of the items using a five-point scale (1 = never, 2 = rarely, 3 = sometimes, 4 = often, and 5 = always or almost every day).[36] There is a one-month recall period.[36] The subscale and total scores are calculated by summing the relevant item scores, with higher scores indicating more cravings.[37]

The original 28-item FCI scale did not include cooked vegetables, fruit juices, raw vegetables, canned fruit, or raw fruit. However, the version used in the pivotal phase III RCTs for NB did; the effects of these items on the total scale score, subscale scores, and psychometric properties are unclear. No validation work was identified for the modified version of the scale that was used for the pivotal trials phase III RCTs for NB.

A psychometric study on the 28-item FCI was conducted in a community sample of 379 patients with obesity (mean BMI of 27.0 kg/m^2, 80% female).[37] Internal consistency, as assessed by Cronbach's alpha, and test-retest reliability (the type of correlation coefficient used was not reported), as assessed two weeks later, were acceptable (0.70 or higher[84]) for the subscales and total score.[37] Convergent validity tests found strong correlations (magnitude of Pearson's R greater than 0.50) between the FCI total and subscale scores and the frequency scale of the conceptual craving scale, and the FCI total score and sweets subscale score with the three-factor-eating perceived-hunger subscale.[37] Moderate correlations (magnitude of R between 0.30 and 0.50[85]) were observed between the FCI total score and sweets subscale, with the conceptual craving intensity scale, and the FCI high fats and fast-food fats with the three-factor-eating perceived-hunger subscale.[37] Correlations of the FCI total and subscale scores with the three-factor-eating disinhibition scale were weak (magnitude of R between 0.10 and 0.30[85]) to moderate.[37]

In another validation study, the 28-item FCI was administered to 122 individuals with obesity and (mean BMI of 37.8 kg/m^2) binge-eating disorder who responded to advertising for treatment studies.[36] Factor analysis supported the original questionnaire structure, although three items were eliminated due to loading on more than one factor (gravy, corn bread, and baked potato). Internal consistency reliability, assessed by Cronbach's alpha, was acceptable (0.70 or higher[84]) for the new 25-item version. The impact of cultural variation in food cravings may affect the results of the FCI.[86]

No evidence for an MID or responsiveness to change was found.

COE Questionnaire

Question 19 of the COE questionnaire ("Generally, how difficult has it been to control your eating?") was used as a secondary end point in the COR-I, COR-II, and the COR-DM trials. The entire questionnaire was used as secondary end points in the COR-BMOD trial. The COE is a self-administered 21-item instrument designed to assess type and intensity of food cravings and the subjective sensations of appetite and mood.[38] It includes six sections that relate to general appetite, overall mood, craving frequency, craving intensity, specific cravings, and perceived level of control over resisting a nominated food item.[38] Items are scored using a VAS, while one question has a participant identify a craved food.[38] A food craving is defined as a strong urge to consume a particular food or drink. Patients are instructed to read each question carefully and place a mark at the point that best represents their experience over the last seven days using a 100 mm line with extremes of 0 (not at all) to 100 (extremely or very often or after every one).[38] There are four subscales: craving for sweet, craving for savoury, positive mood, and craving control.[38]

In a pooled analysis of four separate studies that aimed to measure the psychometric properties COE, 215 obese patients (80% female), with mean BMIs ranging from 23.2 to 30.8 completed the COE.[38] Cronbach's alpha values for internal consistency for the subscales were 0.88 for craving control, 0.74 for positive mood, 0.66 for craving for savoury foods, and 0.67 for craving for sweets.[38] Only the craving-control and positive-mood subscales had acceptable internal consistency relative to the generally accepted threshold of 0.70 or higher.[38,84] Convergent validity was evaluated by examining relationships with the Pearson correlation coefficient between subscales and psychometric eating-behaviour traits (binge-eating scale and three-factor eating questionnaire, including the cognitive control of restraint, disinhibition of eating, and susceptibility to hunger subscales).[38] A strong correlation ($|R| > 0.50$[85]) was observed between the COE craving-control subscale and the binge-eating scale. Moderate correlations ($|R|$ of 0.30 to 0.50[85]) were observed between the COE subscales and psychometric eating-behaviour traits.[38] Associations between the COE subscales and body composition found lower positive mood and craving control and greater craving for sweets were associated greater fat mass, waist circumference, and BMI (weak-to-moderate correlations).[38]

An analysis of the four pivotal, phase III RCTs of NB (n = 1,310) versus placebo (n = 735) in adult patients with obesity sought to determine if the COE craving-control subscale was predictive of weight loss and to examine the component structure of the COE.[87] The factor structure was consistent with the original four subscales, and internal consistency reliability according to Cronbach's alpha was acceptable (0.7 or higher[84]) for all subscales.[87]

No evidence for an MID or responsiveness to change was found. Although psychometric properties of the total score for the COE and subscales have been described, and although the scale has been used on an item-by-item basis in clinical trials of medications to treat obesity, the psychometric properties of single questions of the COE were not found in the literature.

Inventory of Depressive Symptomatology – Subject-Rated

The Inventory of Depressive Symptomatology – Subject-Rated (ISR-SR) is a 30-item tool that measures the severity of depressive symptoms. It is also available in a clinician-rated format.[35] The 30 items include criterion items for MDD from the fourth edition of the *Diagnostic and Statistical Manual of Mental Disorders*. Symptom domain content includes insomnia, sad mood, appetite or weight change, concentration, outlook, suicidal ideation,

involvement, energy/fatigability, psychomotor function, anxiety, mood reactivity, mood quality anhedonia, libido and self-criticalness.[35] Scores for both the IDS-SR and clinician formats are generated by summing the responses to 28 of 30 items (for two pairs of items, only one item is rated).[35] Each symptom item is scored on a scale of 0 to 3, and higher scores indicate greater severity of symptoms.[35] The total score ranges from 0 to 84.[35]

The IDS-SR has been validated in numerous studies of patients with depression and has been shown to measure depression in a manner consistent with the most widely used assessments, including the commonly used depression-rating scales. The IDS-SR has been shown to have acceptable internal consistency reliability in both inpatients and outpatients with (MDD) (Cronbach's alpha ranging from 0.83 to 0.94 for outpatients and 0.79 for inpatients).[88-90] Acceptable concurrent validity with the Beck Depression Inventory (Pearson correlation coefficient R = 0.93) and Hamilton Rating Scale for Depression (R = 0.88) have been reported in outpatients with MDD.[90] Concurrent validity was reported for the Montgomery and Åsberg Depression Rating Scale (R = 0.81) and the depression factor of the Symptom Check List (R = 0.84) for inpatients with MDD.[89]

No information about an estimated MID for the IDS-SR or the psychometric properties of the IDS-SR in the obese population was found.

Short-Form (36) Health Survey

The SF-36 measures general health. It has been used extensively in clinical trials.[32] Each of the eight health domains in the SF-36 has a subscale score that can be determined: physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional, and mental health.[32] There are two component summaries of the SF-36: the PCS and the MCS, which are derived from a scoring algorithm from the eight domains.[32] Scores on the PCS and MCS range from 0 to 100, with a higher score indicating a better health status.[32] Scoring for the summary scales uses norm-based methods; the regression weights and constants are based on the general US population. The PCS and MCS scales are transformed to have a mean of 50 and an SD of 10 in the general US population.[33] The SF-36 has been validated in a variety of disease conditions.[34]

Version 2 of the SF-36, which was made available in 1996, contains minor changes to the original survey. Changes included reduced ambiguity in instructions, better layout, increased item-level response choices, increased cultural and language comparability, and elimination of a response option from the items in the mental health and vitality dimensions.[33]

An increase in a scale score on the SF-36 indicates improvement in health status. Clinically meaningful improvement is generally indicated by a change of two points in the SF-36 PCS and three points in the SF-36 MCS.[33] Based on anchor data, following minimal mean group differences, t score points are described for SF-36 version 2 individual dimension scores: physical functioning, 3; role functioning, 3; bodily pain, 3; general health, 2; vitality, 2; social functioning, 3; role emotional, 4; and mental health, 3.[33] These MID values were determined as appropriate for groups with mean t scores ranging from 30 to 40.[33] For higher t score ranges, MID values may be higher.[33]

The SF-36 has some evidence of validity in the obese population. In a study of outpatients with obesity seeking treatment (N = 475), the construct validity of the SF-36 was explored through main component analysis.[91] This study found that BMI was associated with most factors, but not the factors based on mental health, vitality, and social functioning.[91] In a study of patients with morbid obesity (mean BMI of 41.7 kg/m^2) with a referral to a rehabilitation centre, a factor analysis suggested that the two summary scales (PCS and MCS) had adequate factor loading, but the validity of the original eight subscales was not confirmed in this population.[92]

No information about the MID of the SF-36 in the population with obesity was found.

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