Lead team presentation Naltrexone-bupropion (prolonged-release) for managing overweight and obesity (ID757) – STA

1st Appraisal Committee meeting

Background and Clinical Effectiveness

Committee A

Lead team: Mohit Misra and Pamela Rees

ERG: Kleijnen Systematic Reviews

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Key issues: clinical effectiveness

1. **Positioning**
   - What is the expected positioning of naltrexone-bupropion in the treatment pathway: alternative to orlistat vs 2nd line to orlistat? What are the relevant comparators? Are different types of behaviour modification, such as more intensive forms, relevant?
2. **Population**
   - should effectiveness be considered in a mixed population (overweight and obese) with and without Type 2 Diabetes Mellitus (T2DM)?
3. **Effectiveness of naltrexone-bupropion (NB32) vs placebo**
   - What is the appropriate analysis: Intention to treat (ITT) or modified ITT (mITT)? Implications of large drop out rate, and how to deal with this analytically?
4. **Effectiveness of NB32 vs orlistat**
   - Which trials should be used in the indirect treatment comparison of NB32 vs orlistat?
5. **Generalisability to NHS**
   - Is standard management in the COR trials generalisable?
   - Is the patient population in the trials generalisable?

Overweight and obesity

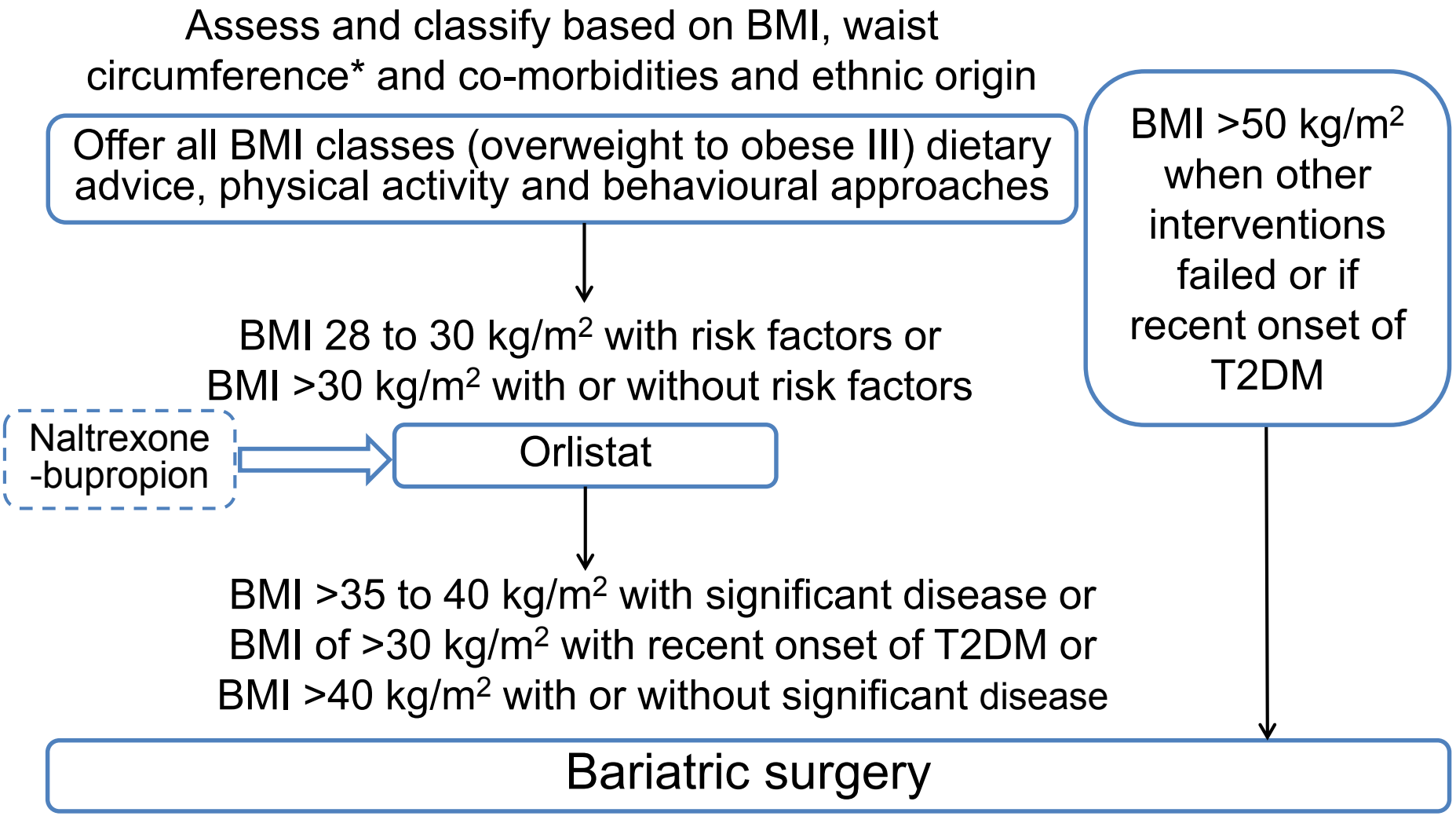
- Chronic condition characterised by increased body fat – people are at an increased risk of developing cardiovascular disease (CVD), Type-2 diabetes mellitus (T2DM), hypertension, hyperlipidaemia, gallstone disease and irregular menstrual cycles
- Body Mass Index (BMI) is the most common method for measuring obesity:
  - 25 kg/m^2 to 29.9 kg/m^2: overweight
  - 30 kg/m^2 to 34.9 kg/m^2: obese I
  - 35 kg/m^2 to 39.9 kg/m^2: obese II
  - 40kg/m^2 or more: obese III
- Prevalence
  - In England, 24% of adults are obese and a further 36% are overweight
  - 7/10 are class 1 obese (BMI of 30 – 34.9), and 1/10 morbidly obese (BMI of 40 or more)
  - Expected prevalence of obesity in 2050 - 60% of adult men and 50% of adult women

Naltrexone-bupropion (NB32)

(Naltrexone 32mg plus bupropion 360mg prolonged-release)

UK marketing authorisation	'Adjunct to a reduced-calorie diet and increased physical activity, for the management of weight in adult patients (≥18 years) with an initial BMI of • ≥ 30 kg/m^2 (obese), or • ≥ 27 kg/m^2 to < 30 kg/m^2 (overweight) in the presence of one or more weight-related co-morbidities (e.g. type 2 diabetes, dyslipidaemia, or controlled hypertension) Treatment should be discontinued after 16 weeks if patients have not lost at least 5% of initial body weight'
Class of drug	Naltrexone is an opioid receptor antagonist and bupropion is a dopamine and noradrenaline reuptake inhibitor. Exact neurochemical effect is unknown but is thought to stimulate pro-opiomelanocortin neuronal firing and modulate food cravings through an effect on the reward pathways of the brain.
Administration and dosage	Administered orally in a prolonged-release tablet. Dose is escalated over a 4-week period to a total dose of 32 mg naltrexone and 360 mg bupropion: Week 1: one tablet in morning; Week 2: one tablet morning & evening; Week 3: two tablets in morning & one in evening; From week 4: two tablets morning & evening
Cost	Acquisition cost (excl. VAT) £73.00 per pack of 112 tablets Predicted lifetime cost £995 (Source: company's submission)

Treatment Pathway



Patient Issues
(Helping Overcome Obesity Problems)

- Living with obesity can be a struggle
- Stigma, Exclusion and Isolation
- Self esteem, quality of life
- Vicious cycle: weight loss – weight gain
- Current support, emphasising diet/exercise, varies between regions
- Need to address underlying mental cause of weight gain
- The technology has a place in the current pathway – no other treatments address appetite or safety

Decision problem

	NICE scope	Company submission
Population	Adults who have a BMI of: • ≥30kg/m^2 (obese) • ≥27kg/m^2 to <30kg/m^2 (overweight) in the presence of one or more weight-related co-morbidities	As per scope
Intervention	Naltrexone-bupropion prolonged-release (NB32)	As per scope
Comparator(s)	• Standard management without NB32 • Orlistat (prescription dose)	As per scope
Outcomes	• BMI • Weight loss • Percentage body fat • Waist circumference • Incidence of Type 2 diabetes • Cardiovascular events • Mortality • Adverse effects of treatment • Health-related quality of life	BMI missing Company considered BMI within the economic modelling, but it was not explicitly provided as a clinical outcome of the 4 COR trials as this was not a pre-defined endpoint
Subgroups	People with Type 2 diabetes	As per scope

Randomised placebo-controlled trials

Trial name	Population	Intervention	Co-Primary Outcomes
COR-I **Phase III multicentre, double-blind** **Location: USA**	Adults with uncomplicated obesity or who were overweight with dyslipidaemia or hypertension	• Naltrexone 32mg per day + bupropion 360mg per day (NB32) • Naltrexone 16mg per day + bupropion 360mg per day	Mean percent change in body weight and proportion of patients with ≥5% decrease in body weight at week 56
COR-II **Phase III, multicentre, parallel-arm, double-blind** **Location: USA**	As above	NB32	Mean percent change in body weight and proportion of patients with ≥5% decrease in body weight at week 28
COR-BMOD **Phase III multicentre, double-blind** **Location: USA**	As above	NB32 + intensive behaviour modification (BMOD)	Mean percent change in body weight and proportion of patients with ≥5% decrease in body weight at week 56
COR-DM **Phase III multicentre, double-blind** **Location: USA**	Adults with T2DM and BMI ≥27 and ≤45kg/m^2	NB32	As above

Note: NB32 and placebo are all given as adjunct to standard management (SM) or intensive SM [BMOD] in COR-BMOD. COR, Contrave obesity research; DM, diabetes mellitus; BMOD, intensive behaviour modification; T2DM, Type 2 diabetes mellitus

Standard management definitions in the COR trials

True to practice in England?

- COR-I and II
  - Participants encouraged to increase physical activity, lose weight and follow the prescribed programme
  - Walking prescribed for 10 mins on most days of the week, gradually increasing to 30 mins
  - Use of meal replacements was discouraged but not a criteria for withdrawal from the study
- COR-DM
  - Same regimen as COR-I and II but 30 mins of walking prescribed in the first instance
- COR-BMOD
  - Included group meetings, instructions to consume a balanced diet and to increase moderate physical activity to 180 mins/week

ERG comments on the trials

- Four main COR trials are of high quality but no trials directly compared NB32 with orlistat
- All trials conducted in the USA
  - Standard care may be different to that in England – regimen seen in COR-BMOD may be more reflective to that seen in England (group meetings mimics weight loss programmes)
  - Majority of participants were female – in England males are more likely to be overweight or obese, 68% vs 58%, respectively in 2015
- Overweight and Asian people are not well represented in the trials
- COR-I, -BMOD and -DM measure the primary outcomes at 56 weeks but there is no information on maintenance of weight loss after this time
- Prior use of orlistat was an exclusion criterion in all 4 COR trials so the effect of NB32 after orlistat has failed has not been examined

Clinical trial results - ≥5% decrease in bodyweight from baseline

Modified intention-to-treat population (mITT) using last observation carried forward (LOCF)

Trial name		N (%), 95% CI	odds ratio (OR) (95% CI), p-value (Higher odds favour NB32)
COR-I	**NB32 (n=471)**	226 (48.0%), 43.5, 52.5	4.9 (3.6, 6.6), <0.001
	Placebo (n=511)	84 (16.4%), 13.2, 19.7	
COR-II	**NB32 (n=825) to week 28**	459 (55.6%), 52.3, 59.0	6.6 (5.0, 8.8), <0.001
	Placebo (n=456)	80 (17.5%), 14.1, 21.0	
COR-BMOD	**NB32 +BMOD (n=482)**	320 (66.4%), 62.2, 70.6	2.9 (2.0, 4.1), <0.001
	Placebo + BMOD (n=193)	82 (42.5%), 35.5, 49.5	
COR-DM	**NB32 (n=265)**	118 (44.5%), 38.5, 50.5	3.4 (2.2, 5.5), <0.001
	Placebo (n=159)	30 (18.9%), 12.8, 25.0	

Clinical trial results - mean % change in body weight from baseline

Modified intention-to-treat population (mITT) using last observation carried forward (LOCF)

Trial name		Baseline mean kg (SD) Assessment point mean kg (SD)	Difference in Least Square (LS) Mean (95% CI), p-value NB32 vs Placebo
COR-I	**NB32 (n=471)**	100.2(16.3) 94.2(17.4)	-4.8 (-5.6, -4.0) <0.001
	Placebo (n=511)	99.3 (14.3) 98.0 (15.2)	
COR-II	**NB32 (n=825)**	100.7 (16.7) 94.2 (17.6)	-4.6 (-5.2, -3.9) <0.001
	Placebo (n=456)	99.3 (16.0) 97.2 (16.2)	
COR-BMOD	**NB32 +BMOD (n=482)**	100.7 (15.4) 91.0 (17.1)	-4.2 (-5.6, -2.9) <0.001
	Placebo + BMOD (n=193)	101.9 (15.0) 96.4 (17.1)	
COR-DM	**NB32 (n=265)**	106.4 (19.1) 101.0 (19.7)	-3.3 (-4.3, -2.2) <0.001
	Placebo (n=159)	105.0 (17.1) 103.0 (17.3)	

Pooled analysis results – random effects model for NB32 vs placebo

Modified intention-to-treat population

- ≥5% reduction in weight at 1 year
  - odds ratio (95% CrI) less than 1 favour NB32
  - **0.26 (0.19 ,0.34)**
  - Statistical heterogeneity score (I^2) 66.6%
- % weight change from baseline at 1 year
  - mean difference (95% CrI) greater than 0 favour NB32
  - **4.39 (3.49, 5.29)**
  - Statistical heterogeneity score (I^2) 70.1%

Adverse Events in the COR trials

- In all 4 trials there were more treatment-emergent adverse events in the NB32 arm compared to placebo
  - Ranging from 57.1% to 76.5% in the COR trials for NB32
- Common AEs across the trials were GI (nausea and constipation) and CNS related (headache and dizziness) – nausea was the most common AE leading to discontinuation, NB32 vs PBO:
  - 19.5% vs 9.8% in COR-I
  - 24.3% vs 13.8% in COR-II
  - 25.7% vs 12.5% in COR-BMOD
  - 29.4% vs 15.4% in COR-DM
- Cardiovascular effects (naltrexone) and psychiatric effects (bupropion) are two AEs of concern outlined in the SmPC
  - No significant numbers of cardiovascular (e.g. increased blood pressure) or psychiatric (e.g. suicidal thoughts) effects reported across the 4 pivotal trials

ERG comments on the COR trial results (1)

- Using a modified-Intention-to-treat (mITT) population could lead to bias:
  - mITT included people who had at least one post-baseline measurement (approximately 20% of patients excluded). Reasons for discontinuation could relate to efficacy or safety of NB32
  - True ITT should be used – results for NB32 vs placebo are still significant but more modest
- Large drop out rates due to adverse events with NB32 in the trials (up to 50%)

ERG comments on the COR trial results (2)

- Inappropriate to pool COR trials because of clinical & statistical heterogeneity:
  - Results from the separate analyses for patients with and without diabetes are preferred
  - COR-BMOD not suitable to be pooled with the other COR trials as standard management was more intensive and greater weight loss was achieved. Placebo arm in COR-BMOD had results approaching the intervention arm of the other trials
  - Use of COR-II to derive treatment effect beyond 28 weeks is inappropriate because NB32 participants with ≥5% weight loss at visits between weeks 28 and 44 were re-randomised

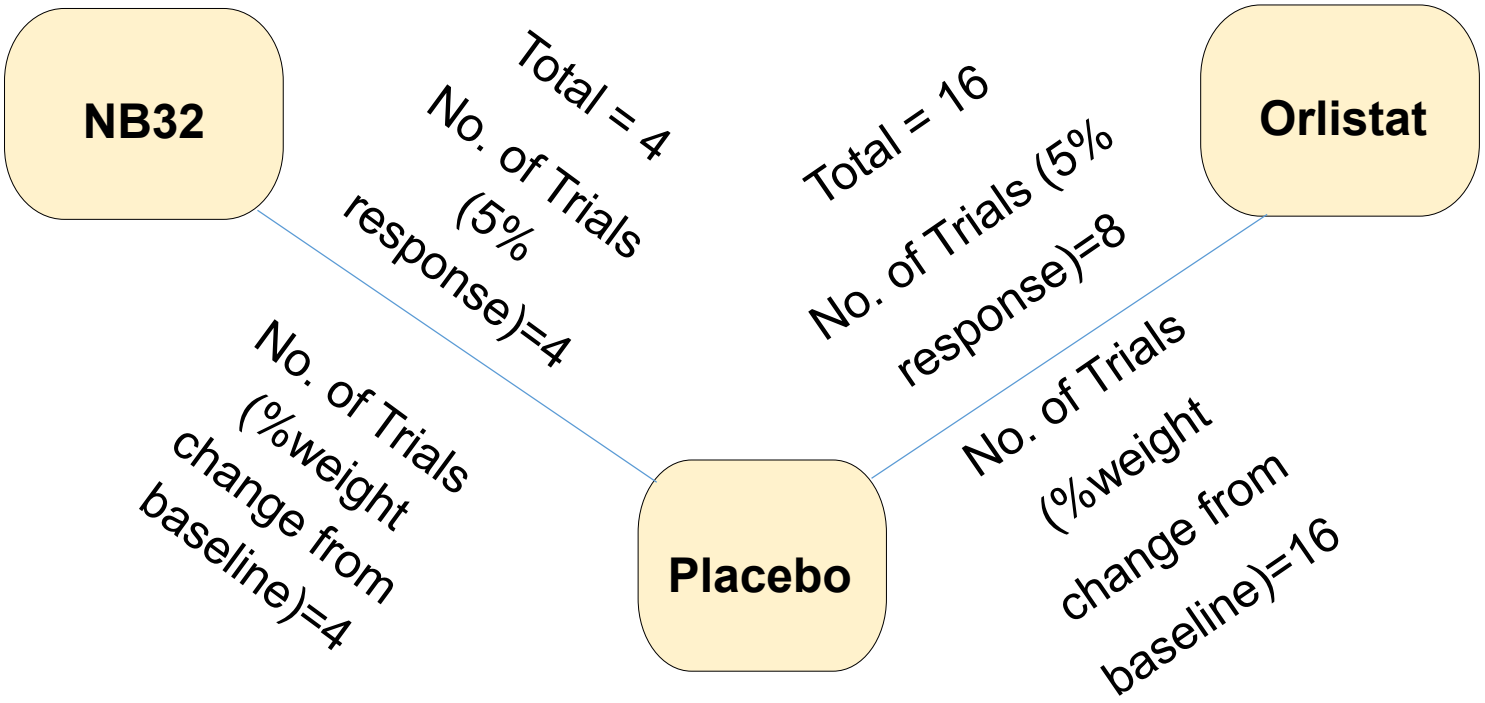
Indirect treatment comparison (ITC) – NB32 vs orlistat

- Company presented an ITC with placebo as the common comparator (using pooled results from meta-analyses for NB32 vs placebo)
- A Bayesian network meta-analysis (NMA) was performed to assess:
  - ≥5% reduction in weight from baseline at 1 year
  - mean % weight change from baseline at 1 year
- Analyses were presented for:
  - People with T2DM
  - People without T2DM
  - All trials regardless of T2DM
- Random effects model used only for all trials, regardless of T2DM. Fixed models used for T2DM and no T2DM subgroups
  - Sensitivity analysis performed to explore heterogeneity (differences in intensity of BMOD and lead-in periods) in trials and found consistent results to the base case

Overview of NB32 vs Orlistat

Drug	Mechanism of Action	Regimen	Side Effects
NB32	Noradrenalin / dopamine re-uptake inhibitor and opioid receptor antagonist Exact neurochemical effect is unknown	Week 1 – daily Week 2 – twice a day Week 3 – 2 in the morning, 1 at night Week 4 – two twice a day Treatment discontinued if not ≥5% weight loss after 16 weeks	GI (nausea and constipation) and CNS related (headache and dizziness)
Orlistat	Gastric and pancreatic lipase inhibitor	120mg three times a day taken before, during or up to 1 hour after main meals Treatment discontinued if not ≥5% weight loss after 12 weeks	Faecal urgency, flatus with rectal discharge, faecal incontinence & fatty and oily stool

ITC – Network of evidence



ITC base case results – NB32 vs orlistat

Modified intention-to-treat population with last observation carried forward

Trials	**≥5% reduction in weight (1 year), odds ratio (95% CrI)**	**Mean % weight change (1 year), mean difference (95% CrI)**
Trials with people with T2DM (Fixed effects) (n = 4)	1.09 (0.63 to 1.88)	0.21 (-0.87 to 1.30)
Trials excluding people with T2DM (Fixed effects) (n = 5)	0.77 (0.61 to 0.96)	1.13 (0.44 to 1.80)
All trials regardless of T2DM (Random effects) (n = 16)	0.80 (0.51 to 1.28)	1.39 (-0.08 to 2.82)
Note, Odds Ratio less than 1 and Mean Differences greater than 0 favour NB32		

ERG comments on ITC

- ERG considers Bayesian NMA methodology is appropriate:
  - Agrees that only fixed models are presentable for T2DM and no T2DM subgroups and are likely to be more reliable
  - Appropriate sensitivity analysis was explored by the company
- Full comparisons not considered by the company:
  - NB32 plus standard management (SM) vs intensive SM
  - NB32 plus intensive SM vs orlistat plus intensive SM
- Additional work by ERG:
  - Using mITT data is main concern – mITT population in NB32 trials (21.9% of patients excluded) very different from in orlistat trials (1.6% excluded)
  - Two additional analyses provided by the ERG

1. Results based on ITT populations for the NB32 trials
2. Comparison of studies with intensive BMOD

Results used in ERGs preferred analysis

ERG preferred ITC analyses

Using Bucher method for ITC and ITT-baseline observation carried forward analysis (ITT-BOCF) and no pooling of NB32 trials - NB32 vs orlistat

Trials	**≥5% reduction in weight (1 year), OR (95%CrI)**	**for mean % weight change (1 year), MD (95% CrI)**
People with T2DM	1.59 (0.89 to 2.79)	-1.21 (-2.30 to -0.11)
People without T2DM	0.61 (0.31 to 1.22)	1.11 (-0.39 to 2.63)
Intensive behaviour modification	1.86 (1.30 to 2.66)	-2.09 (-3.53 to -0.65)
Note, Odds Ratio less than 1 and Mean Differences greater than 0 favour NB32		

Key issues: clinical effectiveness

1. **Positioning**
   - What is the expected positioning of naltrexone-bupropion in the treatment pathway: alternative to orlistat vs 2nd line to orlistat? What are the relevant comparators? Are different types of behaviour modification, such as more intensive forms, relevant?
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