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

1st Appraisal Committee meeting

Cost Effectiveness

Committee A

Lead team: Rita Faria

ERG: Kleijnen Systematic Reviews

6th April 2017

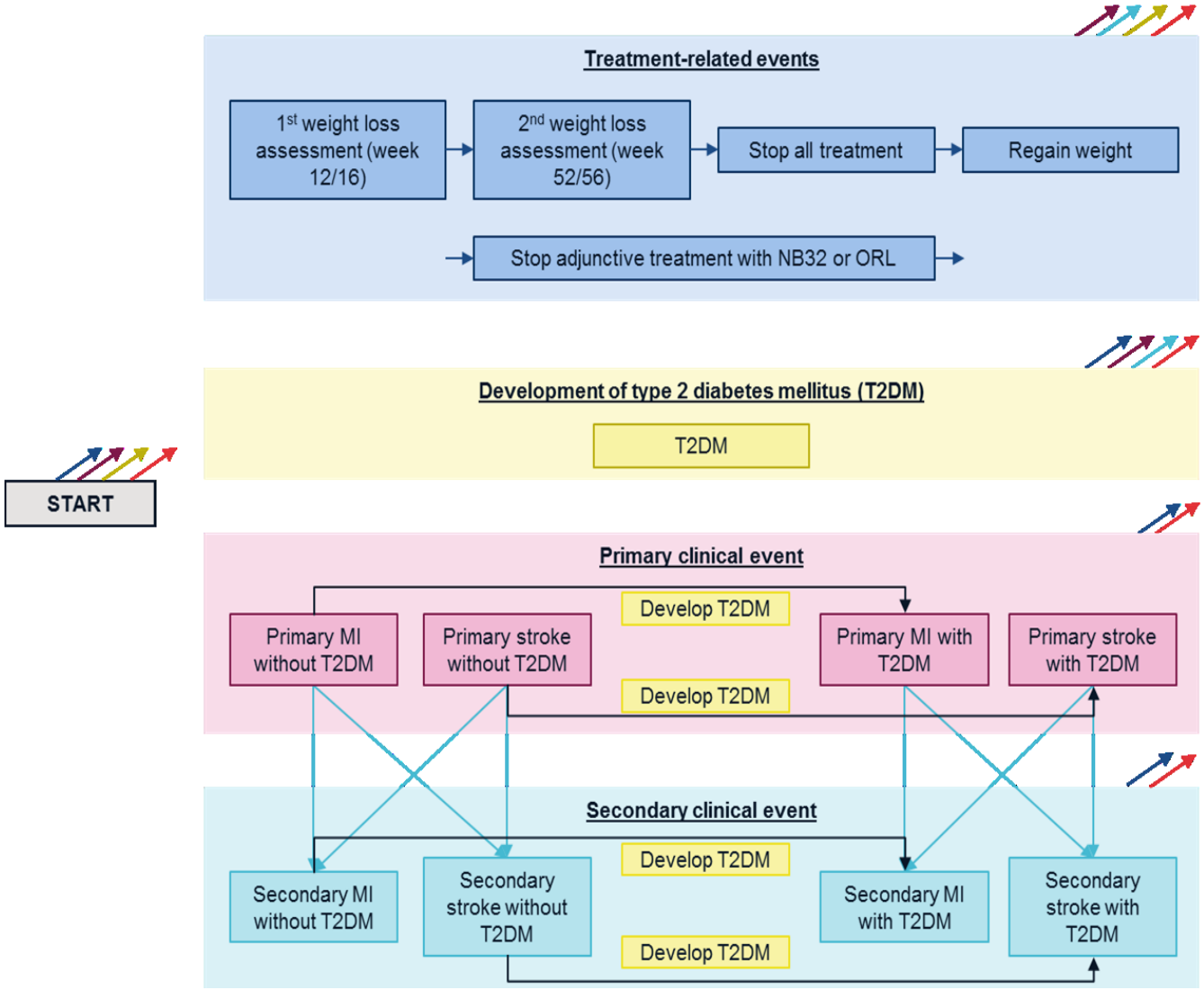
Key issues: cost effectiveness (1)

1. **Model structure**
   - Model structure does not consider retreatment, behaviour modification, and bariatric surgery. What is the committee's view on the model structure?
2. **Model implementation**
   - The ERG highlighted that the model is very slow to run, large variation in ICERs when different random numbers are used and small number of PSA runs, and BMI updated only when events occur. What is the committee's view on the validity of the model and robustness of the results?
3. **Population**
   - Should the cost-effectiveness be considered in the entire population or in subgroups with/without T2DM? What are the characteristics of the population that should inform the model?

Key issues: cost effectiveness (2)

4. **Modelling treatment**
   - What clinical data is appropriate to inform the model? Duration of effect: how fast is weight regained after treatment discontinuation? Treatment duration: is time on treatment appropriately modelled?
5. **Utilities**
   - Is the Public Health England weight management tool appropriate to derive the utilities?
6. **Innovation**.
   - Does the committee consider NB32 to be an innovative therapy?

Company Model – Discrete Event Simulation (DES)



- Lifetime horizon
- Costs & QALYs discounted at 3.5%
- NHS/PSS perspective
- Based on Ara et al, 2012

Key modelling assumptions

1. Model compares NB32, orlistat, and standard management, as per the clinical trials and indirect treatment comparison.
2. Patients cannot be retreated after treatment discontinuation.
3. Bariatric surgery is not included in the model.
4. Treatment affects weight, which affects BMI. BMI affects quality of life, and the risk of cardiovascular events, onset of T2DM, and death.
5. Patients who discontinue NB32 or orlistat continue to receive standard management.
6. Weight is regained once all treatments, including standard management, are discontinued.
7. Weight is regained over time, to the predicted BMI (not BMI at model entry).
8. Assessment times for NB32 and orlistat are assumed equivalent: 1st assessment at weeks 16 and 12; 2nd assessment at weeks 56 and 52.
9. Treatment duration between assessment times is assumed the same between NB32 and orlistat, adjusting for difference in assessment times.

Baseline characteristics

Parameter	Mean value	Justification
Age	47.0 years	COR trial programme patient-level data
Female	79.0%	
Height	Female: 1.64 m Male: 1.78 m	
BMI	Predicted by natural history model; average of 33Kg/m^2	BMI trajectory model by Ara et al.
T2DM at baseline	33.2%	Ara et al.
Insulin use for T2DM patients	33.3%	Clinical opinion
Smoking status	Current: 7.0% Previous: 54.0% Never: 39.0%	Dare et al.
Statin use	79.3%	NB-CVOT study
History of angina	0%	Assumption – no data identified for overweight/obese patients
Other type DM	0%	

ERG comments on baseline characteristics

- Agree with using data from COR trials as effectiveness estimates are derived from this population but other baseline characteristics are questionable
- Baseline BMI is vastly underestimated in the model compared with the trials
  - Therefore utility, and time to T2DM, CV events and death could be overestimated as BMI is included as a predictive factor
- Other baseline characteristics underestimated in the model vs trial data include:
  - % current smokers (7% vs 9-11% in trials)
  - % receiving anti-hypertensive medication (0% vs 15-63% in trials)
  - ERG disagrees with assumption that no patients had a history of angina and/or diabetes other than T2DM – model results therefore not representative
- Some baseline characteristics overestimated:
  - % with T2DM (33.2%). Health Survey for England data suggests 14-15% (overweight and obese)
  - % on statins (79% vs 8-49% in trials)

ERG comments on model and assumptions (1)

1. Modelling structure
   - Inability of model to incorporate re-treatment, behavioural modification treatment and bariatric surgery is a major limitation
2. Implementation
   - Model very slow to run. Simpler approaches (e.g. individual-level state transition model) may have been more appropriate.
3. BMI over time
   - Model does not update BMI frequently enough (after year 1, on average updated once every 10.6 years).
4. Reasonable to use the Ara et al model as a starting point but issues on deviations

ERG comments on model and assumptions (2)

5. Assumption on weight regain. Weight regain is a key assumption and driver in Ara model. Company deviated from assumption that patients would have regained weight to obtain their *baseline* BMI in 3 years and assumed instead that patients would have regained weight to obtain the *predicted* BMI in 3 years
   - ERG not satisfied with this deviation and prefer the assumption used in Ara
   - In response to clarification the company provided an analysis where BMI returned to baseline (ICER vs orlistat increased by £1,536)
   - Linear weight regain over 3 years implemented incorrectly (instantaneously at end)

6. Comparability of assessment times. Company model assumes weight loss with orlistat at weeks 12 and 52 is comparable to weight loss with NB32 at weeks 16 and 56 but no justification given.

Clinical data used in the model (1)

- **NB32 and SM**:
  - Proportion of responders at weeks 16 and 56, and change in body weight from pooled COR trials (modified-ITT analysis with LOCF).
- **Orlistat**:
  - Proportion of responders at weeks 12 and 52, and change in body weight from indirect treatment comparison (modified-ITT population).
- **Time to treatment discontinuation (TTD) for NB32/orlistat**
  - 3 periods: up to week 12/16, between week 12/16 and week 52/56, and from week 52/56 onwards.
  - Periods up to week 52/56 based on pooled COR trials; period 56 onwards based on NB-CVOT trial.
  - Orlistat was assumed the same as NB32, with adjustments for different assessment times, due to lack of data for orlistat.

Clinical data used in the model (2)

- **BMI over time.**
  - BMI over time predicted based on sex and age from the Ara et al model.
- **Impact of weight on events**
  - Changes in body weight , converted to BMI, were used to predict development of T2DM, CV event (stroke or MI) and death using parametric time-to-event models (Weibull) retrieved from Ara et al.

ERG comments on clinical data in the model

- Modified ITT and pooled data from COR trials are inappropriate for estimating treatment effect in the model – estimates should be taken from COR-I and COR-DM only
- TTD is underestimated for all treatments, in particular orlistat:
  - estimates for the period after the 1 year assessment were taken from the NB-CVOT study in which patients had characteristics associated with an increased risk of CV outcomes, potentially leading to a shorter TTD
  - the end of the NB-CVOT study was used as the maximum TTD, whether patients in that study had discontinued or not
  - orlistat follows a similar trajectory to NB32 because patient-level data for orlistat were unavailable, but ERG found publications suggesting that orlistat TTD is longer than the 12.29 months estimated by the model
  - to derive TTD for orlistat, the KM estimates for NB32 TTD for the first 16 weeks were linearly scaled to fit the first 12 weeks of orlistat treatment

Health-related quality of life (HRQoL)

- Mainly disease-specific HRQoL data were collected in the COR trials, therefore company used EQ-5D data from the literature to estimate utilities
- Company used the Public Health England (PHE) weight management assessment tool
- This tool used the Tobit model - regression analysis of individual patient-level EQ-5D data for the Health Survey of England database from 2011 to 2013
- The model is adjusted using various explanatory variables such as BMI, age, gender, and obesity-related conditions
- Impact of AEs on utility scores not incorporated by the company

ERG comments on HRQoL

- PHE model does not appear to be published in a peer-reviewed journal
  - Limited validity information on the model
- Concern that the estimates have no face validity
  - In response to clarification the company compared the values to those of the general UK population and the ERG was satisfied these showed face validity
- ERG agree that the Tobit model is more appropriate than ordinary least squares (OLS)
  - OLS disregards upper and lower bounds commonly used for estimating utilities
- ERG questioned company's claim for not including AE utility decrements
  - In response to clarification the company provided an analysis with utility decrement of 0.05 for all AEs over 1 week
  - The ICERs versus orlistat and SM increased by £188 and £87, respectively
  - ERG was satisfied that the impact of AEs on HRQoL is likely to be small

Resource use – included costs

- Drug acquisition costs
  - NB32 £73.00 per pack (112 tablets), Orlistat £18.44 per pack (84 capsules)
- No administration costs
- NHS resource use associated with medical monitoring
  - GP visits, nurse visit and blood tests
- NHS resource use associated with co-morbidities
  - Adapted from Ara et al.
  - Costs inflated from 2009 to 2015
- NHS resource use associated with managing AEs
  - Calculated from COR-I trials assuming one GP visit for NB32 and SM – orlistat assumed equivalent to NB32
    - NB32, £1.69/week; orlistat, £1.69/week and SM, £0.81/week
  - Outpatient costs according to disease area
- Drug wastage associated with NB32 not considered in base-case model

ERG comments on resource use

- Unclear why a GP visit was included at week 52 for SM
  - ERG removed this cost in its base case
- Unclear why company assumed only a single GP visit for each AE
  - Assuming outpatient costs increases ICER vs orlistat by £4,408
- Questionable whether assuming the same AE costs for orlistat as calculated for NB32 is appropriate
  - No direct safety evidence comparing the drugs
- Unclear why only COR-I was used to derive rate of AEs
  - COR-DM could have been used to inform rates for people with T2DM
- Excluding drug wastage is not a conservative assumption
  - ICER compared to orlistat increased by £3,426 when it is included

Company base case results (deterministic)*

Technology	Total		Incremental		ICER (QALYs)	
	Costs	QALYs	Costs	QALYs	Versus baseline (SM)	Incremental
SM	£6,519	15.36				
orlistat	£6,814	15.41	£294	0.05	£5,538	£5,538
NB32	£7,563	15.44	£750	0.03	**£13,647**	**£32,084**

*The probabilistic analysis shows a similar ICER for NB32 versus standard management (£13,936) and a higher ICER for NB32 versus orlistat (£36,405)
Note, results rounded to 2 decimal places

Subgroup analysis results (deterministic)

- **People with T2DM at baseline**

Technologies	Total		Incremental		ICER (QALYs)	
	Costs	QALYs	Costs	QALYs	Versus baseline (SM)	Incremental
SM	£10,199	14.37				
Orlistat	£10,496	14.43	£297	0.06	**£5,059**	**£5,059**
NB32	£11,216	14.44	£720	0.01	**£14,797**	**£72,069**

- **People without T2DM at baseline**

Technologies	Total		Incremental		ICER (QALYs)	
	Costs	QALYs	Costs	QALYs	Versus baseline (SM)	Incremental
SM	£3,844	15.73				
Orlisat	£4,077	15.77	£233	0.04	**£6,283**	**£6,283**
NB32	£4,811	15.80	£734	0.03	**£15,339**	**£28,291**

Note, results rounded to 2 decimal places

Company's scenario analysis

Scenario			ICERs NB32 vs	
Model setting	**Base case**	**Scenario tested**	**Orlistat**	**Standard Management**
Base case			**£32,084**	**£13,647**
Weight regain	3 years	2 years	**£41,016**	**£14,113**
Weight regain	3 years	5 years	**£29,739**	**£11,880**
Cost of T2DM	£347.57	£175.86 in Year 1 only	**£36,096**	**£13,764**
Utility model	Tobit	OLS	**£36,771**	**£10,285**
AE costs	All GP	All outpatient	**£36,492**	**£15,130**
Discounting	3.5% for costs & effects	1.5% for costs & effects	**£28,323**	**£9,969**
Time horizon	Lifetime	15 years	**£53,514**	**£22,763**

ERG comments on the cost-effectiveness results (1)

Deterministic results

- Company did not run enough patient samples to produce stable ICERs
- ERG estimates that model should run for at least 1,500 samples (company ran 1000) to produce stable results (where convergence occurs), hence results should be interpreted with caution
  - In contrast Ara et al. used a cohort of 1,000,000 patients in their patient-level simulation

ERG comments on the cost-effectiveness results (2)

Probabilistic results

- Probabilistic sensitivity analysis (PSA) excluded key input parameters (TTD, natural history of BMI model, obesity-related events). Also not explored in deterministic SA
- PSA did not run enough samples to produce convergence and stable results (usually a min of a 1,000 but company ran 500)
- Model not fit for purpose due to extremely long run times and inability to perform appropriate PSA and check the model's internal validity to usual standards
- Probabilistic results are preferred for decision-making (NICE DSU guidance) – if the PSA is flawed so is the estimation of mean outcomes

ERG's amended base case analysis (1)

ERG able to adjust/correct some of the highlighted issues in its base-case:

1. Fixed error in the weight regain assumption so it is regained linearly over 3 years rather than being regained instantly after 3 years
2. Used ITT population from COR-I and COR-DM trials instead of a mITT pooled population
3. Used a relative risk instead of mean differences to extrapolate the difference between treatments in change from baseline weight from the secondary to the primary assessment
4. Calibrated the BMI natural history model to reflect baseline BMI as per the COR trials (mean BMI of 36 kg/m^2)

ERG's amended base case analysis (2)

5. Adjusted baseline age, proportion of females, smokers, people taking aspirin, anti-hypertensive medication and statins using baseline characteristics from COR trial programme, stratified for T2DM status, if applicable
6. Removed GP visit cost (52-week assessment) for people receiving standard management
7. Assumed weight regain towards baseline BMI instead of predicted BMI from the natural history model, in 3 years
8. Removed linear scaling assumption for TTD for orlistat

ERG amended deterministic base case results

Technology	Total		Incremental		ICER (QALYs)	
	Costs	QALYs	Costs	QALYs	Versus baseline (SM)	Incremental
ERG base case 1st run						
SM	£5,964	15.11				
orlistat	£6,275	15.20	£311	0.09	**£3,701**	**£3,701**
NB32	£7,017	15.21	£742	0.01	**£10,510**	**£45,694**
ERG base case 2nd run						
SM	£6,141	14.97				
orlistat	£6,455	15.06	£314	0.09	**£3,466**	**£3,466**
NB32	£7,188	15.08	£733	0.02	**£9,813**	**£38,871**
ERG's replication of the company's base case						
SM	£5,974	15.29				
orlistat	£6,219	15.33	£245	0.04	**£5,865**	**£5,865**
NB32	£6,948	15.36	£729	0.03	**£15,568**	**£34,994**

*Company's base case ICER was £32,084 vs orlistat and £13,647 vs standard management
Note, results rounded to 2 decimal places

ERG additional analyses (conditional on ERG's base-case)

Technology	Total		Incremental		ICER (QALYs)	
	Costs	QALYs	Costs	QALYs	Versus baseline (SM)	Incremental
Exploratory analysis – using instantaneous weight regain at 3 years						
SM	£6,007	15.09				
orlistat	£6,311	15.17	£304	0.08	**£3,600**	**£3,600**
NB32	£7,048	15.21	£737	0.04	**£10,021**	**£37,947**
Exploratory analysis – lower proportion of people with T2DM (15%)						
SM	£4,702	15.45				
orlistat	£4,992	15.53	£290	0.08	**£3,738**	**£3,738**
NB32	£5,740	15.55	£748	0.02	**£10,013**	**£28,687**
Subgroup analysis – people without T2DM						
SM	£3,565	15.66				
orlistat	£3,844	15.74	£279	0.08	**£3,488**	**£3,488**
NB32	£4,603	15.77	£759	0.03	**£9,594**	**£25,744**
Subgroup analysis –people with T2DM only						
SM	£11,173	13.98				
orlistat	£11,527	14.09	£354	0.10	**£3,435**	**£3,435**
NB32	£12,213	14.08	£686	-0.01	**£10,535**	**Dominated**

Innovation & equalities

- Company considers NB32 to be innovative:
  - first oral intervention with a multi-modal mechanism of action that is thought to work through actions in the hypothalamus and the dopaminergic reward system to reduce hunger and reward-driven eating
  - provides a new pharmacological treatment option for a disease of increasing prevalence and substantial burden
  - once people withdraw from current treatment there is a lack of safe and effective pharmacological options in current practice
- Company did not identify any potential equality issues

Key issues: cost effectiveness (1)

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