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Cost-Utility Analysis of Rimonabant in the Treatment of Obesity

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ABSTRACT

Objective: To estimate the incremental cost-utility ratio (ICUR) of rimonabant 20 mg/day in the treatment of obesity from a third-party payer's perspective.

Methods: Pooled data from three randomized clinical trials were used to develop a decision tree with five treatment alternatives: 1- and 2-year treatment with rimonabant, 2-year placebo, 1-year rimonabant followed by 1-year placebo, and no treatment. All alternatives, except no treatment, were accompanied by lifestyle interventions. Treatment benefits included gains in quality-adjusted life-years (QALYs) and reduced incidence of type-2 diabetes mellitus and coronary heart disease (CHD). Drug acquisition cost was based on the average wholesale price of a comparator drug minus 15%. One-way and probabilistic sensitivity analyses were conducted to assess the stability of the base-case results.

Results: One-year rimonabant and 1-year rimonabant followed by placebo were extendedly dominated. Rimonabant for 2 years showed an average weight reduction of 8.49 kg, a body mass index reduction of 2.98 kg/m^2 and reduced waist circumference by 8.24 cm (placebo: 3.55 kg, 1.22 kg/m^2, 4.18 cm). Two-year rimonabant was associated with a relative reduction in the 5-year incidence of CHD by 7.15% and of diabetes by 9.28%. Incremental benefits (costs) were 0.0984 QALYs ($5209) compared to no treatment and 0.0581 QALYs ($4182) compared to placebo, producing ICURs of $52,936/QALY (95% confidence interval $39K–$69K) and $71,973/QALY ($51K–$98K), respectively.

Conclusions: Rimonabant combined with lifestyle interventions has the potential to decrease the rate of obesity-related comorbidities and improve health-related quality of life, albeit at considerable cost.

Keywords: cost-utility, obesity, pharmacoeconomics, QALY, rimonabant, weight loss.

Background

The increasing prevalence of obesity in the United States and throughout the world imposes a serious threat on the health of those inflicted and a large burden to the health-care budgets of developed countries. In the United States, among persons aged 40–59 years, 73.1% are either overweight (body mass index: the weight of the body in kilograms divided by the square of its height in meters [BMI] > 25) or obese (BMI > 30). The financial burden of overweight in the United States is estimated at $78.5 billion annually in 1998 ($97 billion in 2006 dollars) [1].

Extensive research has linked obesity to a wide range of comorbidities including coronary heart disease (CHD) and type-2 diabetes mellitus [2–6]. Moreover, even in the absence of comorbidities, obesity significantly impacts health-related quality of life (HRQOL), mainly in the domains of physical functioning and bodily pain. Weight reduction through a variety of interventions is able to improve HRQOL [7–9].

One type of intervention for weight reduction, bariatric surgery, is commonly restricted to morbidly obese patients (BMI > 40) [10]; hence, not an option for many overweight and mildly obese patients. For patients with a BMI of >30 or >27 combined with certain risk factors, pharmacologic treatment can increase weight loss when added to dietary interventions [11,12]. Currently, two pharmacologic agents are FDA-approved for the indication of weight reduction: sibutramine (Meridia, Abbott) and orlistat (Xenical, Hoffman-La Roche). A third treatment option, rimonabant (Sanofi-Aventis), has received market authorization in the European Union on June 21, 2006 [13], and has since been introduced in more than 10 European countries and in Argentina, Chile, Brazil, and Mexico as of May 2007. In the United States, rimonabant is currently under review by the FDA.

As the first therapeutically relevant cannabinoid (CB) antagonist, rimonabant selectively inhibits the receptor subtype CB-1 of the endocannabinoid system with a high affinity in the central nervous system and a lower affinity in peripheral tissues including adipose

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tissue [14]. The inhibition of this receptor is associated with an initial reduction in appetite and food intake, a change in body composition, and a reduction in body weight. Possible explanations for these effects, as suggested by preclinical animal studies, include a central stimulation of anorexia as well as an increase in energy expenditure due to increased thermogenesis. Furthermore, changes in adipose tissue resulting in smaller adipocytes are possibly mediated by peripheral mechanisms [15,16].

To our knowledge, no study evaluating the pharmacoeconomic implications of rimonabant has been published to date. This study aimed to calculate the incremental cost-utility ratio (ICUR) of rimonabant compared to placebo, both combined with a lifestyle intervention, and to a no-intervention alternative. Modeled benefits included gains in HRQOL due to a temporary weight loss and a reduced incidence of the comorbidities type-2 diabetes mellitus and CHD. The model assumed the perspective of a third-party payer in the United States.

Methods

Clinical Trials Data

This analysis employed data from three published phase-III clinical trials on the efficacy of rimonabant: Rimonabant in Obesity (RIO) Europe, RIO-Lipids, and RIO-North America [17–19]. All of the trials followed a similar protocol; included were patients with either BMI > 30 or BMI > 27 with treated or untreated dyslipideamia or hypertension (RIO-Europe and North America; RIO-Lipids: untreated dyslipidaemia only). Patients were at least 18 years of age; exclusion criteria and baseline characteristics were comparable [17–19].

The trials were randomized, double-blinded, placebo-controlled, parallel group, fixed-dose, multicenter studies with a 4-week single-blinded run-in period with placebo. Following this period, patients were randomized to placebo, 5 mg or 20 mg rimonabant to be taken once a day. In addition to drug therapy, patients received lifestyle interventions including a 600 kcal hypocaloric diet, dietician visits every 14 days for the first month and every 28 days thereafter for the remainder of the study, and instructions to increase physical activity. Results were reported after 12 months of treatment for RIO-Europe and RIO-Lipids [17,18]; in RIO-North America, patients on active treatment were re-randomized after 12 months to either continue treatment or switch to placebo [19].

Findings from these clinical trials were pooled using meta-analytic methods. We assessed heterogeneity in the mean values of BMI, weight, and waist circumference at screening and after 1-year for the treatment and placebo groups using Cochran's Q statistic [19,20]. As none of the variables appeared significantly heterogeneous ($P > 0.05$) across trials, we employed a fixed effects model using the inverse squared standard error as individual study weight [20].

Model Specifications

For this analysis, we used a decision tree (Fig. 1) composed of five treatment arms which followed patients for 5 years. The first arm represented no intervention (referred to as NNN, no intervention) and assumed zero weight loss and no change in waist circumference throughout the observation period (illustrated by the gray horizontal line in Fig. 2). This assumption is conservative as weight is likely to increase over time in obese patients [21]. The other arms replicated the clinical trials: 2-year placebo (Fig. 2a, referred to as PPN), 1-year rimonabant 20 mg (Fig. 2b, RNN), 1-year rimonabant 20 mg followed by 1-year placebo (Fig. 2c, RPN), and 2-year rimonabant 20 mg (Fig. 2d, RRN). Patients in all arms except the no-intervention arm received lifestyle interventions while being on placebo or rimonabant. Rimonabant 5 mg was not included in this analysis because of its marginal efficacy as evidenced from the RIO trials. We included the modeled arms to allow for a complete assessment of the clinical trials although not all arms represent realistic treatment options (i.e., placebo). Our model considered a range of sustainability of weight loss from 6 months to 3 years, as described below. We chose a time frame of 5 years based on the assumption that any effects of treatment were limited to the period of reduced weight (maximum 2 years of treatment and 3-year sustainability of weight loss).

Efficacy Measures

Published data on baseline BMI, height, and weight allowed for the calculation of average BMI at screening and after 12 months of treatment for each treatment arm. We used these BMI values to calculate changes in BMI related to each intervention. We calculated standard errors of both BMI and BMI changes from standard errors given for weight and height in the three clinical trials and their covariance as derived from RIO-Lipids, where BMI, weight, and height were reported at a single time point [18]. To achieve this, we utilized the delta method based on a first-order Taylor approximation which is a standard technique to approximate expected values of a function, in this case standard errors [22,23].

To develop the model of change in BMI over time (Fig. 2), we assumed that weight loss during the first 12 months of treatment approximated linearity to the point of average weight loss in the respective arm. The maintenance of reduced body weight during the second year of treatment, as evidenced from RIO-North America [19], was incorporated in the arms PPN and RRN (Fig. 2a,d). In addition, we assumed a linear weight regain to baseline after the end of the

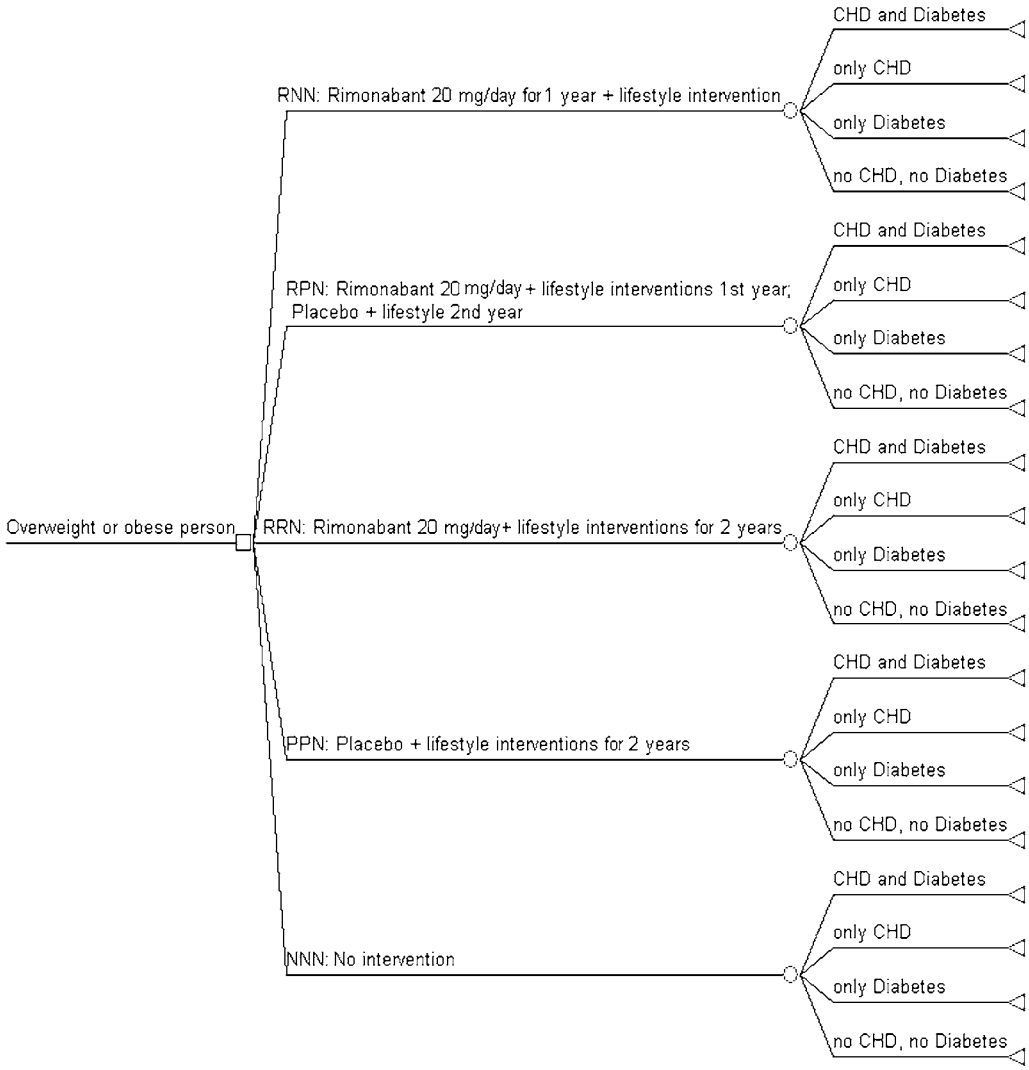

Figure 1 Decision tree: Five arms represent four different treatment options and one no-intervention option. Possible outcomes include coronary heart disease (CHD) and diabetes. The incidences of the outcomes were treated independently; i.e., the probability of experiencing both CHD and diabetes was calculated by multiplying the incidence of diabetes by the incidence of CHD. NNN, no intervention; PPN, 2-year placebo; RNN, 1-year rimonabant; RPN, 1-year placebo; RRN, 2-year rimonabant.

treatment. Information concerning sustained weight loss after complete treatment cessation has not been published for this intervention. Nevertheless, the UK National Institute for Clinical Excellence (NICE) suggests a period of 3 years of weight regain, back to baseline values [24]. However, the rapid regain of body weight after re-randomization to placebo in RIO-North America suggests a return to baseline in a period as short as 1 year after the end of the intervention [19]. We quantified the uncertainty in the sustainability estimate in the sensitivity analysis. Change in waist circumference over time was calculated analogously to change in BMI.

The impact of a reduction of BMI on health state preferences has only been described for orlistat. Participants in a randomized clinical trial of orlistat evaluated their current health state preferences using a visual analog scale [25]. Hakim et al. transformed the derived value into the time trade-off estimate using the Torrance transformation. A one-unit decrease in BMI was associated with a 0.0170 gain in utility units (referred to as utility transformation factor) which we applied in our study. Furthermore, we assumed that weight regain results in a decrease in quality of life to the same extent as it had been improved by the preceding weight loss as suggested by Engel et al. [26].

We expressed change in utility over time as quality-adjusted life-years (QALYs) which were calculated as value of each health state (1 meaning best imaginable health and 0 meaning death) multiplied by the time spent in that health state. We first calculated change in BMI over time as area between the weight loss curve

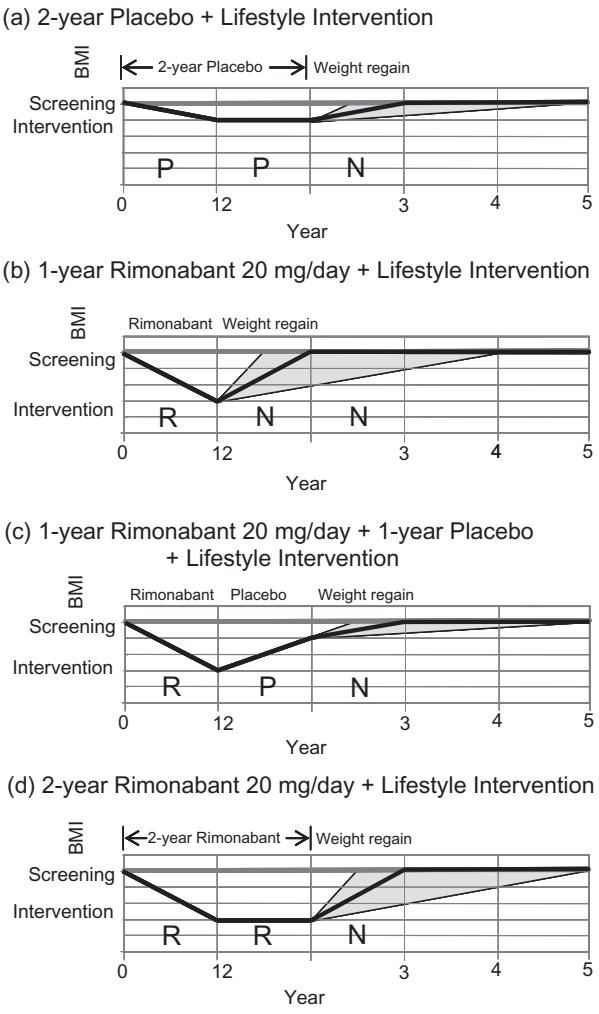

Figure 2 Reduction in body mass index (BMI) over time with different treatment options. The gray straight line depicts a projected consistent BMI for the no-intervention arm; the black line illustrates the mean change in BMI of patients receiving the respective intervention; the gray-shaded area covers times to weight regain included in the sensitivity analysis (0.5–3 years). Screening and Intervention on the *y*-axis represent BMI at the time of screening and BMI for the maximal average reduction due to the intervention, respectively. N, no intervention; P, placebo, R, rimonabant.

and zero weight loss as illustrated in Figure 2 and multiplied the result by the utility transformation factor to achieve QALYs gained.

Changes in Incidences of CHD and Type-2 Diabetes Mellitus

A reduction in BMI is associated with a reduced incidence of type-2 diabetes mellitus [27]. We modeled change in BMI as described previously and its association with the annual incidence of diabetes using the results of two observational studies. Wannamethee et al. reported the association of BMI with the incidence of type-2 diabetes in men in the British Regional Heart Study [27]. Estimates for women were calculated using the results of the Nurses' Health Study [28]. Plotting diabetes incidence versus BMI in the range of 25 to 40 suggested a linear association which was then quantified using linear regression. We found that a one-unit increase in BMI was associated with an increase of the annual incidence of diabetes by 0.098% for men and 0.073% for women. These estimates were weighted to reflect the sex composition in the rimonabant trials resulting in an estimate of 0.079% for our model. To illustrate the incidence calculation, a BMI reduction of 3 over 1 year from baseline BMI would be equated with an entire year spent at a BMI of 1.5 below baseline. We would then multiply 1.5 with 0.079% to calculate the reduced diabetes incidence for that year.

Change in waist circumference was used to predict change in the incidence of CHD (defined here as fatal and nonfatal myocardial infarction [MI]), as waist circumference has been shown to be a better predictor of CHD than BMI [29–31]. Rexrode et al. calculated the risk for CHD in different categories of waist circumference for men using data from the Physicians' Health Study and for women using data from the Nurses' Health Study [6,32]. We used these results to calculate the change in CHD incidence per centimeter change in waist circumference analogous to the calculation of diabetes incidence per change in BMI as described above. For men, a 1 cm increase in waistline was associated with a 0.01140% increase in the annual incidence of CHD; for women, 0.00308%. This resulted in a pooled estimate of 0.00503%.

We were unable to locate any published information describing the conjoint probability of experiencing comorbidities, CHD, and diabetes, as a function of BMI or waist circumference. Therefore, the incidences of CHD and diabetes were treated as being independent; that is, the joint incidence of CHD and diabetes was calculated as the product of the individual rates.

Economic Data

At the time of the analysis, rimonabant was not on the US market; therefore, we had to estimate drug acquisition cost. We used the cost of standard doses of currently approved drugs, orlistat, and sibutramine, to estimate daily treatment cost [33]. The cost of the higher-priced drug, orlistat, was used in the base-case scenario. The publicly available price for prescription drugs in the United States is the average wholesale price (AWP). This price, however, does not reflect actual payments; rather, it is the basis for discounted rates negotiated by different payers [34]. We calculated drug acquisition cost as AWP minus 15% to reflect expenditures of a third party excluding patients' co-payments and varied our cost estimate in the sensitivity analysis [35–37].

Other costs related to the intervention included direct medical costs of dietary counseling and physician

visits. The clinical trials reported 14 dietician visits in the first year. Our cost estimate for a single dietician visit ($30) represented the maximum allowable cost for a 15-minute session paid by the Medical Assistance Administration in the state of Washington [38]. The RIO trials did not report the number of physician office visits. Nevertheless, based on the reporting of laboratory values, blood was drawn at least five times per year. Following that, we assumed one initial (20 min) and four annual follow-up visits (10 min each) in our analysis. The longer initial physician visit was assumed only in the first year. Cost estimates for physician visits were $64 for a 20-minute visit and $36 for a 10-minute visit as paid by Medicare (Current Procedural Terminology [CPT] codes 99201 and 99201) [Available from: http://catalog.ama-assn.org/Catalog/cpt/cpt_search.jsp?checkXwho=done].

The base-case scenario for PPN, RPN, and RRN assumed a 3-year period of reduced weight (2-year treatment and 1-year sustainability as illustrated with the black line in Fig. 2a,c,d). The symmetry of the base-case BMI curves allowed us to keep the model parsimonious, by assuming that comorbidities occurred in the middle of this period, that is, after 1.5 years. Thus, a patient with new onset diabetes would incur treatment costs for the rest of this period (1.5 years). Similarly, for a CHD event, we assumed cost for a nonfatal MI with initial event costs and treatment costs for 1.5 years post MI [39]. We did not include lifetime treatment costs because we assumed that once patients' weights returned to their baseline values, their subsequent risk of CHD and diabetes was equal to the risk among nontreated patients. Thus, any cost-savings associated with reduced CHD and diabetes were assumed to be temporary, together with weight reduction.

Base-case cost estimates and ranges as well as sources of the information used in the analysis are presented in Table 1. All cost estimates were inflated to represent 2006 US dollars using the medical care component of the Consumer Price Index [Available from: http://www.bls.gov/cpi/]. Costs and benefits accruing after the first year were discounted at an annual rate of 3% [40].

Cost-Utility Analysis

The main outcome measures of this study were ICURs of treatment with rimonabant compared to placebo and to no intervention. The ICUR generally describes the costs associated with achieving an additional unit of treatment benefit. ICURs were calculated as the difference in costs between the intervention and the alternative divided by the difference in QALYs gained and were reported as $/QALY. After ranking treatment options based on their ICURs, we eliminated dominated options, as well as extendedly dominated options. An option was considered dominated if it was both more expensive and less effective than the alternatives. Extended dominance describes the phenomenon when the ICUR of a given treatment is higher than the ICUR of the next, more effective option [40].

Sensitivity Analyses

To quantify the uncertainty in the model parameters, we conducted a probabilistic sensitivity analysis using Monte Carlo simulation. The model was recalculated 10,000 times, where each of the parameter estimates was sampled from its distribution for each model recalculation [41]. We modeled sustainability of weight loss, drug cost, cost of MI, and cost of diabetes as lognormal distributions. Triangular distributions were used to model probabilities. We empirically determined input parameters for distributions to achieve sample distribution means approximating the base-case estimates (Table 1).

In addition, we conducted one-way sensitivity analyses to examine the impact of a variation in single parameters on the resulting ICUR. For selected variables, ranges of estimates were extended beyond the values provided in Table 1 to model the impact of even more extreme values on the ICUR; for example, the sensitivity analysis was conducted for drug costs up to $10/day (Fig. 5).

We pooled summary data from the clinical trials using RevMan Analyses 1.0 (Review Manager, Oxford, England). The decision tree, including sensitivity analyses, was programmed in TreeAge Pro2004 (TreeAge Software Inc., Williamstown, MA, USA).

Results

Clinical Data

Data from the three pivotal clinical trials were pooled, and a total of 3418 patients (1254 receiving placebo and 2164 receiving rimonabant 20 mg) were included in this analysis [17–19]. Patients were predominantly female (76.6%), white (87.4%; information on race only available for RIO-Europe and RIO-North America), and on average 45.5 years old. At screening, patients had an average BMI of 37.1, a mean body weight of 103.5 kg, and a mean waist circumference of 108.2 cm.

We found that 2-year placebo combined with lifestyle interventions resulted in an average weight loss from screening of 3.55 kg (95% confidence interval [CI] 3.25–3.85), a BMI reduction of 1.22 (95% CI 1.04–1.40), and a waist reduction of 4.18 cm (95% CI 3.81–4.55). One-year treatment with rimonabant 20 mg reduced the average weight by 8.49 kg (95% CI 8.13–8.85), BMI by 2.98 (95% CI 2.76–3.19), and waist circumference by 8.24 cm (95% CI 7.95–8.54) (Table 1, weight reduction not shown).

Impact on CHD and Diabetes Incidence

Our model computed the 5-year cumulative incidence of CHD without any intervention as 1.16% (116 per

Table 1 Model parameters: base-case and Monte Carlo simulation

	Base case	Range	Distribution*	Comment	Reference
BMI reduction from screening, placebo (kg/m^2)	1.22	1.04–1.40	Triangular (min = 1.04, mode = 1.22, max = 1.40)	Base case: average reduction after 1 year; range: 95% confidence intervals, pooled from RIO trials	[17–19]
BMI reduction from screening, rimonabant (kg/m^2)	2.98	2.76–3.19	Triangular (min = 2.76, mode = 2.98, max = 3.19)		
Reduced waist circumference, placebo (cm)	4.18	3.81–4.55	Triangular (min = 3.81, mode = 4.18, max = 4.55)		
Reduced waist circumference, rimonabant (cm)	8.24	7.95–8.54	Triangular (min = 7.95, mode = 8.24, max = 8.54)		
Utility transformation factor per unit BMI change	–0.0170	–0.0200 to –0.0146	Triangular (min = –0.0200, mode = –0.0170, max = –0.0146)	Base case: time trade-off estimate; min: visual analog scale, max: subgroup of patients	[25]
Change in annual diabetes incidence per BMI change (%)	0.079	0.073–0.098	Triangular (min = 0.073, mode = 0.074, max = 0.98)	Base-case values: weighted to reflect sex composition, min: estimate for women, max: estimate for men	[27,28]
Annual Incidence Diabetes (%), BMI = 37	1.013	0.854–1.533	Triangular (min = 0.854, mode = 0.858, max = 1.533)		
Change in annual CHD incidence per cm waist change (%)	0.00503	0.00308–0.01140	Triangular (min = 0.00308, mode = 0.00320, max = 0.01140)		[6,32]
Annual incidence CHD (%), waist circumference = 108 cm	0.232	0.166–0.447	Triangular (min = 0.166, mode = 0.168, max = 0.447)		
Sustainability of weight loss (years)	1	0.5–3	Lognormal (mean = 0, SD = 0.32)	Base case: RIO trials, max: NICE recommendations	[17–19, 24]
Daily drug cost	5.87	4.00–7.73	Lognormal (mean = 1.769, SD = 0.12)	AWP-15%: Base case: orlistat; min: sibutramine	[33]
Cost of MI, event and subsequent treatment for 1.5 years, discounted at 3%/year	24,579	21,200–28,500	Lognormal (mean = 10.11, SD = 0.77)	Range: 95% credible intervals as observed from Monte Carlo simulation	[40]
Cost of new onset diabetes for 1.5 years, discounted at 3%/year	11,191	9,400–13,500	Lognormal (mean = 9.323, SD = 0.09)		[52]
Dietician visits 1st year; cost (frequency)	420 (14 visits)	240–540 (8–18 visits)	Triangular (min = 240, mode = 420, max = 540)	Base case derived from RIO trials; $30 per visit	[17–19, 38]
Dietician visits 2nd year; cost (frequency)	300 (10 visits)	210–420 (7–14 visits)	Triangular (min = 210, mode = 300, max = 420)		
Physician visits 1st year, cost (composition)	208 ($1 \times 20 + 4 \times 10$ min)	136–264 ($1 \times 20 + 2 \times 10$ min $- 3 \times 20 - 2 \times 10$ min)	Triangular (min = 136, mode = 208, max = 264)	Base case derived from RIO trials; $64/20 min and $36/10 min visit, based on AMA-CPT-codes	[17–19]
Physician visits 2nd year, cost (composition)	144 (4×10 min)	108–208 (3×10 min $- 1 \times 20 + 4 \times 10$ min)	Triangular (min = 108, mode = 136, max = 208)		

*Distribution parameters were empirically chosen to achieve input distributions with means reflecting the base-case estimates.
Note: All costs in 2006 US$.
AMA, American Medical Association; AWP, average wholesale price; BMI, body mass index; CHD, coronary heart disease; CPT, current procedural terminology; MI, myocardial infarction; NICE, National Institute for Clinical Excellence; RIO, rimonabant in obesity.

Table 2 Results: cost-utility ratios of base-case scenario (for a single patient)

	RRN	PPN	NNN	RRN-PPN	RRN-NNN
Costs					
Drug cost	4,222.75	0.00	0.00	4,222.75	4,222.75
Physician cost	347.80	347.80	0.00	0.00	347.80
Dietician cost	711.26	711.26	0.00	0.00	711.26
Cost CHD	264.46	274.50	284.83	−10.04	−20.37
Cost diabetes	514.00	545.05	566.58	−31.06	−52.58
Total costs	6,060.27	1,878.61	851.41	4,181.66	5,208.85
Quality of life				0.00	0.00
QALYs gained	0.0984	0.0403	0.0000	0.0581	0.0984
Incremental cost-utility ratio*				71,973.43	52,935.52
95% confidence interval†				(51K–98K)	(39K–69K)

*In $ per QALY.
†From Monte Carlo simulation.
Note: All costs in 2006 US$.
CHD, coronary heart disease; NNN, no intervention; PPN, 2-year placebo; QALY, quality-adjusted life-year; RRN, 2-year rimonabant.

10,000 persons at risk). This incidence was reduced by 0.042% (4.2/10,000) with placebo (relative risk reduction [RRR]: 3.23%) and by 0.083% (8.3/10,000) with 2 years of rimonabant (RRR: 7.15%). For the no-intervention group, the 5-year cumulative incidence of type 2 diabetes mellitus was 5.06% (506/10,000), reduced by 0.192% (19.2/10,000) with placebo (RRR: 3.80%) and by 0.470% (47/10,000) with rimonabant (RRR: 9.28%).

Cost-Utility Analysis

The treatment options RNN and RPN were extendedly dominated by the remaining options, PPN, RRN, and NNN. Therefore, the options RNN and RPN were not included in further analyses.

The cost-utility analysis of RRN (2-year treatment with rimonabant) showed incremental costs of $5209 and incremental effectiveness of 0.0984 QALYs compared to no intervention, resulting in an ICUR of $52,936/QALY (95% CI $39K–$69K). Compared to PPN (2-year placebo), incremental costs of RRN were $4182 with an incremental effectiveness of 0.0581 QALYs, yielding an ICUR of $71,973/QALY (95% CI $51K–$98K) (Table 2).

Sensitivity Analysis

Applying a probabilistic sensitivity analysis, compared to NNN, RRN was cost-effective at $50,000/QALY in 40.2% of the simulations and compared to PPN in only 1.6% (Fig. 3). An array of acceptability curves for the comparison of RRN and NNN allows for the applicability of the results to different daily drug cost estimates at different willingness-to-pay thresholds (Fig. 4). It shows, for instance, that almost all simulations would show cost-effectiveness at $50,000/QALY if the daily drug cost was $4.00.

The one-way sensitivity analyses identified variables where a variation had a considerable impact on the ICUR. Critical variables were: daily drug cost, change in BMI, sustainability of weight loss, and utility

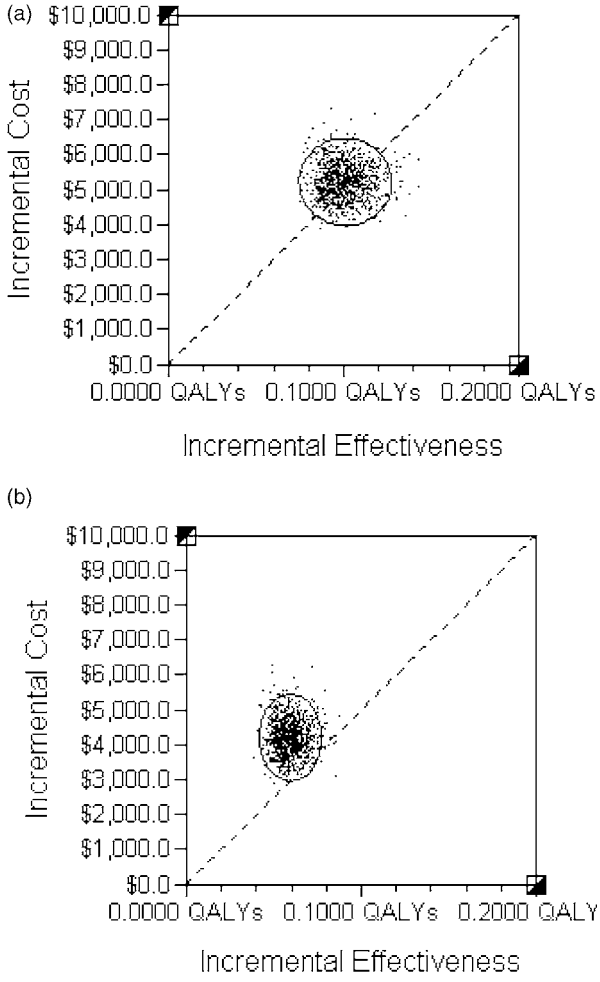

Figure 3 (a) Distribution of incremental cost-utility ratios from Monte Carlo simulation: rimonabant (RRN) vs. no intervention (NNN). The scattered line represents the commonly used $50,000/QALY threshold; points above would not be cost-effective at this threshold. (b) Distribution of incremental cost-utility ratios from Monte Carlo simulation: RRN vs. placebo (PPN). Points above would not be cost-effective at this threshold. QALY, quality-adjusted life-year; incremental cost in 2006 US$.

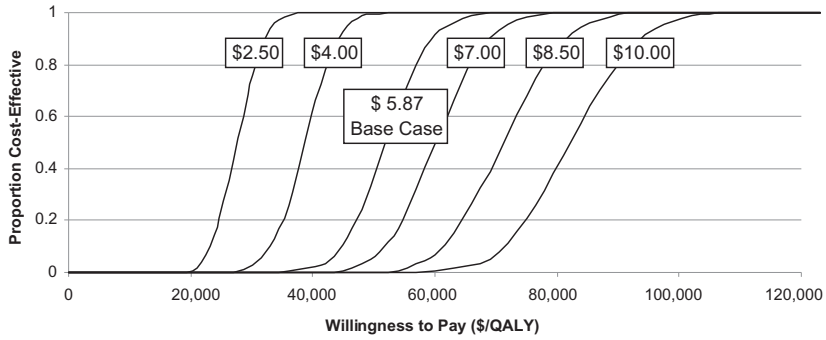

Figure 4 Acceptability curves: rimonabant vs. no intervention. Curves describe proportion of Monte Carlo simulations cost-effective at different willingness-to-pay thresholds; each curve for a separate daily drug cost estimate. QALY, quality-adjusted life-year.

transformation factor. Variables that somewhat affected the ICUR over no intervention were physician and dietician cost. The remaining variables had no major impact on the ICUR (Fig. 5). Because waist circumference is highly correlated with BMI [29], we conducted a sensitivity analysis where both variables were varied simultaneously. The combined influence of both variables on the ICUR, however, resembled the influence of change in BMI alone.

Discussion

Two-year treatment with rimonabant 20 mg in conjunction with lifestyle intervention is efficacious in reducing body weight, BMI, and waist circumference. It also has the potential to reduce the incidence of obesity-related comorbidities such as CHD and diabetes mellitus, and consequently improve HRQOL. These improvements are related to considerable expenditures and have to be viewed in the context of alternative interventions to manage obesity. For orlistat in the United Kingdom, Foxcroft et al. reported a cost-utility ratio of £24,431/QALY (sensitivity range: £10,856–77,197/QALY) [42]. In Ireland, orlistat has shown to be cost-effective at U20AC; €16,954/QALY (range: U20AC; €11,000–35,000/QALY) [43]. Hertzman found a cost-utility ratio of U20AC; €13,125/QALY in Sweden and Maetzel et al. reported $8327 per event-free life-year gained in their US model [44,45]. The cost-utility ratio of the second pharmacologic alternative, sibutramine, was estimated at $9299/QALY [46]. The wide range of cost-effectiveness estimates for pharmacologic weight-loss interventions is due partly to different underlying assumptions across the studies, including ours, such as the inclusion of comorbidities and the use of a treatment-responder approach (described below). Furthermore, time to weight regain after treatment cessation in previous studies is typically 3 years; however, the clinical trials on rimonabant suggest a shorter sustainability of 1 year. Variation in sustainability considerably impacts the ICUR as the results of the sensitivity

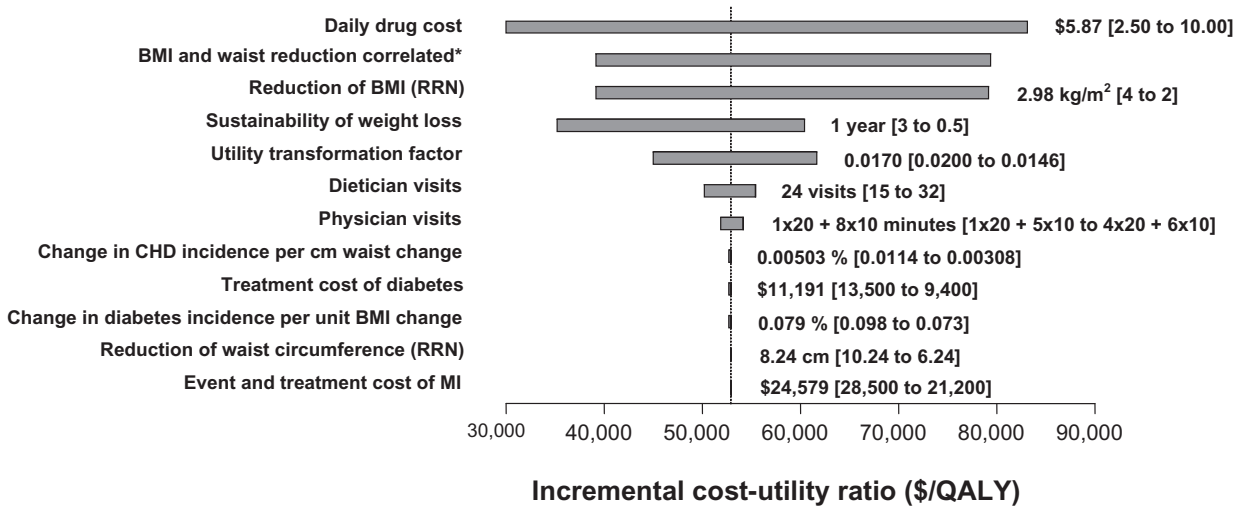

Figure 5 Effects of variation in the model parameters on the incremental cost-utility ratio, RRN vs. NNN. The labels describe the base-case estimates and ranges of variation in parentheses. The dotted line indicates the cost per QALY at the base-case scenario. *BMI and waist change were varied simultaneously with the parameters: reduction of BMI (RRN): 2.98 kg/m^2 [4 to 2], change in waist circumference (RRN): 8.24 cm [10.24 to 6.24]. BMI, body mass index; CHD, coronary heart disease; MI, myocardial infarction; NNN, no intervention; QALY, quality-adjusted life-year; RRN, 2-year rimonabant.

analysis indicate (Fig. 5). Increasing sustainability to 3 years would reduce the ICUR for rimonabant versus no intervention to $35,394/QALY.

Another factor to be taken into consideration is that medical costs, especially drug acquisition costs, differ widely between Europe and the United States. The daily cost for orlistat in the United Kingdom as used by Hertzman [46] is about half the AWP of orlistat in the United States. This difference is likely to contribute to lower ICURs as the results of a variation in daily drug costs in our sensitivity analysis suggest (Fig. 5).

Some of the studies above used the so-called treatment responder approach which may partly account for lower ICURs. This approach, as included in the orlistat guideline of NICE in the United Kingdom, recommends treatment with orlistat only if a patient shows an initial weight loss with diet and exercise alone [24]. Once initiated, physicians may only continue treatment if the patient successfully loses 5% of body weight after 3 months and 10% after 6 months. Hence, this treatment algorithm targets the intervention to patients for whom the drug is likely to show a higher effectiveness, avoiding drug costs associated with nonresponse. In our study, however, we employed data of clinical trials' intention-to-treat population, a population in which not every patient successfully finished the treatment course. Using the treatment responder approach for pharmacoeconomic studies is likely to show more favorable cost-utility ratios due to increased effectiveness. The difference in ICURs based on the approach chosen is obvious in the case of orlistat where Foxcroft and Milne reported an ICUR of £45,881/QALY without a treatment responder approach [47], and in 2005, Foxcroft reported £24,431/QALY using the treatment responder approach [46].

We did not model the treatment responder approach because of the lack of information contained in the clinical trials publications and more so because it is unclear whether a similar treatment guideline would be used for rimonabant in the United States. Again, the sensitivity analyses showed the impact of a potential increase in average effectiveness on the ICUR. If, for instance, the BMI could be lowered by 4 kg/m^2, the ICUR would be reduced to $39,267/QALY compared to no intervention. A treatment responder approach is presumably associated with triage costs resulting from the need to evaluate treatment success. Yet, the sensitivity analysis showed that the cost of physician office visits only marginally impacts the ICUR, and should therefore not be a hurdle in the implementation of this approach.

Our model suggests that the largest benefit to treatment with rimonabant is an improvement in quality of life. Cost-savings due to prevented comorbidities are present, but fairly small (about 1.4%) compared to the treatment costs (derived from Table 2). This conclusion is supported by the sensitivity analysis (Fig. 5) which shows that changes in variables related to comorbidities (waist change, change in diabetes incidence per BMI, change in CHD incidence per cm waist change, and costs of diabetes and MI) have a minor impact on the ICUR. This observation is associated with a relatively low baseline incidence of CHD and diabetes over the observation period. Even a considerable relative decrease in the 5-year incidence of diabetes (9.28%) translates into a smaller absolute decrease due to the low baseline incidence. At an absolute decrease in diabetes risk of 0.47%, about 213 patients need to be treated for 2 years to prevent the occurrence of one case of diabetes in 5 years. This estimate is based on the assumption that the decrease is solely associated with the reduction in BMI. Similarly, the baseline cumulative incidence of CHD over 5 years (1.16%) was associated with a relative decrease by 7.15% with 2 years of rimonabant, which translates into an absolute decrease of 0.083% or 1205 patients needed to be treated to prevent one event. Our model did not include disutility values associated with CHD and diabetes; however, the low incidences of these comorbidities suggest that the impact of comorbidities on the overall quality of life in this study would be very small.

The results of this study should be interpreted with several limitations in mind. First, the model was based on clinical trials where the efficacy of the intervention is generally determined in a controlled environment in which patients may adhere and react differently to the intervention because they are aware that they are part of a study (Hawthorne effect). Patients in efficacy trials usually represent a homogenous population with only limited variability in characteristics and comorbidities which may increase the response to treatment [48]. Basing studies on the effectiveness of the drug under general practice conditions should be an objective of future economic analyses.

Second, the utility transformation factor used to calculate the impact of weight reduction on quality of life is based on a different drug, orlistat. In the reference study, however, data were pooled over the placebo and treatment arms [25]. Thus, it is reasonable to argue that the gain in quality of life is attributed to the reduction in BMI itself rather than to the means of reduction and is therefore applicable to our scenario. Nevertheless, because of the large impact on the ICUR in our model, a utility transformation factor established for the treatment with rimonabant should be used on availability.

Third, because rimonabant was not on the US market at the time of conducting the study, the drug acquisition cost had to be estimated based on similar drugs. However, the monthly cost for rimonabant in the United Kingdom is £55.20 [49], about £10 above the monthly cost for orlistat used by Foxcroft [42]. This supports our assumption that the likely acquisi-

tion cost in the United States is covered by the price range used in our model which is based on US costs for orlistat.

Fourth, we assumed that weight loss and reduction in waist circumference reduce the incidence of diabetes and CHD, respectively. Yet, only the study by Wannamethee et al. showed a longitudinal relationship between weight loss and a reduction in the incidence of diabetes [27]. The other three studies used to estimate disease incidences only reported cross-sectional associations. For instance, Hu et al. reported that a lower BMI level is associated with lower risk for diabetes in women [28]. Similarly, Rexrode et al. [6,32] assessed the cross-sectional association between waist circumference at one point in time and CHD risk. We were unable to identify any longitudinal studies which established a causal relationship between changes in waist circumference and a reduced incidence of CHD.

Finally, recent research has suggested that the benefit of treatment with rimonabant on obesity-related diseases goes beyond what can be explained by weight loss alone [50,51]. Improvements in HbA1c, HDL-cholesterol, and triglycerides independent from weight loss and their impact on comorbidities were not included as benefits in our model and are subject to future research.

These results allow for several policy implications. The high impact of drug acquisition cost on the cost-utility ratio suggests that the ICUR can vary significantly between different purchasers in the United States who pay different fractions of the AWP. In addition, the ICUR is highly influenced by measures of efficacy, with a higher BMI reduction leading to more favorable ICURs. A treatment responder approach as suggested by NICE for Orlistat can help target the intervention to patients where the drug promises a higher effectiveness and thus improve cost-effectiveness. Finally, if an increase in sustainability of weight loss could be achieved, perhaps with ongoing lifestyle interventions after pharmacologic treatment, the benefits could be extended. If this extension is feasible at reasonable cost, a lower ICUR may be the result.

Conclusion

Rimonabant has shown to be efficacious in reducing excess body weight with the potential to decrease the rate of obesity-related comorbidities and improve health-related quality of life, albeit at considerable cost. Future analyses should include real-world effectiveness data, market prices of rimonabant, and benefits not explained by weight loss alone.

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