

ORIGINAL ARTICLE

The cost-effectiveness of bortezomib in relapsed/refractory multiple myeloma: Swedish perspectiveJohn Hornberger^{1,2}, Joseph Rickert¹, Ravinder Dhawan³, Johan Liwing⁴, Johan Aschan⁴, Mikael Löthgren⁴¹Cedar Associates LLC, Menlo Park, CA; ²Stanford University School of Medicine, Stanford, CA; ³Johnson & Johnson, Raritan, NJ, USA;⁴Janssen-Cilag, Sollentuna, Sweden**Abstract**

Objectives: To estimate the cost-effectiveness of bortezomib (BTZ) compared with dexamethasone (DEX) and lenalidomide plus dexamethasone (LEN/DEX) for the treatment of relapsed/refractory multiple myeloma in Sweden. *Methods:* We used partitioned survival analysis to assess survival data decomposed into three states: (i) alive before disease progression; (ii) alive after progression; and (iii) dead. The effects of treatment on time to progression and overall survival (OS) were obtained from published reports of the APEX, MM-009, and MM-010 randomized clinical trials. Costs included drug and administration costs, adverse events, treatment of relapses, and end-of-life costs. Utility estimates were derived from the literature. *Results:* BTZ mean OS was 57.4 months compared with 44.6 and 54.1 months for DEX and LEN/DEX, respectively. Mean lifetime direct medical costs per patient were approximately 2010 SEK 1 904 462, 1 278 854, and 2 450 588 for BTZ, DEX, and LEN/DEX, respectively. Mean incremental cost per quality-adjusted life-year of BTZ compared to DEX was 2010 SEK 902,874 (€95 073) (95% CI: 514 791, 962 416) and was dominant with respect to LEN/DEX. *Conclusion:* BTZ and LEN/DEX are projected to prolong survival relative to DEX. From a Swedish perspective, BTZ is cost-effective compared to DEX and LEN/DEX.

Key words bortezomib; cost-effectiveness; dexamethasone; lenalidomide; multiple myeloma**Correspondence** John Hornberger, MD, MS, 275 Middlefield Road, Suite 200, Menlo Park, CA 94025, USA. Tel: +650 327 2085; Fax: +650 327 1506; e-mail: ujch@stanford.edu

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Multiple myeloma (MM), a clonal proliferation of plasma cells, results in skeletal destruction, anemia, hypercalcemia, renal insufficiency, and death. The annual incidence rate of MM in developed countries is between five and seven cases per 100 000 people (1–3). Based on this incidence rate, we estimate that approximately 3100 cases were diagnosed in Sweden between 2004 and 2008.

Until approximately 4 yr ago, the primary chemotherapy options for relapsed/refractory MM included conventional alkylating agent-based chemotherapy and corticosteroids. Unfortunately, response to treatment with these agents often does not persist, and it is not uncommon for patients to receive several treatments with 1 or more agents (4–6). A study with 355 patients at the Mayo Clinic found that response to treatment decreased progressively with each successive treatment, and most

patients (84%) died within 5 yr of initiating their second treatment.

Bortezomib (BTZ, VECLADE™; Millennium [Takeda], Cambridge, MA, USA; EU authorization in 2005) and lenalidomide (LEN, Revlimid™; Celgene Corp., Summit NJ, USA; EU authorization in 2007) are being used for relapsed/refractory MM, and survival rates for these new regimens have increased substantially (4, 7–9). For example, in a randomized trial with 669 patients having relapsed MM that compared high-dose dexamethasone (DEX) to BTZ, median overall survival (OS) for BTZ was 29.8 months compared with 23.7 months for DEX (7). Similar results were observed in a pooled analysis of two recent trials for patients with at least one previous therapy that compared LEN/DEX to DEX (8–10). These trials were conducted primarily in the United States (US) and

Europe, and reported a median OS of 38.0 months for LEN/DEX and 31.6 months for DEX alone (10).

Many countries, including Sweden, require analyses of the comparative effectiveness and cost-effectiveness of treatments prior to authorizing funding and reimbursement of new agents. The goals of this project were to analyze the comparative effectiveness and cost-effectiveness of the chemotherapy regimens for management of relapsed/refractory MM.

Methods

Model structure

A model was developed based on a 'partitioned survival analysis' analytical framework to compare BTZ, DEX, and LEN/DEX. The model employed a simple architecture that integrated the relevant BTZ, DEX, and LEN/DEX information from pivotal clinical trials. The analytic framework was based on 'partitioned survival analysis' that allowed survival data to be decomposed into three states: (i) alive before disease progression; (ii) alive after progression; and (iii) dead (11, 12).

The Swedish Council on Technology Assessment in Health Care (SBU) or the Swedish Dental and Pharmaceutical Benefits Agency (TLV) do not recommend a specific type of analytic framework. While Markov models are commonly used in oncology, a partitioned survival analysis was used instead because of the lack of access to data required to compute state transition probabilities. In contrast, the Kaplan–Meier estimates of time to progression (TTP) and death for all trials were available in peer-reviewed literature and were sufficient for a reliable partitioned survival analysis. Moreover, partitioned survival analysis is a well-accepted alternative framework (13). The average time after progression was computed as the difference in OS and TTP. A utility score was assigned to each state to account for the effects of disease and treatment on quality of life. Utility scores range from 0 to 1, in which 0 represents the state of death and 1 represents a condition approximating perfect health (or sometimes referred to as best attainable health); values between 0 and 1 represent degrees between these extremes. A patient's lifetime, or cumulative utility, referred to as quality-adjusted life-years (QALYs), is computed as the contribution of the time spent in each state multiplied by the utility assigned to that state (14).

Target population

The target population consisted of individuals aged 18 and older, diagnosed with MM, who relapsed after first-line therapy or who have refractory disease and are eligible for second-line therapy. The patients were

assumed to possess baseline characteristics comparable to the participants of the pivotal clinical trials who had only one prior therapy (7–9, 15).

Interventions

The model compared three regimens: BTZ, DEX, and LEN/DEX. The dosages for each regimen were taken from the same clinical trials identified as data sources for the effects of various regimens. BTZ was administered intravenously, 1.3 mg/m², on days 1, 4, 8, and 11 of cycles 1 through 8 (21-d cycles), then days 1, 8, 15, and 22 of cycles 9 through 11 (35-d cycles) (7, 15). For DEX, patients ingested 40 mg of DEX orally on days 1–4, 9–12, and 17–20 of cycles 1 through 4 (35-d cycles) and on days 1–4 of cycles 5 through 9 (28-d cycles), for a maximum treatment period of 280 d (8, 9). For LEN/DEX, patients received 25 mg of LEN daily on the first 21 d of each 28-d cycle. Patients also received DEX as mentioned earlier for the first four cycles. After the fourth cycle, patients received DEX only on days 1 through 4 of each cycle. Treatment was continued until disease progression or the occurrence of a significant adverse event (8, 9).

Data

The primary data source for the effects of BTZ was the APEX study, a randomized open-label, phase-3 study conducted at 93 centers in Canada, Europe, Israel, and the United States from June 2002 to October 2003 (7, 15). Six hundred and sixty-nine patients having measurable, progressive disease after 1–3 previous treatments were randomly assigned to either BTZ or DEX. The median age of participants was 62 yr in the BTZ arm and 61 yr in the DEX arm, and the percentage of male patients in each arm was 56% and 60%, respectively. The primary end point of the study was TTP. Secondary end points included OS, complete response, and partial response. Patients receiving DEX were permitted to cross-over to the BTZ arm after disease progression. The median follow-up time for surviving patients was 22 months. Median OS was 29.8 months in the BTZ arm and 23.7 months in the DEX arm.

The data sources for DEX and LEN/DEX were the two trials MM-009 and MM-010 (8, 9). The MM-009 trial was conducted in 44 centers in the United States and four in Canada with participants enrolled from February 2003 to April 2004 (8). The MM-010 was conducted with participants enrolled between September 2003 and September 2004 at 41 centers in Europe, six in Australia, and three in Israel (9). The pooled analysis of the MM-009 and MM-010 studies considered 704 patients from both trials who were randomized to receive

either LEN/DEX or DEX alone (10). Previous treatments for MM included radiotherapy, myeloablative therapy with stem-cell transplantation, BTZ and various combinations of BTZ, DEX, doxorubicin, melphalan, thalidomide, and other agents. Participants assigned to the DEX arm ranged from 37 to 82 yr (median 63 yr), while participants assigned to the LEN/DEX arm ranged from 33 to 86 yr (median 63 yr). TTP was the primary end point of the study; secondary end points included OS and response rate. The median follow-up time for all participants was 48 months. Table 1 describes the end points, patient populations, and treatment schedules for the three trials.

Overall survival and time to progression

The model uses TTP and OS to estimate the mean duration a representative patient would spend in two of the three health states for each treatment under consider-

ation: (i) alive before disease progression; and (ii) alive after progression. These quantities were estimated by first deriving hazard rates for TTP and OS from the data and then iteratively computing the probability of being in each health state per 21-d cycle. The hazard ratios reported in the literature were used to estimate the TTP and OS probabilities in each cycle.

Prior to unblinding, no cross-over from DEX to LEN/DEX was reported in the LEN/DEX studies (8). In contrast, cross-over from DEX to BTZ was permitted in the APEX trial after progression. Hence, survival in the DEX arm of APEX is likely to be biased by the use of BTZ relative to the DEX arm of the LEN/DEX studies. To model this situation, we assumed that TTP and OS of the pooled analysis of the DEX arms of the LEN/DEX studies reflected the outcomes of patients when neither BTZ nor LEN/DEX was available (8, 9). In the model, TTP beyond 1.5 yr and OS beyond 2 yr for DEX therapy were extrapolated by assuming a con-

Table 1 Characteristics of key trials

Parameters	BTZ from APEX NCT00048230		LEN/DEX from pooled MM-009 and MM-010	
Participants	669		704	
Primary end point	Time to progression		Time to progression	
Treatment	BTZ	DEX	LEN/DEX	DEX
N	176	175	353	351
Median age (yr)	63	64	63	63
% Male	59.1	58.9	59.5	59.0
Prior therapies (median)	2		2	
Inclusion criteria	Measurable disease		Measurable disease	
Disease stage	One to three		At least 1 prior therapy	
No. prior lines of therapy	≥30 000		≥75 000	
Platelets (μL)	≥10		≥20	
Creatinine clearances (mL/min)	500		1000	
Minimum ANC (absolute neutrophil count) (cells/mm)				
Patient characteristics				
ECOG* performance status	–		<2	
Serum aminotransferase level (IU/L)	–		Not >3x normal	
Serum bilirubin level (mg/dL)	–		Not >2x normal range	
Serum creatinine level (mg/dL)	–		<2.4	
Exclusion criteria				
Previous treatment	Velcade therapy		>3 prior therapy for MM	
Refractory	To high-dose DEX		To high-dose DEX	
Other factors	Peripheral neuropathy ≥ grade 2 Significant coexisting illness		Patients with abnormal lab values (serum creatinine > 2.5 mg/dL)	
Dose and schedule	1.3 mg/m ² d 1, 4, 8, 11 of 21 d cycle		25 mg/d for 21 d out of 28 d cycle + 40 mg of DEX on days 1–4, 9–12 and 17–20	
			40 mg of DEX on days 1–4, 9–12 and 17–20	

BTZ, bortezomib; DEX, dexamethasone; LEN/DEX, lenalidomide + dexamethasone.

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stant hazard rate equal to the hazard rate computed for the last time period covered by the published data. The empirical hazard ratios reported in the pooled MM-009 and MM-010 analysis were used to model TTP and OS for the LEN/DEX arm (10).

Utilities

Utilities were assigned after conducting a literature review of published utility scores (16–19). The range of utility values obtained using the EuroQol EQ-5D for other chemotherapy treatments ranged from 0.81 at 6 and 18 months for intensive chemotherapy to 0.64 for non-responders (19). No published data were available on the utility loss associated with adverse events. Because the total incidences of adverse events were approximately similar, the events were temporary, and assessments of the utility of chemotherapy included all aspects of chemotherapy, we assumed that there was no difference between treatments in utility associated with adverse events (Table 3).

Costs

The incidence rates for Grade 3/4 adverse events associated with DEX were calculated as a simple average of the rates from the APEX, MM-009, and MM-010 trials. Incidence rates associated with LEN/DEX were the average rates from the MM-009 and MM-010 trials. The rates for BTZ came from the APEX trial (Table 2). Costs of treating chemotherapy-associated severe adverse events, cost of care for patients with MM per regimen, as well as unit chemotherapeutic drug costs in Sweden, were obtained from a Swedish chart review study (20) (Table 3). Drug costs were computed on unit price multiplied by mean duration of therapy and mean

dose. The costs for intravenous administration of BTZ were obtained from the price list in the southern health care region (20). BTZ was associated with higher incidence of thrombocytopenia (30%) and pain, including neuropathy, (15%), whereas LEN/DEX was associated with higher incidence of neutropenia (21%) and deep-vein thrombosis (10%). The estimated costs for treating serious adverse events for BTZ, DEX, and LEN/DEX were SEK 58 868, SEK 47 095, and SEK 56 671, respectively (Table 4) (21). The model does not stratify costs for neuropathy, an event known to be associated with BTZ, because the source used for the Swedish cost data does not report the cost of neuropathy separately. Therefore, the incidence rates for neuropathy and pain are combined into a single event reported as pain to

Table 3 Model inputs

Parameters	BTZ	LEN/DEX	DEX
Cost discount rate (%)	3.0	3.0	3.0
Effects discount rate (%)	3.0	3.0	3.0
Time horizon, yr	10.00	10.00	10.00
Hazard rates			
Mortality	0.57	0.71	0.013
Progression	0.56	0.34	0.076
2nd line costs (2010 SEK)			
Chemotherapy costs	340 572	1 129 224	19 989
Administration costs	34 221	0	0
Cost of adverse events (2010 SEK)	58 868	56 671	47 095
Cost of other care (2010 SEK)	17 636	17 636	17 636
Monthly cost of ≥3rd line (2010 SEK)	31 334	31 334	31 334
QoL adjustment (utility)			
Prior to relapse	0.81	0.81	0.81
After relapse	0.645	0.645	0.645

Table 2 Incidence of Grade 3/4 adverse events

Severe adverse event	Cost per event (SEK 2010)	Incidence			Cost (SEK 2010)		
		BTZ (%)	DEX (%)	LEN/DEX (%)	BTZ	DEX	LEN/DEX
Anemia	62 715	10.0	11.0	8.4	6272	6899	5268
Thrombocytopenia	53 795	30.0	6.0	10.2	18 815	3763	6397
Neutropenia	69 459	14.0	1.0	21.0	8780	627	13 170
Cardiac	33 466			2.9	0	0	1819
Pain (limb, abdominal, neuropathy, bone)	34 684	15.0	6.0		9407	3763	0
Fatigue	7300	5.0	4.0	6.1	3136	2509	3826
Stroke	106 225				0	0	0
Syncope	66 388			2.0	0	0	1254
DVT and PE	35 827			10.1	0	0	6334
Others	53 640	1.0	32.0	11.5	627	20 069	7212
		75.0	60.0	72.2	47 036	37 629	45 280

Sources: Richardson *et al.* (15) (Table 3 on page 2495), Rajkumar 2006 (38) (Table 2 on page 434).

Table 4 Model results

Outcomes	BTZ	LEN/DEX	DEX	Difference BTZ vs.	
				LEN/DEX	DEX
Mean overall survival (month)	57.4	54.1	44.6	3.4	12.9
Mean discounted overall survival (month)	51.9	48.8	40.5	3.0	11.3
% Alive at 1 yr	86	82	76	3	10
% Alive at 2 yr	72	67	57	6	16
% Alive at 5 yr	43	40	30	3	13
QALYs (months)	35.4	34.9	27.1	0.46	8.3
2nd-line costs (2010 SEK)					
Drug and administration	374 793	1 129 223	19 989	-754 431	354 804
Management of AEs	58 868	56 671	47 095	2198	11 774
Cost of other care	197 779	369 684	102 576	-171 904	95 204
Costs of 3rd and higher lines (2010 SEK)	1 273 021	895 010	1 109 195	378 011	163 826
Total cost	1 904 462	2 450 588	1 278 854	-546 126	625 607
Cost per discounted LYG (2010 SEK)				BTZ cost saving	662 621
Cost per QALY (2010 SEK)				BTZ cost saving	902 874

BTZ, bortezomib; DEX, dexamethasone; LEN/DEX, lenalidomide + dexamethasone.

accurately report the costs of these adverse events and adjust for the limitations imposed by the Swedish cost data.

The mean number of administrations for patients receiving BTZ in the APEX trial was 24.7 (range 1–44) (22). The drug cost per administration was SEK 13 788, and the cost for services to administer BTZ intravenously was SEK 1463. Patients assigned to DEX had a mean of 38.3 doses of DEX (20, 23). The cost for twenty-seven 1.5 mg tablets of DEX was SEK 298 (24). The cost of twenty-one 25 mg capsules of LEN was SEK 76 053 (23, 25). In second line before progression, monthly cost of care excluding chemotherapy-related costs was estimated to be SEK 17 636. In third line after progression, monthly cost of care, including chemotherapy-related costs, was estimated to be SEK 31 334.

All unit costs were reported in 2010 Swedish Krona. The model assessed costs over the lifetime of the representative patient or 10 yr, whichever was shorter. Both costs and benefits were discounted at 3% per year, as recommended by the Swedish Pharmaceutical Benefits Board (26) (Table 3). To allow readers outside of Sweden to better understand the results of the cost effectiveness analysis, the ICER was also reported in Euro. The conversion was based on publicly available average Euro-Krona exchange rate for 2010.

Sensitivity analyses

Both one-way sensitivity and probabilistic sensitivity analyses (PSA) were used to assess the impact of key parameters as well as to find out which parameters were the most important drivers for the model. The key parameters included are hazard ratios affecting OS and TTP, cost of the regimens (e.g., drug and administration

costs and cost of other care), utility values, and the discount rates. In the probabilistic sensitivity analysis, hazard ratios typically are estimated as having log normal distributions [$\ln(\text{hazard ratio}) \sim \text{Normal}(\mu, \sigma^2)$]. Costs commonly have a skewed distribution, so log normal distributions were used for all cost variables. Because unit costs of drugs are fixed, they typically would not vary according to a probability distribution. However, even though compliance with treatment in APEX was high, the number of administrations varied. We therefore varied the total costs according to log normal distributions centered on their point estimates and having standard deviations (SD) of 0.1. Utilities were varied according to beta distributions. Within the base case, we assumed that the duration of treatment effect was limited to 3 yr based on the median survival of the APEX trial having been updated to 29.8 months and a survival benefit still persisting for the BTZ cohort (15).

Quality of evidence and analytic validity

Based on standard methods of grading evidence, (Appendix S1) the estimate of treatment effect between BTZ, DEX, and the other treatment regimens is based on Level I evidence (5, 7–9, 15, 27–31). Data on the costs associated with managing severe treatment-related adverse events and costs of medical procedures were taken from recently published Swedish literature (Appendix S2) (21, 32).

Results

Table 3 summarizes all input parameters to the model. Mean OS for BTZ, DEX, and LEN/DEX were projected to be 57.4, 44.6, and 54.1 months, respectively (Table 4).

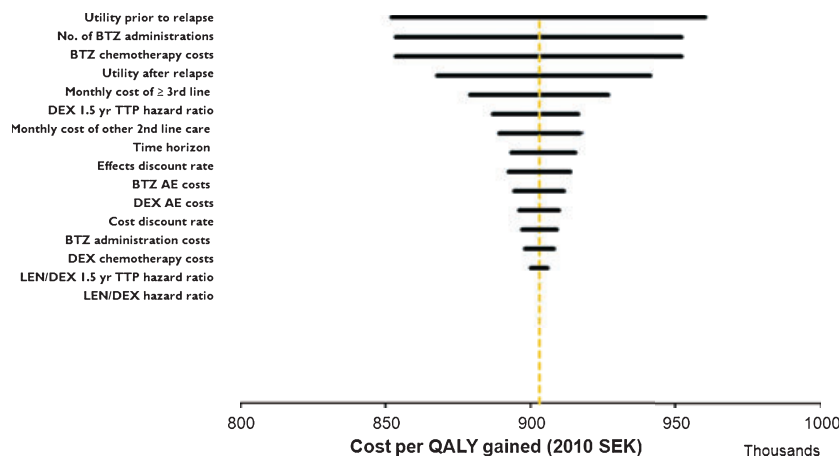


Figure 1 One-way sensitivity analyses, bortezomib vs. dexamethasone.

Quality-adjusted life years gained for BTZ were 2.95 months, whereas the QALYs for DEX and LEN/DEX were 2.26 and 2.91 months, respectively.

Mean lifetime direct medical costs per patient were approximately 2010 SEK 1 904 462, 1 278 854, and 2 450 588 for BTZ, DEX, and LEN/DEX, respectively (Table 4). BTZ increased both costs and QALYs relative to DEX. Mean incremental cost per QALY of BTZ compared to DEX was SEK 902 874 (€95 073) (95% CI: 514 791, 962 416). BTZ showed a cost savings with respect to LEN/DEX.

The results of the one-way sensitivity analyses of BTZ vs. DEX (Fig. 1) show that the four most influential parameters were (i) utility prior to relapse, (ii) BTZ chemotherapy costs, (iii) number of BTZ administrations, and (iv) utility after relapse.

Discussion

This study is the first to explore the economic implications of emerging chemotherapeutic options for relapsed/refractory MM. Both BTZ and LEN/DEX have been shown in randomized controlled trials to improve survival over DEX in patients with relapsed/refractory MM. Our analysis further suggests that the benefit in terms of QALYs gained for each of these drugs relative to DEX exceeds 0.65 (~8 months), while mean discounted OS for both drugs over DEX exceeds 8 months.

The purpose of this analysis is to provide National Swedish authorities and regional health care decision makers with supportive evidence on the relative effectiveness and incremental cost-effectiveness of BTZ vs. LEN/DEX or DEX.

The Swedish pricing and reimbursement authority (TLV) has no explicit cutoff threshold for an incremental cost-effectiveness ratio. BTZ was found to be cost-effective relative to DEX and to be cost saving relative to LEN/DEX. Note that the World Health Organization

(WHO) reports an affordable cost-effectiveness threshold as less than three times per capita GDP (approximately 993 000 SEK in 1Q 2010) (33–35). The cost-effectiveness of BTZ relative to DEX is well below this threshold. Cost-effectiveness ratios tend to decline as more follow-up data on survival are gathered that illustrate the persistency of treatment effect on survival. Our analysis suggests that BTZ may be a cost-effective alternative to DEX for relapsed/refractory patients. This is in line with the decision taken by the Swedish Dental and Pharmaceutical Benefits Agency (36). Furthermore, our analysis suggests that BTZ is a cost-effective alternative to LEN/DEX for relapsed/refractory patients. This is also in line with the decision taken by the Swedish Dental and Pharmaceutical Benefits Agency, where LEN/DEX is reimbursed only for those patients for whom treatment with BTZ is unsuitable (37).

Conclusions drawn from the model are clearly contingent on the information derived from the clinical trials, and one must exercise caution in interpreting results. Two issues are of particular importance. First, although the majority of patients crossed over after the premature termination of the APEX study, there were a few patients in the DEX arm who had progressed before termination and crossed over to BTZ earlier. The hazard ratios may in fact have been even lower if the trial had lasted longer and if relapse after DEX had involved treatment with other currently available therapies (and not just BTZ). Second, the duration of treatment effect remains unknown at this point.

Despite the difficulties involved in integrating information from several clinical trials, the model captures the fundamental uncertainties within its analytical framework. The effect of uncertainty on the cost-effectiveness of the treatments modeled can best be appreciated by considering the effect of decreasing the uncertainty associated with the model parameters varied in the PSA. Decreasing the SD of the distributions associated with

these parameters by 50% results in a 53% decrease in the width of the 95% CI for the mean cost per QALY of BTZ vs. DEX reported earlier, while decreasing the SD by 75% results in a 77% decrease in the width of the CI. Decreasing SD of only the top four parameters identified by the one-way sensitivity analysis reported above results in an approximate 50% decrease in the width of the CI. These results suggest that while a substantial amount of uncertainty captured by the model is associated with just four parameters, overall, uncertainty scales approximately linearly with the parameter set varied in the PSA.

Our analysis indicates that the new class of treatments for MM exemplified by BTZ and LEN/DEX show promise in increasing survival and improving the quality of life for patients with MM. Given the high mortality rates associated with relapsed MM and the age of the affected population, the potential for increasing survival at manageable incremental cost should be of paramount importance to both clinicians and patients alike.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Appendix S1. Validity of economic analyses

Appendix S2. Grading of evidence

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