MIFAMURTIDE FOR OSTEOSARCOMA

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Date completed 16 January 2009

Source of funding: This report was commissioned by the NIHR HTA Programme as project number 08/77/01.

Declared competing interests of the authors: None.

Acknowledgements

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We would also like to thank Andrea Shippam, Project Administrator, ScHARR, for her help in preparing and formatting the report.

Rider on responsibility for report: The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

This report should be referenced as follows:

Pandor A, FitzGerald P, Stevenson M, Papaioannou D. Mifamurtide for osteosarcoma: A Single Technology Appraisal. ScHARR, The University of Sheffield, 2009.

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List of abbreviations

ASCO	American Society of Clinical Oncology
CEAC	Cost-Effectiveness Acceptability Curve
CI	Confidence Interval
CIC	Commercial-In-Confidence
EQ-5D	EuroQol-5D
ERG	Evidence Review Group
ESMO	European Society of Medical Oncology
HRQoL	Health-Related Quality of Life
ICER	Incremental Cost Effectiveness Ratio
ITT	Intention-To-Treat
mg/d	milligrams per day
mg/dL	milligrams per decilitre
MLE	Maximum Likelihood Estimate
MS	Manufacturer's Submission
MR	Manufacturer's Responses
NICE	National Institute for Health and Clinical Excellence
PSA	Probabilistic Sensitivity Analyses
QALY	Quality Adjusted Life Year
RCT	Randomised Controlled Trial
RR	Relative Risk
SPC	Summary of Product Characteristics
µmol/L	micromoles per litre

1 SUMMARY

1.1 Scope of the submission

The manufacturer's submission (MS) generally reflects the scope of the appraisal issued by NICE, and is appropriate to the NHS. The majority of the MS reflects the use of mifamurtide in individuals with osteosarcoma who have undergone surgical resection; however, it does not reflect the broader population outlined in the NICE scope (individuals with osteosarcoma related to Paget's disease, individuals with metastatic disease and individuals with relapsed osteosarcoma). The MS defines the intervention as mifamurtide as an add-on treatment to post-operative multi-agent adjuvant chemotherapy (3- or 4- agent adjuvant chemotherapy using high dose methotrexate, doxorubicin, cisplatin with/without ifosfamide). The decision problem defines the population and the intervention in relation to the proposed licensed indication (mifamurtide is indicated as a combination therapy with post operative multi-agent chemotherapy in children (from two to 12 years), adolescents (from 12 to 18 years) and young adults for the treatment of high-grade resectable, non-metastatic osteosarcoma after macroscopically complete surgical resection), a more tightly defined group than that stated in the NICE scope. The MS considered post-operative multi-agent chemotherapy as the most relevant comparator, as reflected in the scope. The outcome measures identified in the scope were all relevant and included overall survival, disease-free survival, adverse effects and health related quality of life. The results provided are presented in terms of cost per quality adjusted life year (QALY) with a time horizon of 12.25 years within the base case, which is extended to 20, 40 and 60 years within the sensitivity analyses, with the perspective of costs taken from an NHS and Personal Social Services perspective.

1.2 Summary of submitted clinical effectiveness evidence

- The evidence in the submission is derived from one head-to-head, phase III, four-arm (Regimen A, methotrexate, doxorubicin and cisplatin; Regimen A+, Regimen A plus mifamurtide; Regimen B, methotrexate, doxorubicin, cisplatin and ifosfamide; Regimen B+, Regimen B plus mifamurtide), multi-centre, randomised, open-label, active controlled, two by two factorial design trial comparing mifamurtide in addition to multi-agent chemotherapy (Regimens A+ and B+) with multi-agent chemotherapy alone (Regimens A and B) in individuals with high grade, resectable, non metastatic osteosarcoma (primary analysis). Additional supplementary data (requested by the

ERG) also compared individual mifamurtide containing regimens (Regimen A+) to chemotherapy regimens most commonly used in the UK (Regimen A).

- The results of the randomised controlled trial (RCT) suggest that after a median follow up of 7.9 years, the addition of mifamurtide to multi-agent chemotherapy (Regimens A+ and B+ combined) increased overall survival (hazard ratio, 0.72; 95% CI, 0.53 to 0.97; p=0.0313) and disease-free survival (hazard ratio, 0.78; 95% CI, 0.61 to 1.01; p=0.0586) in patients (less than 30 years age) with high grade, resectable, non metastatic osteosarcoma compared with chemotherapy alone (Regimens A and B combined). Additional post hoc analysis that compared the addition of mifamurtide to Regimen A (Regimen A+) with chemotherapy alone (Regimen A) showed non-significant improvements in overall survival (hazard ratio, 0.75; 95% CI, 0.49 to 1.16; p=0.1949) and disease-free survival (hazard ratio, 0.96; 95% CI, 0.67 to 1.38; p=0.8357).

- Although the adverse event profile was generally similar in those receiving mifamurtide (in combination with multi-agent chemotherapy) compared with those receiving multi-agent chemotherapy alone, more mifamurtide recipients discontinued treatment prematurely (the statistical analysis comparing the rates of discontinuation between the treatment groups were not reported in the MS or in the requested supplementary data). Although no reasons were given, the MS assumes that many parents withdrew subjects (or patients withdrew) from mifamurtide treatment since it was an investigational drug of unproven benefit and was uncomfortable or inconvenient when added to an existing multi-agent chemotherapy.

1.3 Summary of submitted cost effectiveness evidence

- The decision analytic model structures and assumptions are based on Markov model methodology which is an appropriate modelling strategy for the problem outlined in the submission. The scope of the model(s), together with various extensions and structural modifications are appropriate for appraising the submission.

- The various cost and resource parameters are appropriate and, in general, adequate values have been used for the analyses in the MS (including supplementary data).

- A probabilistic sensitivity analysis (PSA) was not submitted in the MS or undertaken by the manufacturer when requested by the Evidence Review Group (ERG).

- Results were provided from analyses of data pooled across the two mifamurtide arms (Regimens A+ and B+) and across two non-mifamurtide arms of the RCT (Regimens A and B). Additional supplementary data was requested by the ERG that compared Regimens A+ with Regimen A.

- Very little information about adverse events was incorporated into the cost-effectiveness model. In particular, a potentially important and significant adverse effect of treatment, hearing loss, was omitted from the original MS analyses. The ERG considered this omission to be a key issue.

1.4 Commentary on the robustness of submitted evidence

1.4.1 Strengths

- The MS conducted adequate systematic searches for clinical- and cost- effectiveness studies of mifamurtide for the treatment of osteosarcoma. It appears unlikely that any additional trials would have met the inclusion criteria had the search been widened to include conference proceedings.

- The RCT is of reasonable methodological quality (with some limitations), and measured a range of outcomes that are as appropriate and clinically relevant as possible.

- The base case decision model covers the major health states for patients with osteosarcoma, who may or may not receive mifamurtide in a RCT setting.

1.4.2 Weaknesses

- The processes undertaken by the manufacturer for data extraction and applying quality criteria to included studies are not explicitly clear in the MS. These factors limit the robustness of the systematic review.

- The included RCT is not an absolute reflection of the population with osteosarcoma in the UK, so the external validity may be questionable.

- Potentially important adverse and progression-related events (including relapse itself, long-term side effects of treatment, and palliative care) were not adequately represented in the original MS models of the follow-up beyond the end of the RCT.

- A PSA was not undertaken, despite a request by the ERG.

- The MS assumes that a duplicate of the RCT would produce identical results.

1.4.3 Areas of uncertainty

- There is uncertainty around the clinical- and cost-effectiveness of mifamurtide in combination with multi-agent chemotherapy (Regimens A+ and B+ combined) to multi-agent chemotherapy alone (Regimens A and B combined) in individuals with metastatic disease, recurrent disease, older patients (greater than 30 years of age) and other osteosarcomas.

- Although it is probable that the addition of mifamurtide to multi-agent chemotherapy (Regimens A+ and B+ combined) increases overall survival and disease-free survival compared with multi-agent chemotherapy alone (Regimens A and B combined), the size of the actual treatment effect of mifamurtide is uncertain, given the trial design limitations (open label design, delayed adminstration and failure to receive mifamurtide after randomisation, imbalance of histological response to neoadjuvant therapy and disparity of survival events in the subset of patients who did not enter the maintenance phase) and the interpretation of the statistical analyses (wide confidence intervals with similar point estimates for efficacy). It is unclear whether a more clinically relevant assessment for a UK population would be derived from an analysis comparing patients randomised to mifamurtide and multi-agent chemotherapy (Regimens A+ and B+ combined) with patients randomised to no mifamurtide and multi-agent chemotherapy (Regimens A and B combined) or comparing individual mifamurtide containing regimens (Regimen A+) to chemotherapy regimens most commonly used in the UK (Regimen A).

- As discussed in Section 1.4.2, a PSA was not provided. However, a limited PSA conducted by the ERG (Section 6) suggests that treatment with mifamurtide may not be effective if the hearing-loss rates observed in the RCT are incorporated in the model. This is particularly the case if a common rate of hearing loss for all treatment arms is assumed.

- Importantly, the addition of mifamurtide to multi-agent chemotherapy may not be effective if one assumes the RCT results for treatment arms which represent current UK practice (Regimens A+ versus A) hold.

- Cost-effectiveness results, as measured by incremental cost-effectiveness ratios (ICERs), are not sensitive to assumptions about adverse and progression-related events in the extrapolated time horizon period, which suggests that the results are driven largely by base-case scenario inputs.

- It is unclear why ICERs are so dependent on whether ifosfamide is part of the treatment. This is certainly a source of variability in the model outputs.

- Uncertainty of ICERs has not been adequately explored in the MS, which lacked a PSA. The ERG note that assumptions regarding hearing loss and the hazard ratio markedly affect the results.

1.5 Key issues

The lack of clarity around whether the clinical evidence from the RCT used in the MS should be pooled according to mifamurtide/non-mifamurtide treatment is a major issue.

The main drivers of the ICERs are:

- The choice of treatment regimens, which lead to quite different estimates of effectiveness.

- Lack of clarity about the number of doses of mifamurtide required for each patient, a factor which impacts substantially on the total cost of this treatment.

- The rate of hearing loss, particularly if the rate is higher with the addition of mifamurtide to multi-agent chemotherapy, as this adverse event substantially reduces the overall effectiveness of treatment.

These elements combine to introduce substantial variability in the model outputs and consequently raise the level of uncertainty considerably.

2 BACKGROUND

2.1 Critique of manufacturer's description of underlying health problem

The manufacturer's description of the underlying health problem is well described and accurate. The overview covers the incidence of osteosarcoma in England/the UK and appears to be based on credible sources. A description of the aetiology, diagnosis, prognosis, and treatment pathways (including adverse affects) for patients with osteosarcoma is also provided and the impact the disease has on health-related quality of life (HRQoL), is emphasised.

2.2 Critique of manufacturer's overview of current service provision

The manufacturer's overview of current service provision is adequate although some discussion around specific points is required.

The MS (p18-19) suggest that a standard chemotherapy regimen for treating osteosarcoma has not been defined; however, most osteosarcoma patients in the UK undergo a 3-agent chemotherapy regimen (neoadjuvant and adjuvant) combining high dose methotrexate, doxorubicin and cisplatin. Although some discussion has been provided (as additional information) by the manufacturer on the effectiveness of these treatments as a multi-agent chemotherapy, the optimal combination (dose, timings, duration) of these agents is unclear.

The MS (p29) suggest that the activity of mifamurtide is not affected by concomitant therapy; however, the reference used to support this statement is based on expert opinion. Moreover, the mifamurtide summary of product characteristics (SPC) states (p108, MS) that "limited studies of the interaction of mifamurtide with chemotherapy have been conducted. Although these studies are not conclusive, there is no evidence of interference of mifamurtide with the anti-tumour effects of chemotherapy and vice versa." Further discussion is needed in the MS.

The MS (p29-30) refers to the guidelines issued by NICE and the National Collaborating Centre for Cancer for the NHS in England and Wales on improving outcomes for people with sarcoma. However, it is unclear how these compare to other relevant guidelines.

3 CRITIQUE OF MANUFACTURER'S DEFINITION OF DECISION PROBLEM

A summary of the decision problem addressed by the MS is shown in Table 1.

Table 1: Decision problem as issued by NICE and addressed by the MS

	Final scope issued by NICE	Decision problem addressed in the submission
Population	People with osteosarcoma who have had surgical resection	Individuals with high-grade resectable, non-metastatic osteosarcoma following surgical resection.
Intervention	Mifamurtide in combination with post-operative multi-agent chemotherapy	Mifamurtide in combination with post-operative multi-agent chemotherapy including: doxorubicin, methotrexate, cisplatin and/or ifosfamide
Comparator(s)	Post-operative multi-agent chemotherapy alone	Post-operative multi-agent chemotherapy alone
Outcomes	The outcome measures to be considered include: • Overall survival • Disease-free survival • Adverse effects of treatment • Health-related quality of life	The outcome measures considered included: • Overall survival • Disease-free survival • Adverse effects of treatment • Health-related quality of life
Economic Analysis	The base case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The base case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective.	Cost-effectiveness of treatments expressed in incremental cost per quality-adjusted life year over a lifetime horizon. Costs considered from NHS and Personal Social Services perspective. No probabilistic sensitivity analysis was undertaken
Other considerations	If the evidence allows, and if included in the marketing authorisation, the following groups will be included • people with osteosarcoma related to	The three subgroups identified are not within the proposed marketing authorisation indication

Paget's disease

- people with metastatic osteosarcoma
- people with relapsed osteosarcoma

3.1 Population

The manufacturer's statement of the decision problem appropriately defines the population as individuals with high-grade resectable, non-metastatic osteosarcoma following surgical resection. However, the MS does not include any further details on the mean age at diagnosis of the UK osteosarcoma patient population (against which to compare the characteristics of patients in the clinical trial).

3.2 Intervention

Mifamurtide (liposomal muramyl tripeptide phosphatidyl ethanolamine) is an immune adjuvant macrophage stimulant. Although mifamurtide does not have a UK marketing authorisation (at the time of writing), the anticipated target indication is (in children from the age of 2 to 12 years, adolescents from the age of 12 to 18 years and young adults) for the treatment of high-grade resectable non-metastatic osteosarcoma after macroscopically complete surgical resection and in combination with post-operative multi-agent chemotherapy. The proposed recommended dose for all patients is 2 mg/m^2 body surface area and is to be administered as an intravenous infusion (over one hour) twice weekly for 12 weeks, with dosing at least three days apart, followed by once weekly treatment for an additional 24 weeks (total of 48 infusions over 36 weeks).

3.3 Comparators

The decision problem addressed in the MS states that the standard comparators to be considered are post-operative multi-agent chemotherapy alone (three- or four-agent adjuvant chemotherapy using high dose methotrexate, doxorubicin, cisplatin with or without ifosfamide). The ERG acknowledges that these multi-agent therapies are the most appropriate and relevant comparators for all patients with osteosarcoma; however, some points need further clarification.

In the UK, most chemotherapy regimens in clinical practice comprise doxorubicin, cisplatin and high dose methotrexate; however, the most effective combination of these agents has not been defined. Although the use of ifosfamide, as part of a four-arm chemotherapy regimen, is uncommon in the UK (p49, MS); it is used in many centres across Europe.[1] At present it is not clear whether a four drug combination (high dose methotrexate, doxorubicin, cisplatin and ifosfamide) offers a notable clinical advantage over a three drug combination (high dose methotrexate, doxorubicin, cisplatin).[2]

Although the use of ifosfamide is limited in the UK, it is currently used as part of an adjuvant regimen (in combination with etoposide, cisplatin, doxorubicin, and methotrexate) for patients experiencing a poor histological response to preoperative chemotherapy in an ongoing European and American Osteosarcoma (EURAMOS) 1 trial, (http://www.ctu.mrc.ac.uk/euramos/euramos_i_trial.asp). This trial involves a collaboration across eleven European countries (including clinical centres in the UK), the USA and Canada. In addition, the options for second-line chemotherapy for recurrent osteosarcoma depend on the primary treatment but will often be based on high-dose methotrexate, ifosfamide and etoposide.[1]

3.4 Outcomes

The NICE scope outlines four clinical outcome measures and one measure of cost-effectiveness. All of these are stated to have been addressed in the MS (p9-10). Clinical outcome measures included overall survival, disease-free survival, adverse effects of treatment and HRQoL. These are all appropriate and clinically meaningful outcomes, and there are no other valid outcomes which the ERG would have expected to be included. Incremental cost per quality adjusted life year (QALY) was used as a measure of cost-effectiveness, which is in accordance with the NICE reference case.

3.5 Time frame

The manufacturer's statement of the decision problem defines the time frame as a lifetime horizon. The MS states (p62-63, 65) that a time horizon of 12.25 years was chosen as it corresponded to the follow-up duration (from commencement of the maintenance phase) in the INT-0133 trial, thus allowing the cost-effectiveness to be assessed on observed data only.

However, the manufacturer considered this as a conservative approach because a differential mortality effect between mifamurtide and the comparator will persist beyond 12.25 years. As mifamurtide is indicated for children, adolescents and young adults with the potential for a long life expectancy, the economic evaluation also considered time horizons of 20 and 40 years beyond the RCT duration as scenario analyses. The ERG's clinical advisors were concerned that the model time horizon of 40 years was short for the expected survival of osteosarcoma treated patients, and that a 60 year model would be more complete. Also, different treatment and post-treatment events, e.g. amputation or limb salvage, can result in slightly different survival profiles, so discounting of utilities according to the impact of adverse events should have been considered.

3.6 Other relevant factors

The consequences of adverse events associated with treatment of osteosarcoma are given inadequate coverage in the original MS. In particular, the results of the key trial which show that the incidence of deafness is higher in the mifamurtide arm were ignored, on the grounds of expectation that this is actually caused by the platinum-based cisplatin treatment. The ERG note that objective hearing loss was statistically significant, greater in those that had mifamurtide compared with those that did not. A subsequent request for sensitivity analyses based on the trial results was undertaken by the manufacturers.

4 CLINICAL EFFECTIVENESS

4.1 Critique of manufacturer's approach

4.1.1 Description of manufacturers search strategy and comment on whether the search strategy was appropriate.

The searches undertaken by the manufacturer to identify all relevant randomised controlled trials (RCTs) were conducted in September 2008. The search strategy utilised terms to identify the condition (osteosarcoma), the intervention (mifamurtide) and the type of evidence (RCTs, systematic reviews and meta-analysis). Searches were restricted to the English language and to citations published from 1990. The MS does not provide any justifications for these restrictions. Despite this, the strategy is simple but effective and the methodological filters used to identify types of evidence are representative of some of the best ones available. Five electronic bibliographic databases were searched (MEDLINE, MEDLINE in Process, EMBASE, The Cochrane Library including NHS EED, and Health Economic and Evaluations Database (HEED)). Key databases overlooked include the Science Citation Index (Web of Science) and BIOSIS; however, it is unlikely that they would have yielded any additional key results. Searches were supplemented by citation searching on key papers and from scanning of bibliographies of retrieved items. An extensive number of additional sources (including current research registers and health services research-related organisations) were searched via the internet. However, no conference proceedings were searched. For cancer topics, key references are often found in the conference proceedings of the American Society of Clinical Oncology (ASCO) and the European Society of Medical Oncology (ESMO). Nevertheless, the search strategies were of good quality to retrieve important citations relating to all eligible studies of which the ERG and its clinical advisors are aware.

4.1.2 Statement of the inclusion/exclusion criteria used in the study selection and comment on whether they were appropriate.

The MS describes an appropriate method of identifying and screening references for inclusion in the systematic review. Two independent reviewers applied pre-specified inclusion and exclusion criteria to citations identified by the searches, and discussed any unclear references

until consensus was reached. Details of the inclusion and exclusion criteria, as specified in the MS, (p34, 125) for the systematic review of the literature is summarised in Table 2.

Table 2: Inclusion/exclusion criteria in the MS study selection

Criteria	Clinical effectiveness
Inclusion	• Population Children, adolescents and young adults diagnosed with high-grade, non-metastatic osteosarcoma • Intervention Neoadjuvant chemotherapy with high-dose methotrexate, doxorubicin and cisplatin with/without ifosfamide followed by adjuvant therapy with the same regimen plus mifamurtide • Comparator Neoadjuvant and adjuvant chemotherapy with high-dose methotrexate, doxorubicin and cisplatin with/without ifosfamide • Outcome overall survival, disease-free survival, quality of life and safety
Exclusion	• Reviews and commentaries • Animal studies • Non English language papers

The specified inclusion and exclusion criteria were appropriate and reflect the information given in the decision problem. However, the MS does not explicitly report any inclusion criteria relating to the study design. The ERG assumes that the review of clinical effectiveness was limited to phase III RCTs only. As the reporting of clinical harms is often inadequate in controlled clinical trial publications because they exclude patients at high risk from harms,[3] may be too short to identify long-term or delayed harms, or may have sample sizes too small to detect uncommon events,[4,5,6,7] the MS (p35) included non-randomised controlled trials using mifamurtide, to inform on safety considerations. The MS did not state whether published systematic reviews and meta-analysis would be considered in the review, although the identification of these were a part of the search strategy (Appendix 2, p123, MS).

4.1.3 Table of identified studies. What studies were included in the submission and what were excluded.

The MS identified one head to head randomised open label phase III controlled trial (Intergroup Study 0133, INT-0133) assessing the use of mifamurtide as an add-on to multi-agent chemotherapy in children, adolescents and young adults with osteosarcoma.[8,9] Details of the study design and patient characteristics are summarised in Table 3.

Table 3: Characteristics of included studies

Study	Design	Participants	Interventions [a]	Outcomes	Follow up
Intergroup Study 0133[8,9]	Phase III, four-arm, multi-centre (178 sites primarily in the USA), randomised, open-label, active controlled, two by two factorial design trial (n=678)	Inclusion criteria Children, adolescents and young adults (male and female ≤30 years of age) with newly diagnosed (≤ 1 month from diagnostic biopsy) malignant, high-grade non-metastatic resectable osteosarcoma	Regimen A: doxorubicin, methotrexate cisplatin (n=174) Regimen A+: doxorubicin, methotrexate cisplatin, mifamurtide (n=167) Regimen B: doxorubicin, methotrexate, cisplatin, ifosfamide (n=166) Regimen B+: doxorubicin, methotrexate, cisplatin, ifosfamide, mifamurtide(n=171)	Primary efficacy endpoint: Overall survival with disease-free survival as an intermediate endpoint Secondary endpoints (assumed by ERG): Adverse events Histological response	Median 7.9 years (most up to date follow-up)

[a] *Regimen A*: Initially, patients received two doses of doxorubicin (25mg/m^2/day over 72 hours), two doses of cisplatin (120mg/m^2) and four doses of methotrexate (12g/m^2) over 10 weeks (neoadjuvant induction therapy), followed by definitive surgical resection of primary tumour (while not receiving chemotherapy). Maintenance adjuvant therapy was scheduled to begin at Week 12 and consisted of four doses of doxorubicin (25mg/m^2/day over 72 hours), two doses of cisplatin (120mg/m^2) and eight doses of methotrexate (12g/m^2) over 21 weeks.
Regimen A+: Initially, patients received two doses of doxorubicin (25mg/m^2/day over 72 hours), two doses of cisplatin (120mg/m^2) and four doses of methotrexate (12g/m^2) over 10 weeks (neoadjuvant induction therapy), followed by definitive surgical resection of primary tumour (while not receiving chemotherapy). Maintenance adjuvant therapy was scheduled to begin at Week 12 and consisted of four doses of doxorubicin (25mg/m^2/day over 72 hours), two doses of cisplatin (120mg/m^2) and eight doses of methotrexate (12g/m^2) and 48 doses of mifamurtide (2mg/m^2; which could be dose escalated to a maximum of 2mg/m^2 plus 2mg) over 36 weeks.
Regimen B: Initially, patients received two doses of doxorubicin (25mg/m^2/day over 72 hours), two doses of ifosfamide (1.8g/m^2/d over five days) and four doses of methotrexate (12g/m^2) over 10 weeks (neoadjuvant induction therapy), followed by definitive surgical resection of primary tumour (while not receiving chemotherapy). Maintenance adjuvant therapy was scheduled to begin at Week 12 and consisted of four doses of doxorubicin (25mg/m^2/day over 72 hours), three doses of ifosfamide (1.8g/m^2/d over five days) and eight doses of methotrexate (12g/m^2) over 28 weeks.
Regimen B+: Initially, patients received two doses of doxorubicin (25mg/m^2/day over 72 hours), two doses of ifosfamide (1.8g/m^2/d over five days) and four doses of methotrexate (12g/m^2) over 10 weeks (neoadjuvant induction therapy), followed by definitive surgical resection of primary tumour (while not receiving chemotherapy). Maintenance adjuvant therapy was scheduled to begin at Week 12 and consisted of four doses of doxorubicin (25mg/m^2/day over 72 hours), three doses of ifosfamide (1.8g/m^2/d over five days), eight doses of methotrexate (12g/m^2) and 48 doses of mifamurtide (2mg/m^2; which could be dose escalated to a maximum of 2mg/m^2 plus 2mg) over 36 weeks.
NOTE: All regimens also received leucovorin (administered to counteract methotrexate toxicity, minimum 10 doses to achieve a methotrexate level below 0.1µM) and Regimen B and B+ received mesna to prevent haemorrhagic cystitis in patients receiving ifosfamide (initial mesna dose of 360mg/m^2 over 60 minutes with ifosfamide, then as a 3 hour infusion followed by three oral doses or 15 minute bolus infusions every 3 hours. Rigorous hydration also specified for 4-24 hours after the start of ifosfamide dosing)

The MS (p35, 129-131) also identified two phase II non-randomised controlled trials (Protocol 08 and Protocol 10) that provided additional data on the safety of mifamurtide and one ongoing single arm open-label study (MTP-OS-403), which is evaluating mifamurtide in patients with lung metastases as a result of progression of osteosarcoma in a compassionate use programme.[10]

The manufacturer's QUORUM flow diagram relating to the literature searches conforms to the QUORUM statement flow diagram (www.consort-statement.org/QUOROM.pdf); however, the MS does not provide a full and explicit breakdown of the reasons why studies were rejected, especially after papers were retrieved for detailed evaluation.

4.1.4 Details of any relevant studies that were not included in the submission?

The ERG is confident that all relevant studies were included in the MS (repeat searches using the manufacturers search terms did not identify any additional citations) and details of ongoing trials that are likely to be reporting additional evidence within 12 months were reported.

4.1.5 Description and critique of manufacturers approach to validity assessment

The manufacturer did not provide a formal appraisal of the validity of the included mifamurtide trials in their original submission. At the request of the ERG (provided as supplementary data) the manufacturer applied the quality assessment criteria developed by NICE to the INT-0133 trial, but it is not clear whether this was done by a single reviewer or consensus of multiple reviewers. The completed validity assessment tool, as reported in the addendum to the MS, is reproduced (with minor changes) in Table 4.

Table 4: Validity assessment of completed trials included by the manufacturer

Validity assessment	Trial
	INT-0133
How was allocation concealed?	Randomisation was performed centrally by the Children's Oncology Group Data Centre. Randomisation assignment was not concealed
What randomisation technique was used?	Prior to the start of the study, a randomisation assignment sheet was constructed for each stratum. The treatments were assigned on the sheet in permuted block sizes of 4. The assignments were generated using the CCG-developed, FORTRAN-based program RANDTAB. When a patient was to be enrolled from an institution, an institutional Clinical Research Associate called the Telephone Study Registrar at the Children's Oncology Group Operations Centre.
Was a justification of sample size provided?	The convention for the cooperative group at the time the protocol was written was to justify in the document the number of patients enrolled and the time at which the initial analysis would be available. For INT-0133 trial, the first analysis planned was for an intermediate endpoint and the study was sized for that endpoint. This is described and justified based on observations from prior studies.
Was follow up adequate?	Yes, in the 2006 and 2007 datasets, almost 95% of patients are accounted for at 3 years and more than 80% are accounted for beyond 5 years. The 2007 dataset was the subject of a satisfactory inspection carried out by the European Medicines Agency.
Were the individuals undertaking the outcomes assessment aware of allocation?	Blinding is not needed to assess patient survival, which was the first stated aim of study INT-0133. Blinding of treatment was not considered feasible in study INT-0133 because (i) it was not acceptable to expose children or adolescents to 48 placebo injections and (ii) the adverse effects that usually result from initial mifamurtide doses (including low grade fever, chills and headache) would make it difficult to blind the study. In addition, central third party reading of relapse scans is not standard for paediatric osteosarcoma studies because relapse is considered in terms of newly detectable disease in a person previously in remission, rather than by an assessment of disease response or progression based on tumour size.
Was the design parallel-group or crossover?	Parallel group
What was the study design?	The INT-0133 trial had a four-arm multi-centre, randomised and open-label design.
Was the RCT conducted in the UK; if not, is clinical practice likely to differ from UK practice?	The INT-0133 trial was conducted in North America. The patient characteristics and clinical practices for osteosarcoma do not differ between the US and most of Europe, including the UK. This is illustrated by the ongoing EURAMOS study in which the USA and most EU cooperative groups, including those in the UK, participate.
How do the included RCT participants compare with patients who are likely to receive the intervention in the UK?	The participants in study INT-0133 trial are highly representative of patients likely to receive the intervention in the UK.
What dosage regimens were used in the RCT?	The four study treatment arms comprised 10 weeks of induction therapy comprising: • Regimen A - two doses of doxorubicin (25m g/m^2/day over 72 hours), two doses of cisplatin (120 mg/m^2) and four doses of high dose methotrexate

Validity assessment	Trial
	INT-0133
	(12 g/m^2). • Regimen B - two doses of doxorubicin (25 mg/m^2/day over 72 hours), two courses of ifosfamide (1.8 g/m^2/day x 5 days) and four doses of high-dose methotrexate (12 g/m^2). Followed by definitive surgery and then maintenance therapy of: • Regimen A - four doses of doxorubicin, two doses of cisplatin and eight doses of methotrexate. • Regimen A+ - four doses of doxorubicin, two doses of cisplatin and eight doses of methotrexate plus mifamurtide • Regimen B - four doses of doxorubicin, four doses of cisplatin, three courses of ifosfamide and eight doses of methotrexate. • Regimen B+ - four doses of doxorubicin, four doses of cisplatin, three courses of ifosfamide and eight doses of methotrexate plus mifamurtide. Mifamurtide was given as twice-weekly intravenous infusion for 12 weeks followed by once weekly intravenous infusion for 36 weeks. The starting dose of MEPACT was 2 mg/m^2, which could be dose-escalated to 2 mg/m^2 + 1 mg and then to 2 mg/m^2 + 2 mg until biological activity was seen. Other chemotherapies were used at the same doses as for induction therapy.
Are these dosage regimens used within the SPC?	Most patients in INT-0133 study (>90%) received mifamurtide at 2 mg/m^2, the same dosage as recommended in the SPC. The schedule of treatment, 48 doses over 36 weeks, was the same in study INT-0133 as that recommended in the SPC, which will form part of the terms of the marketing authorisation to be granted by the European Commission.
Were the study groups comparable?	Yes, the mifamurtide and no-mifamurtide groups were comparable with respect to gender, age, and race. Patients were stratified at randomisation for important prognostic factors and so groups were also comparable for tumour location and lactate dehydrogenase. The only imbalance was identified after neoadjuvant chemotherapy and definitive surgery, with more patients in the mifamurtide group showing a poor histological response to neoadjuvant chemotherapy. Since this was determined after definitive surgery, it was impossible to control at randomisation.
Were the statistical analyses used appropriate	Yes, standard and appropriate statistical methodologies were used that were consistent with the statistical principles described in the various guidelines adopted by the International Conference on Harmonisation and have been accepted by the regulatory authorities in the European Union, United States and Japan. Standard statistical methodologies were used in all efficacy analyses. The product-limit estimator of Kaplan and Meier was used to estimate the survival curves, and the Cox proportional hazards regression model was used to estimate the reduction in risk of death. The log-rank statistic, as described in the study protocol was used to test for treatment differences with respect to overall survival.
Was an intent-to-treat analysis undertaken	Yes, the primary analysis on which the conclusions were based is an intent-to-treat analysis.
Were there any confounding factors that may attenuate the interpretation of the results	For the primary study aim, overall survival, there were no confounding factors.
RCT, randomised controlled trial; SPC, Summary of Product Characteristics	

The majority of the data for the validity assessment appears to be derived from the trial protocol (which was not available to the ERG) and is not published in the peer reviewed articles. As a result, it was not possible for the ERG to check the validity of the manufacturer's quality assessment; however, some further discussion around specific points is required.

The MS states (p36, 46) that randomisation was performed centrally with stratification (by a computer) and treatment assignments were concealed (central randomisation system). However, the manufacturer's validity assessment (Table 4) suggests that randomisation assignment was not concealed. The ERG notes that there has been some confusion in the MS between the terms allocation concealment and open label design. The ERG acknowledges that adequate methods of randomisation and allocation concealment were used in the INT-0133 trial; however, patients and investigators were all unblinded (open label design) to the assigned treatment. Double blinding protects against performance bias and measurement bias[11] and its absence in randomised controlled trials tends to result in larger treatment effects.[12] With many cytotoxic cancer drugs, the nature of the interventions precludes blinding (i.e. drug toxicities or manner of administration) for the practical and ethical reason that informed dose monitoring and adjustment is required. Although it is almost universally absent from oncology trials, blinded outcome assessment can enhance bias reduction.[13]

The MS states (p35-39) that all patients were randomised at study entry to one of four groups (Regimen A, methotrexate, doxorubicin and cisplatin; Regimen A+, Regimen A plus mifamurtide; Regimen B, methotrexate, doxorubicin, cisplatin and ifosfamide; Regimen B+, Regimen B plus mifamurtide); however, mifamurtide administration was delayed until the maintenance (adjuvant) phase (week 12). Supplementary data provided by the manufacturer suggest that approximately 10% of patients enrolled and randomised to regimens containing mifamurtide did not enter the maintenance phase and therefore did not receive mifamurtide. Furthermore, the number of disease-free survival events and the number of deaths in the subset of patients who did not enter the maintenance phase were not balanced between the four groups. It is not clear how these disparities may have influenced or biased the results.

The MS (together with the supplementary evidence provided by the manufacturer) did not clearly specify the primary and secondary outcome measures of the INT-0133 trial. The

primary outcome measure was overall survival (defined as time from study randomisation to death from any cause) with disease-free survival (defined as time from study randomisation to disease progression/recurrence of osteosarcoma, or death from any cause) as an intermediate endpoint. The ERG assumes that the secondary outcome measures were histological response and adverse events. Although the sample size power calculations were adequately powered for the disease-free survival intermediate endpoint, the ERG notes that the INT-0133 trial was not powered to assess overall survival.

Although mifamurtide was not administered until the maintenance (adjuvant) phase, tumour response to preceding neoadjuvant (induction) therapy is a known prognostic factor in osteosarcoma. Supplementary data provided by the manufacturer suggest an imbalance of histological response to neoadjuvant chemotherapy between treatment groups, particular in those patients assigned to Regimen A+, which had a greater proportion of patients with poor (5-100% viable tumour) histological response. Excluding patients without data, 64% had unfavourable histological response in Regimen A+, compared with 52%, 53% and 50% in Regimens A, B and B+, respectively. It is not clear how these differences may have influenced or biased the results.

The MS suggest that the participants in the INT-0133 trial were similar to the UK population (p49, 52, MS). The ERG observed that the mean age of the participants in the INT-0133 trial was approximately 14 years (range 1.4 to 30.4 years). The ERG clinical advisors noted that the age of patients in the INT-0133 trial was slightly younger than the typical age of an osteosarcoma patient in England and Wales (mean age: 16 years in boys and 15 years in girls) (Dr J Whelan, University College Hospital, London: personal communication, 2008). In addition, Bielack et al.,[14] suggest that the incidence of osteosarcoma is highest between the age of 15 and 19 years. The ERG notes that the INT-0133 trial is not an absolute reflection of the population with osteosarcoma in the UK, so the external validity may be questionable.

The manufacturer's supplementary data states that the overall compliance to study treatments was good; however, no compliance rates are provided for each group. In general, the validity of a study may be threatened if attrition is more than 20%.[15] In the INT-0133 trial, 31.5% (11% before maintenance phase and 20.5% during maintenance phase) of patients

discontinued treatment (further details are provided in Section 4.2.1). However, all withdrawals were accounted for and an intention to treat (ITT) analysis was undertaken.

The rationale for the mifamurtide dose (2 mg/m^2) and duration of treatment (36 weeks with a total of 48 infusions) was not explicitly clear in the MS. The ERG notes that the rationale in the INT-0133 trial for the dose and duration of treatment was based on a non-randomised open label single centre phase II study of 33 patients with recurrent osteosarcoma.[16] This study found that 24 weeks of mifamurtide therapy (2 mg/m^2 twice weekly for 12 weeks then once weekly for an additional 12 weeks) was more effective than 12 weeks of twice weekly treatment. The manufacturer's supplementary evidence states that when the longer treatment period was associated with a better survival outcome and without increased toxicity, the treatment schedule was further extended to 36 weeks in the INT-0133 trial so that the administration of mifamurtide would extend slightly beyond the longest chemotherapy administration. The ERG notes that it may be possible that the best biological effects of mifamurtide may be seen at a lower dose and shorter duration.

The MS (p50) states that approximately 10% of patients who received at least one dose of mifamurtide in the INT-0133 trial underwent dose escalation due to a lack of biological activity at the starting dose (as specified in the protocol). Conversely, the SPC (p108-122, MS) stipulates a fixed mifamurtide dose of 2 mg/m^2 (maximum 4mg per cycle). The ERG notes that the fixed dose may not be sufficient for a small group of patients (particularly adults) whose individual areas exceed 2 m^2.

The manufacturer's supplementary data suggest that approximately 29% of patients who entered the maintenance (adjuvant) phase of the INT-0133 trial received between 46 and 48 cycles of mifamurtide therapy and 18% of patients (MS data suggest 20%) exceeded the recommend maximum of 48 infusions. The ERG notes that it is unclear if survival rates differ according to the number of doses received.

The MS (p44, 47) states that a specialist filter required for reconstitution and administration of mifamurtide was not available from 15 June 1995 to 15 January 1996. During this period 8 of the 51 patients randomised to a mifamurtide group did not receive mifamurtide therapy.

The ERG notes that the MS failed to provide any details on whether the patients who received mifamurtide received the full dose; however, all randomised patients were included in the the ITT analysis.

The supplementary data provided by the manufacturer states that the dosage and timings of methotrexate, doxorubicin and cisplatin in each regimen were essentially the same in the INT-0133 trial and in the comparator arms of the ongoing EURAMOS 1 study. Although the total doses were the same, the ERG notes that the individual dosage and duration of each chemotherapy drug was different except for methotrexate. Similarly, the dosage and duration of ifosfamide therapy was higher in the EURAMOS 1 study than the INT-0133 trial. It is noteworthy that while the use of ifosfamide is limited in the UK, it is currently used as part of an adjuvant regimen in combination with etoposide, cisplatin, doxorubicin, and methotrexate for patients experiencing a poor histological response to preoperative chemotherapy. In contrast, in the INT-0133 trial, ifosfamide is used in combination with cisplatin, doxorubicin, and methotrexate only (Regimen B) and therefore does not ideally reflect current UK clinical practice.

4.1.6 Description and critique of manufacturers outcome selection

As discussed in Section 3.4, The ERG considers the manufacturer's outcome selection to be relevant and appropriate. The outcome measures described in the decision problem generally reflect those in the INT-0133 trial and include overall survival, disease-free survival, HRQoL (not assessed in the INT-0133 trial) and adverse events.

4.1.7 Describe and critique the statistical approach used

The statistical analysis of the INT-0133 trial was adequately reported in the MS (p43-46, 50). The primary aim of the study was to improve overall survival; however, the study was sized for the first planned analysis of the intermediate disease-free survival endpoint, a recognised surrogate marker of overall survival in cancer trials. The INT-0133 trial was conducted as a factorial design and the sample size calculations were based on the assumption that, from an initial long-term disease-free survival of 60% in patients receiving neither ifosfamide nor mifamurtide, the study would be able to detect a 12% increase in disease-free survival after a 3.9 years accrual period, with an additional two years for follow-up, with 80% power and 5%

significance (two-sided). The study assumed that 50% of treatment failures occur within 1.3 years. Using these assumptions, the study planned for 585 patients with non-metastatic resectable disease. Due to logistical problems with the availability of filters required for mifamurtide administration, accrual was extended to allow randomisation of an additional 60 patients following a protocol amendment.

The study analysis specified a two by two factorial analysis approach with two factors: the chemotherapy factor (randomisation to one of two different chemotherapy regimens) and mifamurtide (randomisation to receive mifamurtide or not). Overall and disease-free survival curves were calculated according to the Kaplan-Meier product-limit estimator method, from randomisation to the date of the event of interest or the date of last follow up. For outcomes measured from study entry and involving the study regimens, the stratified log-rank test was used, with stratification by the randomisation stratification factors and the chemotherapy factor. The Cox proportional hazards regression model was used to estimate the treatment effect. Differences in the incidence of adverse events between treatment groups were assessed using Fischer's exact test. All randomised patients were included in the ITT analysis, including those patients whose treatment was affected by the lack of availability of filters for mifamurtide administration. Although appropriate statistical methods were used, the ERG notes that the assumption of absence of interaction between regimens is crucial to the validity of the factorial approach.[9]

4.1.8 Summary statement

The manufacturer's search strategy was well reported and the submission appears to contain all relevant head-to-head RCTs. The validity assessment tool used to assess the included study was satisfactory, although details of the process, in terms of whether it was performed by two independent reviewers, are missing. The outcomes selected were relevant and statistical methods were well described. The submitted evidence adequately reflects the decision problem defined in the submission, although there appears to be some small inconsistencies which probably relate more to reporting than actual differences.

4.2 Summary of submitted evidence

This section presents the main clinical efficacy evidence from a head to head, phase III RCT (INT-0133) comparing the use mifamurtide as an add-on to multi-agent chemotherapy versus multi-agent chemotherapy alone.

An independent analysis of the intermediate endpoint (disease-free survival) by the Children's Oncology Group suggested that an interaction precluded the planned analysis (referred to in the MS as the 2003 data) by factorial design.[9] A re-analysis of the survival data with extended follow-up (referred to in the MS as the 2007 data) found that there was no evidence of interaction between the addition of mifamurtide to chemotherapy for disease-free survival (p=0.102) and overall survival (p=0.60).[8] Although a borderline p-value for the intermediate endpoint (disease-free survival) was interpreted as evidence of no interaction, the ERG note that the absence of evidence is not evidence of absence.[17] The main analyses in the MS (using the 2007 data), were analysed by factorial design (marginal analyses) and compares patients randomised to mifamurtide and multi agent chemotherapy (Regimen A+ and B+ combined) with patients randomised to no mifamurtide and multi-agent chemotherapy alone (Regimen A and B combined).

4.2.1 Summary of results

In the MS, the efficacy results were inadequately or incompletely reported (p53-55, MS). A tabulated summary of the 2007 data (the most up to date and comprehensive data of INT-0133 trial), as reported by the manufacturer and constructed (data re-tabulated in a consistent and more transparent format) by the ERG, is presented in Table 5 and Table 6 (data for 2003 and 2006 are presented in the Appendix 1). Additional information, not reported in the MS, was provided by the manufacturer in the clarifications of questions raised by the ERG

Overall survival

The overall survival data showed that the addition of mifamurtide to chemotherapy (Regimen A+ and Regimen B+ combined) significantly enhanced overall survival compared with chemotherapy alone (Regimen A and Regimen B combined: no mifamurtide). For the intention-to-treat population, the hazard ratio for death was 0.72 (95% CI: 0.53 to 0.97; p=0.0313) at a median follow-up of 7.9 years corresponding to a 28% relative reduction in

overall mortality. An additional post hoc analysis (requested by the ERG) that compared individual mifamurtide containing regimens (Regimen A+) with chemotherapy regimens most commonly used in the UK (Regimen A) showed an improvement in overall survival (hazard ratio, 0.75; 95% CI, 0.49 to 1.16; p=0.1949), corresponding to a non-significant 25% relative reduction in overall mortality.

Post hoc subgroup analyses (p55, MS and supplementary data) also showed a consistent benefit in overall survival for the addition of mifamurtide to chemotherapy across a broad range of demographic (age, gender, ethnicity, study site, geographic location) and prognostic factors (tumour size, lactate dehydrogenase, alkaline phosphatise level and background chemotherapy) compared with chemotherapy alone. Only one subgroup of patients (>16 years of age) did not show a benefit for the addition of mifamurtide to chemotherapy. The manufacturer's supplementary information suggests that the small sample size in this age group as well as the excess of poor histological responders may have contributed to this observation. The ERG and their clinical advisors have no reasons to dispute the statement made by the manufacturer.

Disease-free survival

The primary outcome analyses of the INT-0133 trial focussed on disease-free survival as an intermediate endpoint for overall survival. The addition of mifamurtide to chemotherapy (Regimen A+ and Regimen B+ combined) increased disease-free survival compared with chemotherapy alone (Regimen A and Regimen B combined), although this was not statistically significant. For the intention-to-treat population, the hazard ratio for remaining disease-free was 0.78 (95% CI: 0.61 to 1.01; p=0.0586) at a median follow-up of 7.9 years corresponding to a 22% reduction in the risk of progression, recurrence or death. An additional post hoc analysis (requested by the ERG) that compared Regimen A+ with Regimen A showed a non-significant improvement in disease-free survival (hazard ratio, 0.96; 95% CI, 0.67 to 1.38; p=0.8357) corresponding to a 4% relative reduction in the risk of progression, recurrence or death.

Table 5: Summary of overall survival using the 2007 data set

Interventions (Regimens)[a]	Median follow up (years)	Numbers followed in each group (n)	Event in each group (n)	Hazard Ratio (95% CI; p-value)[b]
Overall survival using 2007 data set				
A (control)	7.8	174	51 (29%)	-
A+	8.1	167	37 (22%)	-
B	8.3	166	49 (30%)	-
B+	7.4	171	36 (21%)	-
Primary analysis				
A/B combined vs. A+/ B+ combined [c]	7.9	340 vs. 338	100 (29%) vs. 73 (22%)	0.72 (0.53, 0.97; p=0.0313)
Additional analysis requested by the ERG				
A vs. A+	-	174 vs. 167	51 (29%) vs. 37 (22%)	0.75 (0.49, 1.16; p=0.1949)
A vs. B	-	174 vs. 166	51 (29%) vs. 49 (30%)	0.97 (0.66, 1.44; p=0.8884)
A vs. B+	-	174 vs. 171	51 (29%) vs. 36 (21%)	0.70 (0.46, 1.08; p=0.1093)
B vs. A+	-	166 vs. 167	49 (30%) vs. 37 (22%)	0.75 (0.49, 1.15; p=0.1832)
A+ vs. B+	-	167 vs. 171	37 (22%) vs. 36 (21%)	0.92 (0.58, 1.45; p=0.7135)
B vs. B+	-	166 vs. 171	49 (30%) vs. 36 (21%)	0.68 (0.44, 1.05; p=0.0825)

[a] Regimen A, methotrexate, doxorubicin and cisplatin; Regimen A+, Regimen A and mifamurtide; Regimen B, methotrexate, doxorubicin, cisplatin and ifosfamide; Regimen B+, Regimen B and mifamurtide

[b] p-value from log rank test stratified by ifosfamide use and randomisation strata for Regimens A+ and B+ combined versus Regimens A and B combined; p-value from Cox model stratified by randomisation strata for pair-wise comparisons of A, A+, B, B+

[c] Test of the hypotheses of no interaction between chemotherapy intervention and mifamurtide was p=0.60,[8] which does not meet conventional level of significance of less than 0.1. Therefore, marginal analyses appropriate

Table 6: Summary of disease-free survival using the 2007 data set

Interventions (Regimens)[a]	Median follow up (years)	Numbers followed in each group (n)	Event in each group (n)	Hazard Ratio (95% CI; p-value)[b]
Disease-free survival using 2007 data set				
A (control)	7.8	174	62 (36%)	-
A+	8.1	167	58 (35%)	-
B	8.3	166	71 (43%)	-
B+	7.4	171	49 (29%)	-
Primary analysis				
A/B combined vs. A+/ B+ combined [c]	7.9	340 vs. 338	133 (39%) vs. 107 (32%)	0.78 (0.61, 1.01; p=0.0586)
Additional analysis requested by the ERG				
A vs. A+	-	174 vs. 167	62 (36%) vs. 58 (35%)	0.96 (0.67, 1.38; p=0.8357)
A vs. B	-	174 vs. 166	62 (36%) vs. 71 (43%)	1.17 (0.83, 1.65; p=0.3588)
A vs. B+	-	174 vs. 171	62 (36%) vs. 49 (29%)	0.76 (0.52, 1.11; p=0.1612)
B vs. A+	-	166 vs. 167	71 (43%) vs. 58 (35%)	0.81 (0.57, 1.15; p=0.2354)
A+ vs. B+	-	167 vs. 171	58 (35%) vs. 49 (29%)	0.78 (0.53, 1.14; p=0.1985)
B vs. B+	-	166 vs. 171	71 (43%) vs. 49 (29%)	0.63 (0.44, 0.91; p=0.0144)

[a] Regimen A, methotrexate, doxorubicin and cisplatin; Regimen A+, Regimen A and mifamurtide; Regimen B, methotrexate, doxorubicin, cisplatin and ifosfamide; Regimen B+, Regimen B and mifamurtide

[b] p-value from log rank test stratified by ifosfamide use and randomisation strata for Regimens A+ and B+ combined versus Regimens A and B combined; p-value from Cox model stratified by randomisation strata for pair-wise comparisons of A, A+, B, B+

[c] Test of the hypotheses of no interaction between chemotherapy intervention and mifamurtide was p=0.102,[8] which does not meet conventional level of significance of less than 0.1. Therefore, marginal analyses appropriate

Critique of efficacy data reported

There are a number of issues that may limit the robustness of the efficacy data reported in the MS. Although the addition of mifamurtide to chemotherapy significantly improves overall survival compared with chemotherapy alone, the study was not adequately powered to assess this endpoint. It is worth noting that clinical trials of cancer treatments used in the adjuvant setting are rarely adequately powered to detect significant differences in overall survival and, when these become apparent, it is usually after lengthy follow-up.

The INT-0133 trial was designed as a factorial study and the absence of interaction between regimens was crucial to the validity of the factorial approach. The first analysis by the Children's Oncology Group published in 2005[9] suggested that an interaction precluded the planned factorial analysis. Based on additional follow-up, a re-analysis of the disease-free- and overall- survival data published in 2008,[8] found that there was no evidence of interaction between the addition of mifamurtide to chemotherapy (p=0.102 and p=0.60, respectively). Hunsberger et al.,[18] suggest that although a p-value of 0.102 was interpreted as evidence of no interaction, a borderline p-value cannot be interpreted as evidence of no interaction but note that the evidence (or magnitude) of the interaction has been reduced in the re-analysis. More importantly, Hunsberger et al.,[18] urge caution in interpreting the pooled survival analyses because in the presence of an interaction among treatments, a pooled analysis will produce an estimate of the mifamurtide treatment effect that may be either too large or too small depending on whether ifosfamide is present or not. Given that the effect of treatment on survival is expected to be mediated in large measure through its effect on disease-free survival, the concern of interaction carries over to the analysis of overall survival. In this situation, Hunsberger et al.,[18] suggest that a more clinically relevant assessment would be provided by comparing the individual mifamurtide containing regimens to the three drug chemotherapy control arm regimen; however, the drawback of this approach is that the study was not sized to allow such comparisons to be made with reasonable statistical power. Nevertheless, using this approach, the individual overall survival analyses show that none of the comparisons are statistically significant. While the direction and magnitude of effect are similar for the addition of mifamurtide to Regimen A (hazard ratio; 0.75; 95% confidence interval: 0.49 to 1.16; p=0.1949) and the addition of mifamurtide to Regimen B (hazard ratio; 0.68; 95% confidence interval: 0.44 to 1.05; p=0.0825), the confidence intervals are wide. As a result, it is possible that the hazard ratio of adding mifamurtide to A compared with A alone is truly identical to the hazard ratio of adding mifamurtide to B compared with B alone.

Alternatively, it is possible that the hazard ratio of adding mifamurtide to A compared with A alone differs from that of the hazard ratio of adding mifamurtide to B compared with B alone.

The INT-0133 trial only included patients less than 30 years of age with high grade, resectable, non metastatic osteosarcoma of the bone. The ERG notes that this comprises approximately 65% of all patients with osteosarcoma. However, there is no information to support its use for patients with osteosarcoma outside the eligibility criteria of this trial.

Finally, as discussed in Section 4.1.5, trial design limitations such as the open label design, delayed adminstration of mifamurtide (including failure to receive mifamurtide after randomisation), imbalance of histological response to neoadjuvant therapy and disparity of events (disease-free and overall survival) in the subset of patients who did not enter the maintenance phase may have also influenced or biased the results. In addition, cisplatin was omitted in the ifosfamide containing arms during the neoadjuvant chemotherapy phase. As a result the role of ifosfamide may have been hampered due to the lack of clarity as to its contribution as a substitute or adjunct.[14]

Safety and tolerability

The MS reports safety and tolerability data from the INT-0133 trial. Additional safety data were reported from phase I and phase II studies.

A summary of the rates of discontinuation, including reasons for premature termination are presented in Table 7. Although the rates of discontinuation in the INT-0133 trial were higher in both the mifamurtide containing groups (Regimen A+ and Regimen B+) than in the no mifamurtide containing groups (Regimen A and Regimen B) during the adjuvant phase, the statistical analysis comparing the rates of discontinuation between the treatment groups were not reported in the MS or in the requested supplementary data. The MS states (p48) that most of the withdrawals were not due to toxicities that required significant intervention, were life threatening, or necessitated truncation of mifamurtide therapy. The MS assumes that many parents withdrew subjects (or patients withdrew) from mifamurtide treatment since it was an

investigational drug of unproven benefit and was uncomfortable or inconvenient (no further details provided by the manufacturer) when added to an existing multi-agent chemotherapy.

The rates of discontinuation from the INT-0133 trial suggest that mifamurtide in combination with multi-agent chemotherapy is reasonably tolerated. Standard (neoadjuvant and adjuvant) chemotherapy in the UK (methotrexate, cisplatin and doxorubicin) is completed in approximately 30 weeks. A further 18 weeks of weekly administration of mifamurtide would be needed to be consistent with the schedule in the INT-0133 trial. The ERG note that a significant portion of patients with osteosarcoma are teenagers and young adults who may resist prolongation of treatment. The commonest cause for declining randomisation in EURAMOS 1 is believed to be a desire not to prolong therapy.[19]

Table 7: Number (%) of patients discontinuing treatment in the INT-0133 trial (Data derived from manufacturer's supplementary information)

	Interventions [a] (n)				Primary analysis (n)	
	Regimen A	Regimen A + (includes mifamurtide)	Regimen B	Regimen B + (includes mifamurtide)	Regimen A and Regimen B combined	Regimen A+ and Regimen B+ combined
Subjects randomised	174	167	166	171	340	338
Subject s who received neoadjuvant induction therapy	170 (98%)	164 (98%)	164[b] (99%)	169 (99%)	334 (98%)	333 (98%)
Subject s who received adjuvant maintenance therapy	153 (88%)	145 (87%)	148 (89%)	158 (92%)	301 (89%)	303 (89%)
Subjects who completed the study	130 (75%)	108 (65%)	120 (72%)	106 (62%)	250 (74%)	214 (63%)
Primary reason for premature termination during neoadjuvant phase:	21 (12%)	22 (13%)	19 (11%)	13 (8%)	40 (12%)	35 (10%)
Progressive Disease	6 (29%)	6 (27%)	4 (21%)	3 (23%)	10 (25%)	9 (26%)
Removed for Toxicity	0	0	2 (11%)	1 (8%)	2 (5%)	1 (3%)
Withdrawal by Parent or Patient	3 (14%)	4 (18%)	5 (26%)	4 (31%)	8 (20%)	8 (23%)
Withdrawal by Physician	3 (14%)	1 (5%)	0	0	3 (8%)	1 (3%)
Major Protocol Deviation	2 (10%)	4 (18%)	6 (32%)	3 (23%)	8 (20%)	7 (20%)
Death	2 (10%)	0	0	0	2 (5%)	0
Lost to Follow-Up	0	0	0	0	0	0
Other	1 (5%)	4 (18%)	0	0	1 (3%)	4 (11%)
Did not receive therapy	4 (19%)	3 (14%)	2 (11%)	2 (15%)	6 (15%)	5 (14%)

Table 7 (cont): Number (%) of patients discontinuing treatment in the INT-0133 (Data derived from manufacturer's supplementary information)

	Interventions [a] (n)				Primary analysis (n)	
	Regimen A	Regimen A + (includes mifamurtide)	Regimen B	Regimen B + (includes mifamurtide)	Regimen A and Regimen B combined	Regimen A+ and Regimen B+ combined
Primary reason for premature termination during adjuvant phase	23 (13%)	37 (22%)	28 (17%)	52 (30%)	51 (15%)	89 (26%)
Progressive Disease	9 (39%)	8[c] (22%)	7 (25%)	9 (17%)	16 (31%)	17 (19%)
Removed for Toxicity	1 (4%)	1 (3%)	4 (14%)	2 (4%)	5 (10%)	3 (3%)
Withdrawal by Parent or Patient	8 (35%)	20 (54%)	6 (21%)	26 (50%)	14 (27%)	46 (52%)
Withdrawal by Physician	0	1 (3%)	4 (14%)	6 (12%)	4 (8%)	7 (8%)
Major Protocol Deviation	2 (9%)	5 (14%)	5 (18%)	4 (8%)	7 (14%)	9 (10%)
Death	1 (4%)	1 (3%)	0	1 (2%)	1 (2%)	2 (2%)
Lost to Follow-Up	0	1 (3%)	0	1 (2%)	0	2 (2%)
Other	0	0	1 (4%)	2 (4%)	1 (2%)	2 (2%)
Deemed Ineligible	2 (9%)	0	1 (4%)	1 (2%)	3 (6%)	1 (1%)

Note: Percentages may not add up to 100% due to rounding

[a] Regimen A, methotrexate, doxorubicin and cisplatin; Regimen A+, Regimen A and mifamurtide; Regimen B, methotrexate, doxorubicin, cisplatin and ifosfamide; Regimen B+, Regimen B and mifamurtide

[b] One patient with prior surgery went directly to maintenance chemotherapy and did not have induction chemotherapy. This patient is not included in the total of 164.

[c] One patient had progressive disease documented at surgery. This patient is included among those with progressive disease.

In the INT-0133 trial, only serious (Grade 3) and life-threatening (Grade 4) severity events were recorded. A summary of the pooled (including data reported separately for each group) serious and life threatening treatment related adverse events, as reported by the manufacturer and constructed (data re-tabulated in a consistent and more transparent format) by the ERG is presented in Table 8. With the exception of hearing loss, the number of adverse events appeared to be similar across the combined treatment groups (no statistical analysis was reported in the supplementary data provided by the manufacturer). The MS suggest that mifamurtide significantly increased the incidence of objective (11.5% with mifamurtide versus 7.1% without, p=0.047) and subjective (3.6% versus 0.6%, p=0.007) hearing loss. The individual comparisons showed that the increased incidence of auditory problems occurred only in patients treated with three arm chemotherapy plus mifamurtide (Regimen A+) compared with those treated with three arm chemotherapy alone (Regimen A). The ERG notes that while it is plausible that hearing loss was caused by cisplatin (oxotoxicity is commonly associated with cisplatin therapy and the frequency of hearing loss reported for patients treated with mifamurtide was within the range expected with cisplatin alone), it is possible that not all this difference is attributed to cisplatin (mifamurtide significantly increased the incidence of objective (p=0.047) and subjective (p=0.007) hearing loss). In addition, mifamurtide administration is known to be associated with hypotension; however, the incidence of Grade 3 or 4 hypotension was lower in patients receiving mifamurtide (0.3% versus 2.1%; p=0.069).

Additional data (only reported as a brief narrative summary in the MS) from Phase I and II studies of over 700 patients suggest that mifamurtide is generally well tolerated. The MS states (p56-57) that the most common adverse events in patients and healthy subjects treated with mifamurtide alone were fever, chills, fatigue, headache, nausea/vomiting, myalgia and tachycardia, hypotension, hypertension and dyspnoea. The majority of these adverse events (chills, fever and pyrexia) were reported as mild to moderate in severity and were easily managed with paracetamol or acetaminophen, without compromising treatment efficacy.

Table 8: Severe or life threatening[a] treatment-related adverse events in the INT-0133 trial occurring in 2% or more patients in the maintenance (adjuvant) phase

	Interventions [b] (n)				Primary analysis (n)	
	Regimen A	Regimen A + (includes mifamurtide	Regimen B	Regimen B + (includes mifamurtide)	Regimen A and Regimen B combined	Regimen A+ and Regimen B+ combined
Number of patients	174	167	166	171	340	338
Adverse events						
Gastrointestinal disorders						
Stomatitis	94 (54%)	82 (49%)	61 (37%)	73 (43%)	155 (46%)	155 (46%)
Abdominal pain	4 (2%)	6 (4%)	3 (2%)	5 (3%)	7 (2%)	11 (3%)
Constipation	6 (3%)	7 (4%)	3 (2%)	3 (2%)	9 (3%)	10 (3%)
Diarrhoea	6 (3%)	3 (2%)	5 (3%)	11 (6%)	11 (3%)	14 (4%)
Nausea & vomiting	36 (21%)	35 (21%)	23 (14%)	24 (14%)	59 (17%)	59 (17%)
Nervous system disorder						
Central-cerebellar	6 (3%)	7 (4%)	8 (5%)	6 (4%)	14 (4%)	13 (4%)
Skin disorders	14 (8%)	4 (2%)	8 (5%)	11 (6%)	22 (6%)	15 (4%)
Ear disorders						
Hearing – objective	8 (5%)	26 (16%)	16 (10%)	13 (8%)	24 (7%)	39 (12%)
Hearing – subjective	1 (1%)	10 (6%)	1 (1%)	2 (1%)	2 (1%)	12 (4%)
Other						
Infection	48 (28%)	33 (20%)	33 (20%)	40 (23%)	81 (24%)	73 (22%)
Fever	5 (3%)	2 (1%)	3 (2%)	4 (2%)	8 (2%)	6 (2%)
Electrolytes						
Sodium	5 (3%)	2 (1%)	2 (1%)	0 (0%)	7 (2%)	2 (1%)
Potassium	10 (6%)	8 (5%)	11 (7%)	8 (5%)	21 (6%)	16 (5%)
Calcium	5 (3%)	2 (1%)	2 (1%)	3 (2%)	7 (2%)	5 (1%)
Magnesium	3 (2%)	6 (4%)	2 (1%)	3 (2%)	5 (1%)	9 (3%)
Laboratory investigations						
Haematological						
White blood cell count	40 (23%)	29 (17%)	44 (27%)	53 (31%)	84 (25%)	82 (24%)
Absolute neutrophil count	84 (48%)	75 (45%)	71 (43%)	85 (50%)	155 (46%)	160 (47%)
Platelets	56 (32%)	48 (29%)	43 (26%)	49 (29%)	99 (29%)	97 (29%)
Haemoglobin	14 (8%)	14 (8%)	14 (8%)	18 (11%)	28 (8%)	32 (9%)
Second malignancy	4 (2%)	4 (2%)	3 (2%)	3 (2%)	7 (2%)	7 (2%)
Hepatic						
Aspartate aminotransaminase	48 (28%)	52 (31%)	66 (40%)	60 (35%)	114 (34%)	112 (33%)
Alanine aminotransaminase	84 (48%)	86 (51%)	102 (61%)	91 (53%)	186 (55%)	177 (52%)
Total bilirubin	19 (11%)	12 (7%)	17 (10%)	16 (9%)	36 (11%)	28 (8%)
Pancreas						
Glucose	14 (8%)	4 (2%)	12 (7%)	10 (6%)	26 (8%)	14 (4%)
Renal						
Blood urea nitrogen	2 (1%)	1 (1%)	0 (0%)	2 (1%)	2 (1%)	3 (1%)
Creatinine	3 (2%)	4 (2%)	2 (1%)	2 (1%)	5 (1%)	6 (2%)
Creatinine clearance	5 (3%)	1 (1%)	9 (5%)	1 (1%)	14 (4%)	2 (1%)

Note: Percentages may not add up to 100% due to rounding

[a] Definitions of severity according to the Children's Cancer Group Toxicity and Complications criteria where Grade 3 is classed as severe and Grade 4 as life threatening

[b] Regimen A, methotrexate, doxorubicin and cisplatin; Regimen A+, Regimen A and mifamurtide; Regimen B, methotrexate, doxorubicin, cisplatin and ifosfamide; Regimen B+, Regimen B and mifamurtide

Critique of safety data reported

The reporting and interpretation of the safety and tolerability data is generally good. Although only Grade 3 and Grade 4 adverse events defined by the Children's Cancer Group Toxicity Scale were recorded in the INT-0133 trial (the unblinded nature of the trial may have affected the reporting of these also), the MS (including supplementary data) failed to report p-values for most comparisons. The ERG appreciates that the serious adverse events are important but all reported adverse events are required, as a high proportion of patients suffering mild effects could still represent a reasonably high cumulative QALY loss. Additional data was also provided from phase I and II studies which recorded adverse event data at all severity grades; however, none of these were tabulated or reported by Grade in the MS.

It is well recognised that RCTs have a limited ability to assess drug toxicity.[20] Mifamurtide safety data need to be supplemented by other types of study, including post-marketing surveillance studies, which can follow-up larger numbers of patients for longer periods of time, and which generally collect data relating to the target population treated in normal clinical practice rather than to highly selected populations treated under specialised conditions.

4.2.2 Critique of submitted evidence syntheses

No evidence synthesis in the form of a meta-analysis was possible as there was only one RCT, and this was reported by narrative means.

4.2.3 Summary

The MS probably contains unbiased estimates of the treatment effect of mifamurtide (in combination with multi-agent chemotherapy) within the stated scope of the decision problem. This is based on the results of a single RCT which is of reasonable methodological quality when judged using the NICE quality assessment criteria, but the reporting of the trial results is neither totally transparent and nor are all results fully tabulated for each outcome. It is difficult to interpret the data with full confidence due to the trial design limitations (open label design, delayed adminstration and failure to receive mifamurtide after randomisation,

imbalance of histological response to neoadjuvant therapy and disparity of survival events in the subset of patients who did not enter the maintenance phase) and the complexity in interpretation of the statistical analyses (despite no evidence to suggest that the validity of the factorial approach was methodologically inappropriate). Whilst these factors make it difficult to accurately assess the size of the treatment effect, these limitations probably do not significantly affect the overall results especially in the light of clarifications received from the manufacturer. The results suggest that after a median follow up of 7.9 years the addition of mifamurtide to multi-agent chemotherapy (Regimens A+ and B+ combined) increased overall survival (hazard ratio, 0.72; 95% CI, 0.53 to 0.97; p=0.0313) and disease-free survival (hazard ratio, 0.78; 95% CI, 0.61 to 1.01; p=0.0586) in patients (less than 30 years age) with high grade, resectable, non metastatic osteosarcoma compared with chemotherapy alone (Regimens A and B combined) and is generally safe and reasonably tolerated. However, it is unclear whether a more clinically relevant assessment for a UK population would be derived from an analysis comparing individual mifamurtide containing regimens (Regimen A+) to chemotherapy regimens most commonly used in the UK (Regimen A). In addition, the prolonged therapy (addition of mifamurtide to multi-agent chemotherapy) compared to UK standard treatment may affect adherence rates.

5 ECONOMIC EVALUATION

5.1 Overview of manufacturer's economic evaluation

5.1.1 Natural history

- The major disease stages of osteosarcoma have been identified and modelled adequately via health states (MS, Table 7, p67).

- The original MS is based on a base case modelled out to the primary trial (INT-0133) follow-up time horizon of 12.25 years (Section 3.5) but sensitivity analyses were provided for 20 and 40 years in the MS, and provided in a subsequent request a 60-year time horizon.

- The primary trial was conducted on individuals less than 30 years of age and this circumstance necessarily impacts on the accuracy of summary measurements applied to modelling in the broader population described in the MS (Section 2, p10).

- In the original MS, individuals who were disease-free at the end of the trial follow-up period were assumed to remain in that state. This was considered an unrealistic assumption by the ERG and subsequent sensitivity analyses for various recurrence rates were obtained from the manufacturer.

5.1.2 Treatment effectiveness within the submission

The decision analytic model structures and assumptions are based on Markov model methodology which is an appropriate modelling strategy for the problem outlined in the submission. The states included in the model, all defined with respect to the post-treatment maintenance phase of the RCT, are:

- Absence of disease

- Disease progression

- Relapse/recurrence

- Absence of disease following relapse/recurrence

- Progression following relapse/recurrence

- Death

The probabilities in the MS (including supplementary data provided by the manufacturer) which are used in the model are derived in an appropriate manner. The source is usually relevant trial data and/or expert clinical opinion. However, the estimated probabilities of transition between the health states are fixed values, which is less than satisfactory. According to the MS (Section 7.2.12.2, p88), this approach was used to deal which changes in transition probabilities over time, an explanation which the ERG consider irrelevant. This is of particular concern because there are a considerable number of small or zero estimated transition probabilities (Table 34, p154, of the MS). For example, these are used to re-allocate patients who transition to a drop-out (withdrawal) state in the model (Section 10.5.9 of the MS, p145), a process which is artificial and therefore already subject to uncertainty.

Somewhat unusually, there is no discussion or evaluation of the effect of treatment on the economic evaluation. While various summary measures of effectiveness (of mifamurtide) have been provided in the MS and subsequent requests, there is no consideration of the variability of these estimates in the economic evaluation. For example, hazard ratios for disease-free and overall survival are key outcomes of the RCT, are presented in the MS together with corresponding confidence intervals, but no attempt has been made to explore the effect of different hazard ratio values on the cost-effectiveness results.

In the original MS, modelling out to the longer time-horizons was done under the assumption that patients without disease at the end of the trial follow-up period would remain disease-free. This was considered unrealistic by the ERG, who requested (and received) additional data incorporating recurrence rates of 2% and 5%. These were modelled as increased costs for the base case, and had little effect on the ICERs.

- The rate of limb salvage used in the manufacturer's model (75%) is based on UK rates which are slightly higher than the rates in the INT-0133 trial (64%). However, this rate does not vary appreciably across treatment arms, so that the impact on cost-effectiveness estimates should be minimal.

- The effect of treatment was measured by QALYs based on utilities derived from two separate information sources (Section 5.1.3 for discussion).

- The manufacturer provided additional ICERs for a time horizon to 60 years beyond the RCT follow-up, as the ERG considered this to represent a more complete time horizon. These did not differ substantially from the results for 40 years.

- A limited sensitivity analyses based on the hazard ratio for disease-free survival was undertaken out by the ERG and is discussed in Section 6.

5.1.3 Health related quality of life

Health related quality of life was incorporated into QALY calculations based on utilities (and disutilities). The utilities used in the MS base case model were obtained from: (a) a separate survey of survivors from the INT-0133 trial using the EuroQoL-5D (EQ-5D) scale, and (b) a review of NICE appraisals of cancer technologies.

Limitations of (a) include the following:

- That the trial was limited to individuals less than 30 years of age, who constitute a substantial but not complete population of osteosarcoma patients.

- That the survey was conducted some years after the patients experienced the health states of interest.

- That the survey was conducted (necessarily) on survivors.

- That the sample size was small (n = 22, Section 7.5.8.2, p77, MS).

Therefore, the ERG has some reservations about the following:

- The generalisability of this survey to the osteosarcoma population in general.

- Potential recall bias.

- Potential inflation of utility values due to not sampling from patients who have died.

- The accuracy of the results.

any of which may affect the validity of the resulting utilities.

The review of NICE appraisals, (b), identified five completed and one ongoing appraisal, but these focussed on older cancer patients (age 45 or over), and were therefore not considered relevant in terms of generalisability to the osteosarcoma population. However, as there were very few participants in the EQ-5D survey who had experienced recurrence/relapse or disease progression (or both), age-adjusted utility values were derived for these two states (or both combined) from the studies found through (b). The adjustment was done by a published method,[21] and resulted in modest increases in utilities: from 0.61 to 0.66 for the recurrence/relapse state and from 0.39 to 0.49 for the other two states.

While there were substantial rates of adverse events associated with the treatments under scrutiny (MS, Section 6.7.2, p57), the original MS model effectively included rates for only one relatively minor adverse event (for infusion complications) in the base case model (MS, Section 7.2.7.4, p74). In particular, a clear, and statistically significant, difference between hearing-loss rates in the primary trial (15% for mifamurtide arms versus 8% for non-mifamurtide arms) was omitted. This was partly due to clinical advice that the most likely cause is the platinum-based treatment (cisplatin) in the combination therapy (MS, Section 7.2.7.4, p74), and that the rates were consistent with current evidence. While the ERG recognises that this serious adverse event is known to be associated with platinum-based treatment, the approach in the MS is considered inadequate as a similar level of hearing loss would be expected in both non-mifamurtide and mifamurtide arms (Section 6).

The use of a maximum number of doses of mifamurtide (Section 5.1.4) could probably result in a relative increase in the number of associated adverse events, which would result in a corresponding decrease in HRQoL as a result of this rate rise.

5.1.4 Resources and costs

In the base case, the maximum number of mifamurtide doses (and cycles) is used, although it is unclear from the MS whether either of these limits is adhered to in practice. This strategy

increases the cost of the treatment and could also result in a relatively high incidence of related adverse events, which could also lead to increased associated costs.

The effective omission of adverse effects and recurrences from the original model will deflate costs. However, sensitivity analyses by the manufacturer in response to requests for further data show that the impact of the latter on the ICER is minor.

The ERG considered the estimated cost of treating hearing loss in the original MS (£50) to be low. A request to the manufacturer for additional data based on different costs was not requested. However, the ERG conducted sensitivity analyses using the model provided by the manufacturer, revealing no change.

5.1.5 Discounting

A discount rate of 3.5% per annum was used, in accordance with the NICE base case.[22]

5.1.6 Sensitivity analyses

Sensitivity of results to changes in model inputs was explored in the MS by altering values of inputs considered important. These are listed in Tables 12 (p87) and 14 (p89) of the MS.

With a few, notable, exceptions described in this report, the sensitivity analyses conducted by the manufacturer revealed only minor differences in the cost-effectiveness results. The major exceptions are time horizon, number of doses of mifamurtide used, and hearing loss.

As mentioned previously, PSA was not included in the original MS. A subsequent request for PSA to be carried out by the manufacturer was declined. This was on the grounds that there was insufficient information to allow adequate definition of probability distributions, and that the original analyses were adequate, in the circumstances, for UK practice. Further, as the original sensitivity analyses were conducted using extreme values for some parameters, the manufacturer considered the results to be conservative. The ERG did not agree with this view.

Exploratory PSA analyses were conducted by the ERG to gauge the extent of variability in results (Section 6).

5.1.7 Model validation

Validation of the MS models was conducted adequately. A subsequent discovery, reported by the manufacturer, of a discounting error in QALYs and costs applied at 40 and 60 years could not have been identified by this process.

A half-cycle correction was not applied to the models included in the MS. According to the manufacturer, this was largely due to the difference in length of the first cycle size (9 months versus 6 months). However, preliminary analyses by the manufacturer, taking the first cycle to be six months in length, showed biased cost-effectiveness results in favour of mifamurtide (manufacturer's response to clarifications, B6, p40). This is because corresponding withdrawals would be assumed to happen at month 3 rather than month 4.5, resulting in lower mifamurtide costs. The MS states that TreeAge staff were consulted on this matter, but concludes that the package is unable to accommodate this complication in a satisfactory way.

5.2 Critique of approach used

The following is a summary of the approach used:

- The decision analytic model structures and assumptions are based on Markov model methodology which is an appropriate modelling strategy for the problem outlined in the submission. The scope of the model(s), together with various extensions and structural modifications are appropriate for appraising the submission.

- The various identified parameters used in the model are appropriate estimates of the modelled quantities. However the use of inputs has been inadequate in some cases. In particular, the handling of transition probabilities, long-term effects of disease and treatment, and adverse events are discussed at length in various parts of this report.

- Results in the MS were provided from analyses of data pooled across the two mifamurtide arms (Regimens A+ and B+) and across two non-mifamurtide arms of

the RCT (Regimens A and B). As there are potentially significant differences in clinical effectiveness between the four individual arms, this approach may be questionable.

- A PSA was not submitted in the MS or undertaken by the manufacturer when requested by the ERG. This omission is considered a major weakness of the submission.

5.3 Results included in manufacturer's submission

Table 9 summarises the ICER results presented in the MS (including supplementary data provided by the manufacturer), including the various sensitivity analyses (Section 5.1.6). Some results for the extrapolation by 20 years beyond the base case, those for the current trial follow-up duration of 12.25 years, are omitted because the longer time horizons were considered by the ERG to be more realistic. Results for the base case and for extrapolation by 40 and 60 years are presented in bold.

These results indicate that the ICERs are relatively insensitive to most of the inputs explored in this way. The obvious exceptions to ICER estimates are: time horizon, the cost of mifamurtide (either direct cost, in terms of the number of doses administered or in terms of the number of vials required per dose), the rate of hearing loss (particularly if there is a higher rate associated with mifamurtide treatment), and treatment choice (in particular, the comparison of Regimen A+ versus A, which would represent current UK standard practice)

In addition, budget impact estimates for mifamurtide for the next five years were included in the MS (MS, Table 10; Section 8.1., p96). The ERG considered that assumptions of a 50% uptake in the first two years followed by 80% uptake were likely to underestimate the true rate of uptake. A sensitivity analysis assuming an 80% rate throughout the five-year period was requested, and the results are also presented in Table 10. These indicate that the impact of a high rate of uptake of mifamurtide would be substantial.

Table 9: Base case, one- and two-way sensitivity analyses provided by the manufacturer

Parameter	input		Non-mifamurtide		mifamurtide		Incremental		ICER	Source
	initial	alternative	Cost	QALY gain	Cost	QALY gain	Cost	QALY gain		
Base case (12.25 years)			**£35K**	**6.419**	**£154K**	**6.679**	**£119K**	**0.26**	**£457,624**	**MS, p88, Table 13**
extrapolation		by 20 yrs	£35K	13.29	£154K	14.31	£119K	1.02	£116,879	MR, p31, Table 15 (new)
extrapolation		by 40 yrs	£35K	16.79	£154K	18.20	£119K	1.41	£84,786	MR, p32, Table 16 (new)
extrapolation		by 60 yrs	£35K	18.54	£154K	20.14	£119K	1.60	£74,558	MR, p39, Table B4c
number of mifamurtide doses	48	36	NR[2]	NR	£124,213[3]	NR	£89,213[2]	0.26	£343,126	MS, p89, Table 14; BCM[4]
number of cycles of 2nd line chemo	5	4, 10	NR	NR	NR	NR	NR	0.26	£457,571, £457,890	MS, p89, Table 14
cost of palliative care	£3,403	£5,105	NR	NR	NR	NR	NR	0.26	£457,561	MS, p89, Table 14
proportion of outpatient visits for mifamurtide group	30%	0	NR	NR	NR	NR	NR	0.26	£447,160[3]	MS, p89, Table 14
probability of lung metastases for mifamurtide group	0.5	0.75	NR	NR	NR	NR	NR	0.26	£456,889	MS, p89, Table 14
utility for disease progression	0.39	0.22	NR	NR	NR	NR	NR	0.26	£464,027	MS, p89, Table 14
utility for maintenance phase (cycle 1)	1	0.20	NR	NR	NR	NR	NR	0.26	£457,624	MS, p89, Table 14
utility of post-recurrence disease progression	0.39	0.22	NR	NR	NR	NR	NR	0.26	£458,018	MS, p89, Table 14
utility for recurrence	0.61	0.22	NR	NR	NR	NR	NR	0.27	£435,535	MS, p89, Table 14
annual rate of recurrence	0	5%	£34K	6.419	£153K	6.679	£119K	0.26	£457,606	MR, p37, Table B3a
proportion of patients requiring 2 vials	0	5%	£34K	6.419	£158K	6.679	£125K	0.26	£480,000	MR, p40, Table B5
proportion of patients requiring 2 vials	0	10%	£34K	6.419	£164K	6.679	£131K	0.26	£502,337	MR, p40, Table B5
rate of hearing loss events	0 & 0	8% & 15%[5]	£35K	6.297	£154K	6.439	£119K	0.142	£837,214	MS, p89, Table 14; BCM
rate of hearing loss events	0 & 0	9% & 10.5%	£34K	6.297	£153K	6.509	£119K	0.230	£517,163	MR, p42, Table B7

Parameter	input		Non-mifamurtide		mifamurtide		Incremental		ICER	Source
	initial	alternative	Cost	QALY gain	Cost	QALY gain	Cost	QALY gain		
rate of hearing loss events	0 & 0	7% & 19.5%	£34K	6.310	£153K	6.364	£119K	0.054	£2,196,430	MR, p42, Table B7
disease progression utility	0.39	0.49	£34K	6.422	£153K	6.684	£119K	0.262	£453,939	MR, p44, Table B8b
regimen A+ vs. regimen A			£31K	6.508	£151K	6.673	£119K	0.165	£724,313	MR, p48, Table B15a
regimen B+ vs. regimen B			£36K	6.359	£155K	6.685	£119K	0.325	£364,637	MR, p48, Table B15c
proportion of withdrawals from recurrence state who have progressed	0	50%	£34K	6.417	£153K	6.676	£119K	0.259	£460,232	MR, p56, Table B22b
proportion of withdrawals from recurrence state who have progressed	0	100%	£34K	6.412	£153K	6.666	£119K	0.254	£468,571	MR, p56, Table B22a
extrapolation by 40 years			**£35K**	**16.79**	**£154K**	**18.20**	**£119K**	**1.41**	**£84,786**	**MR, p32, Table 16 (new)**
rates of annual endoprosthesis	0	4%	£80K	16.79	£203K	18.20	£124K	1.41	£87,884	MR, p35, Table B2b
rates of annual endoprosthesis	0	8%	£92K	16.79	£217K	18.20	£125K	1.41	£88,738	MR, p35, Table B2b
annual rate of recurrence	0	5%	£35K	16.79	£154K	18.20	£119K	1.41	£84,778	MR, p38, Table B3a
disease recurrence utility	0.61	0.66	£35K	16.8	£154K	18.2	£119K	1.4	£84,888	MR, p43, Table B8a
disease progression utility	0.39	0.49	£35K	16.79	£154K	18.20	£119K	1.41	£84,659	MR, p44, Table B8b
utility of post-recurrence disease progression	0.39	0.49	£35K	16.79	£154K	18.20	£119K	1.41	£84,847	MR, p44, Table B8b
regimen A+ vs. regimen A			£33K	17.733	£152K	18.208	£120K	0.476	£251,297	MR, p48, Table B15a
regimen B+ vs. regimen B			£38K	15.95	£157K	18.14	£119K	2.19	£54,399	MR, p48, Table B15c
extrapolation by 60 years			**£35K**	**18.54**	**£154K**	**20.14**	**£119K**	**1.60**	**£74,558**	**MR, p39, Table B4c**
rates of annual endoprosthesis	0	4%	£85K	18.54	£209K	20.14	£124K	1.60	£77,628	MR, p35, Table B2b
rates of annual endoprosthesis	0	8%	£99K	18.54	£224K	20.14	£125K	1.60	£78,475	MR, p35, Table B2b
annual rate of recurrence	0	5%	£36K	18.54	£155K	20.14	£119K	1.60	£74,550	MR, p38, Table B3a

Parameter	input		Non-mifamurtide		mifamurtide		Incremental		ICER	Source
	initial	alternative	Cost	QALY gain	Cost	QALY gain	Cost	QALY gain		
disease recurrence utility	0.61	0.66	£35K	18.54	£154K	20.14	£119K	1.60	£74,637	MR, p43, Table B8a
utility of post-recurrence disease progression	0.39	0.49	£35K	18.54	£154K	20.14	£119K	1.60	£74,459	MR, p44, Table B8b
regimen A+ vs. regimen A			£33K	19.626	£153K	20.215	£120K	0.528	£226,372	MR, p48, Table B15a
regimen B+ vs. regimen B			£38K	17.57	£157K	20.07	£119K	2.5	£47,589	MR, p48, Table B15c

[1] MR, Manufacturers response to clarifications
[2] NR: not reported
[3] estimated by the ERG from the price of mifamurtide and the ICER.
[4] BCM: results for base-case model
[5] 8% for no-mifamurtide arms, 15% for mifamurtide arms

Table 10: Budget impact of rates of uptake of mifamurtide during 2009/2010 for 5 years after

Uptake rate	2009	2010	2011	2012	2013
50% in 2009, 2010, 80% thereafter	£4,657,371	£4,695,520	£7,571,952	£7,632,990	£7,694,028
80% throughout	£7,449,875	£7,510,913	£7,571,952	£7,632,990	£7,694,028

5.4 Comment on validity of results presented with reference to methodology used

The results presented in the manufacturer's submission and responses to requests are consistent with the inputs used, the approach to modelling and the model itself. The model is simple enough that the important factors can be seen to have expected results. The work undertaken by the ERG (Section 6) supports the view. The results are valid for the methodology used.

5.5 Summary of uncertainties and issues

There do not appear to be errors in the model programming, and alternative input values have been informed by trial data or clinical expertise. If one accepts that these factors do not impact on the results, then one possibility is that the results of the model are driven largely by the inputs (and assumptions) for the base-case scenario. Indeed, the MS highlights the importance of this scenario to the model.

However, this approach has lead to at least one important weakness in the economic model: the state transition probabilities for the base case scenario have not been modelled but were included as fixed proportions. This was apparently done in order to account for changes over time. But it results in a lack of flexibility as the probabilities are used for health state transition beyond the base case scenario and to re-allocate patients who dropped out in the RCT. Of particular concern is the number of small, even zero, probabilities which are present. A key feature is that uncertainty is ignored, which incorrectly implies a trial re-run would yield identical results.

The ICER estimates vary considerably over the modelled time horizons. The ERG believes that a 60 year extrapolation is most appropriate.

It is clear the number of doses of mifamurtide administered is the main driver of costs and ICER values. It is somewhat mystifying as to why information provided by the manufacturer on this variable has been limited. It is clear, for example that the number of doses received in the RCT varies considerably, but it has been difficult to determine the number of patients who received the full course of 48 doses.

Another important variable is the potential difference in hearing loss between mifamurtide and non-mifamurtide groups. Again, the amount of information provided on this variable is minimal and discussion related to the impact of this variable is almost totally omitted from the MS.

There is also uncertainty about the effect of interaction between ifosfamide and mifamurtide on the trial results. The sensitivity analysis results for the treatment groups with and without ifosfamide underscores the importance of this question in regard to the cost-effectiveness of mifamurtide. For example, the two results for base-case scenario of £724,313 for Regimens A+ versus A, compared with £364,637 for Regimens B+ versus B (Table 9) are quite different. Evidence of this substantial uncertainty is still present in the results of the extrapolation to 60 years beyond RCT follow-up (ICERs: £226,372 and £47,589) respectively. It is seen that pooling mifamurtide (A+ and B+ combined) and non-mifamurtide arms (A and B combined) yields an ICER of £74,558 at 60 years.

If one accepts there is no interaction between ifosfamide and mifamurtide, then these results can be considered to arise from two separate trials comparing the treatment of osteosarcoma. If so, they would indicate a great degree of uncertainty in the true cost-effectiveness of mifamurtide.

6 ADDITIONAL WORK UNDERTAKEN BY THE ERG

6.1 Additional sensitivity analyses

6.1.1 Introduction

As PSA was not provided by the manufacturer, various sensitivity analyses, including PSA for hearing loss rates was undertaken by the ERG. In addition, a sensitivity analysis of the effect of treatment was conducted using the probabilities of transition from the disease-free state of the submitted model, and the hazard ratio for disease-free survival reported in the MS. As previously indicated, these probabilities were included as fixed values in the model, but by substitution of values appropriately adjusted to reflect desired hazard ratio values of interest, a sensitivity analysis can be undertaken.

Further, analyses were conducted for 48 doses of mifamurtide, and results for 36 doses were obtained by subtracting the cost of the 12 doses of mifamurtide (£28,500) from the incremental cost results for the 48 doses, as there is no apparent dose-response relationship for mifamurtide. Also, analyses were conducted separately for 40- and 60-year extrapolations as well as the base case scenario. The analyses were conducted for both the pooled treatment arms (Regimens A+ and B+ versus Regimens A and B) and Regimens A+ versus A.

6.1.2 Methods

Hearing loss rates PSA

Three options were considered, based on the circumstances of the RCT:

(a) That there were two independent rates of hearing loss events for mifamurtide and non-mifamurtide arms

This scenario was implemented by defining a beta distribution for the hearing loss rate of each treatment arm in the model Note that Normal distributions were considered less desirable as the observed rates are relatively small, meaning that the distributions they arise are likely to be skewed, and the Normal distribution is not bounded by 0.

(b) That there was a common hearing loss event rate for mifamurtide and non-mifamurtide arms, with that the difference between the arms modelled as a relative-risk (RR)

This scenario is based on assumptions that all patients received standard multi-agent chemotherapy. Note that the difference between the rates for the two arms may be due to mifamurtide or could be due to another, perhaps unmeasured, variable.

This scenario was implemented by the definition of separate distributions for the common rate and for the RR. Specifically, a beta distribution was defined to represent the rate for the non-mifamurtide arm, and the relative-risk was assumed to have a log-normal distribution. That is, log-RR was assumed to have an approximate Normal distribution, which is a standard assumption in epidemiology.[23]

(c) That there is a common rate of hearing loss events across mifamurtide and non-mifamurtide arms

This is motivated by the plausible claim that hearing loss is not caused by mifamurtide rather by platinum-based treatments, such as cisplatin, which is a common component of treatment combinations for osteosarcoma and other cancers in general, and which was used for all patients in the RCT. This scenario was implemented by defining a single beta distribution for hearing loss in the model.

The parameters of all beta distributions were set to the number of affected and unaffected individuals in the corresponding arm, or the pooled totals across relevant arms where required. This defines a distribution with mean equal to the observed rate (or proportion, in this case) and with variance almost the same as that of the observed proportion. The variances of the beta and binary distributions so defined are practically identical for the sample sizes in the RCT.

For example, the estimate of objective hearing loss event rate (Table 8) across all treatment arms of the RCT (63/578 = 0.1090) was modelled by a beta distribution with parameters 63 and 515 (=578 – 63). The distribution of the log-RR for pooled treatment arms (RR =

39/338/(24/340) = 1.635), was assumed to Normal with mean 0.491 [=log(1.635)] and a standard deviation 0.248. The following table gives further details of the distributions used to assess the effect of hearing loss (Table 11).

Table 11: Distributions used in ERG PSA analysis of hearing loss adverse events

Input	**Distribution and parameters**	**Analysis**
Probability of hearing loss AE for non-mifamurtide arms	beta(24, 316) beta(8, 166)	Pooled treatment arms Regimens A+ vs. A
Probability of hearing loss AE for mifamurtide arms	beta(39, 299) beta(26, 141)	Pooled treatment arms Regimens A+ vs. A
Logarithm of relative-risk of hearing loss AE – mifamurtide vs. non-mifamurtide	Normal(0.491, 0.248) Normal(1.220, 0.390)	Pooled treatment arms Regimens A+ vs. A
Common hearing loss AE across treatment arms	beta(63, 515) beta(34, 341)	Pooled treatment arms Regimens A+ vs. A
AE, adverse events		

Other analyses

As mentioned in Section 4.1.4, sensitivity analyses of the cost associated with a hearing loss adverse event was conducted, using an alternative value of £200 (originally £50). This was done for each time horizon. However, the new cost made minimal difference to the results.

The effectiveness of mifamurtide, as measured by the disease-free survival hazard ratio, was assessed by applying values of interest to the probability of transition from the disease-free state to other states in the next cycle (i.e. six month time period). The target states included in the model were: recurrence, death, withdrawal, and remaining disease-free. This is because the specific probabilities are estimates of the conditional probabilities of surviving during each 6 month period, i.e. the disease-free transition probability, or changing to another state in the subsequent period of the RCT.

These are the interval-specific factors of a Kaplan-Meier product limit estimator.[24] In particular, the disease-free survival probability up to any time point of interest is the product

of the transitional probabilities for the time periods culminating in the time period which ends at the time point of interest. By definition, the resulting estimate is the non-parametric maximum likelihood estimate (MLE) of the survival probability up to the time-point of interest. Therefore under a proportional hazards assumption, which was a reasonable assumption for the RCT (manufacturer's responses, p17), the disease-free survival probability for a different hazard is the disease-free survival probability MLE raised to the power of the hazard ratio of interest. That is, if *S* is the estimated probability that a patient in a group of interest remains disease-free up to a certain time point, and *h* is a hazard ratio for a second group compared to the first, then S^h is the MLE for the corresponding disease-free survival in the second group.

Also, by considering the remainder probability R = 1 - S, and the probability of the converse event (not remaining in a disease-free state up to the same time point), it is relatively simple to show that $R^h = 1 – S^h$.

Finally, it was assumed that when the compliment (C) of the conditional probability of remaining disease-free for a certain time point consists of the sum of individual probabilities for a series of mutually exclusive events, the corresponding component of R^h for any one of these events, which contributes an amount *c* to *C*, is $c \times R^h/C$. That is, the component of R^h for an event in a time interval is proportional to the probability of that event.

Ideally one would model a survival function S(t) for disease-free survival, which is assumed to be continuous across time intervals, and, together with a distribution function for h, which is assumed to be constant over time, with a multinomial distribution for the non-disease-free states. A full PSA of effectiveness would then be relatively simple. However, as discussed in this report and implied by the preceding discussion, this was not possible without substantially modifying the submitted model structure, which was not considered feasible in the time available.

Therefore the results presented in this report are based on varying the value of the hazard ratio for disease-free survival, based on the values provided by the manufacturer. Specifically, for

results based on pooled mifamurtide and non-mifamurtide treatment arms, the results are based on a hazard ratio of 0.78 (95% confidence interval: 0.61 to 1.01), and for the Regimens A+ versus A, the hazard ratio used was 0.96 (0.67 to 1.38).

Numerical results of the sensitivity analyses carried out by the ERG are presented in Tables 12 and 13. Figures presenting cost-effectiveness (CE) plane plots and cost-effectiveness acceptability curves (CEACs) for the analyses relating to hearing loss rates both for pooled treatment arms, and for Regimens A+ versus A are included in Appendix 2. The results are based on objective hearing loss rates. Unless otherwise stated, results are for 48 doses of mifamurtide. In the figures, results for 36 doses of mifamurtide are approximated without re-analysis by subtracting the cost of 12 doses (£28,500) from the corresponding results for 48 doses.

6.1.3 Results

The results in Tables 12 and 13 highlight the fact that there is a substantial amount of uncertainty in the results if one varies hearing loss rates, effectiveness, and treatment regimen. Note that the mifamurtide treatment does not become dominated exactly as the hazard rate exceeds one, due to the approximate nature of these analyses: QALYs can still be gained even when the hazard ratio is against the treatment.

Table 12: Additional sensitivity analyses of hearing loss effects conducted by the ERG

Parameter	input distributions		Incremental quantities				ICER (cost/QALY gained)	
	mifamurtide	non-mifamurtide	Cost	95% CI	QALY gain	95% CI	mean	95% CI
Pooled Treatment arms								
Base case (12.25 years)			**£119K**		**0.26**		**£457,624**	
independent rates of hearing loss AE	beta(39, 299)	beta(24, 316)	£119K	(119,026, 119,030)	0.18	(0.120, 0.256)	£669,456	(465,774, 990,060)
common baseline hearing loss AE rate + log-RR	beta(24,316) & N(0.491, 0.248)	beta(24, 316)	£119K	(119,026, 119,032)	0.18	(0.058, 0.257)	£535,839	(455,661, 1,800,805)
common hearing loss AE rate	beta(63, 515)	beta(63, 515)	£119K	(119,024, 119,028)	0.25	(0.197, 0.312)	£475,530	(381,718, 604,088)
+40 years extrapolation			**£119K**		**1.41**		**£84,786**	
independent rates of hearing loss AE	beta(39, 299)	beta(24, 316)	£119K	(119,203, 119,208)	1.33	(1.259, 1.397)	£89,680	(85,310, 94,702)
common baseline hearing loss AE rate + log-RR	beta(24,316) & N(0.491, 0.248)	beta(24, 316)	£119K	(119,203, 119,209)	1.32	(1.201, 1.402)	£90,259	(85,007, 99,264)
common hearing loss AE rate	beta(63, 515)	beta(63, 515)	£119K	(119,201, 119,205)	1.40	(1.342, 1.457)	£85,243	(81,839, 88,857)
+60 years extrapolation			**£119K**		**1.60**		**£74,558**	
independent rates of hearing loss AE	beta(39, 299)	beta(24, 316)	£119K	(119,233, 119,237)	1.52	(1.451, 1.588)	£78,483	(75,081, 82,158)
common baseline hearing loss AE rate + log-RR	beta(24,316) & N(0.491, 0.248)	beta(24, 316)	£119K	(119,234, 119,243)	1.46	(1.261, 1.572)	£81,679	(75,827, 94,586)

Parameter	input distributions		Incremental quantities				ICER (cost/QALY gained)	
	mifamurtide	non-mifamurtide	Cost	95% CI	QALY gain	95% CI	mean	95% CI
common hearing loss AE rate	beta(63, 515)	beta(63, 515)	£119K	(119,221, 119,245)	1.59	(1.190, 1.954)	£76,307	(61,015, 100,212)
A+ vs. A								
+40 years extrapolation								
independent rates of hearing loss AE	beta(26, 141)	beta(8, 166)	£119K	(119,508, 119,514)	0.30	(0.193, 0.397)	£416,615	(301,343, 620,311)
common baseline hearing loss AE rate + log-RR	beta(8, 166) & N(1.220, 0.390)	beta(8, 166)	£119K	(119,507, 119,522)	0.28	(-0.064, 0.439)	£507,452	(-1,245,261, 2,052,030)
common hearing loss AE rate	beta(34, 341)	beta(34, 341)	£119K	(119,503, 119,508)	0.47	(0.402, 0.541)	£254,810	(220,828, 297,531)
+60 years extrapolation								
independent rates of hearing loss AE	beta(26, 141)	beta(8, 166)	£119K	(119,516, 119,522)	0.35	(0.241, 0.446)	£351,652	(267,909, 495,732)
common baseline hearing loss AE rate + log-RR	beta(8, 166) & N(1.220, 0.390)	beta(8, 166)	£119K	(119,515, 119,530)	0.33	(-0.019, 0.491)	£380,654	(-483,118, 1,335,617)
common hearing loss AE rate	beta(34, 341)	beta(34, 341)	£119K	(119,511, 119,516)	0.52	(0.456, 0.595)	£228,983	(200,847, 262,370)

Table 13: Sensitivity analyses of effectiveness of mifamurtide conducted by the ERG

Hazard ratio	**Extrapolation to 40 years**			**Extrapolation to 60 years**		
	Incremental cost	QALY gain	ICER	Incremental cost	QALY gain	ICER
Pooled treatment arms						
0.61 (lower 95% CI limit ~=0.78*0.8)	£119K	2.48	£48,059	£119K	2.83	£42,182
0.78*0.9 = 0.702	£119K	1.89	£63,107	£119K	2.15	£55,432
Base case (HR = 0.78)	**£119K**	**1.41**	**£84,786**	**£119K**	**1.60**	**£74,558**
0.78*1.1 = 0.85	£119K	0.94	£126,911	£119K	1.07	£111,844
0.78*1.2 = 0.94	£119K	0.49	£244,091	£119K	0.55	£216,430
1.01 (upper 95% CI limit ~= 0.78*1.29)	£119K	0.07	£1,597,451	£119K	0.08	£1,524,342
Regimens A+ vs. A						
0.67 (lower 95% CI limit ~=0.96*0.7)	£119K	1.99	£60,108	£119K	2.25	£52,974
0.96*0.8 = 0.77	£119K	1.46	£81,859	£119K	1.65	£72,322
0.96*0.9 = 0.87	£119K	0.96	£124,505	£119K	1.08	£110,538
Base case (HR = 0.96)	**£119K**	**0.48**	**£251,297**	**£119K**	**0.53**	**£226,372**
0.96*1.1 = 1.06	£119K	0.01	£12,794,677	£119K	0.000	Dominated
0.96*1.2 = 1.16	£119K	-0.44	Dominated	£119K	-0.52	Dominated
1.38 (upper 95% CI limit ~= 0.96*1.44)	£119K	-1.46	Dominated	£119K	-1.68	Dominated

7 DISCUSSION

7.1 Summary of clinical effectiveness issues

The manufacturer's submission to NICE includes a systematic review of the clinical-effectiveness literature and narrative reporting of a single RCT that met the inclusion criteria of the review (INT-0133 trial). The ERG has two main areas of concern relating to clinical effectiveness issues in the manufacturer's submission; first, the limited evidence base and its relevance to the NHS, and second, the interpretation of the included RCT. Whilst the submitted evidence generally reflects the decision problem as defined in the manufacturer's submission, it is not totally representative of all patients with osteosarcoma in the UK (e.g. individuals with metastatic disease, recurrent disease, older patients and osteosarcoma related to Paget's disease or other primary sites). The submitted evidence consists of the only published RCT concerning mifamurtide and as such may be helpful for answering some questions concerning osteosarcoma treatment that will impact on the NHS. The MS states that after a median follow up of 7.9 years the addition of mifamurtide to multi-agent chemotherapy (Regimens A+ and B+ combined) increased overall survival (hazard ratio, 0.72; 95% CI, 0.53 to 0.97; p=0.0313) and disease-free survival (hazard ratio, 0.78; 95% CI, 0.61 to 1.01; p=0.0586) in patients (less than 30 years age) with high grade, resectable, non metastatic osteosarcoma compared with chemotherapy alone (Regimens A and B combined). Given the trial design limitations and the interpretation of the statistical analyses (wide confidence intervals with similar point estimates for efficacy), it is unclear whether a more clinically relevant assessment for a UK population would be derived from an analysis comparing individual mifamurtide containing regimens (Regimen A+) to chemotherapy regimens most commonly used in the UK (Regimen A). This additional post hoc analysis (requested by the ERG) that compared Regimen A+ with Regimen A showed a non-significant improvement in overall survival (hazard ratio, 0.75; 95% CI, 0.49 to 1.16; p=0.1949) and disease-free survival (hazard ratio, 0.96; 95% CI, 0.67 to 1.38; p=0.8357).

7.2 Summary of cost effectiveness issues

The ICER values are quite sensitive to assumptions made around hearing loss. Sensitivity analyses of the base case model indicate that the ICER for mifamurtide increases by at least £30,000 per QALY for each percentage point that the hearing loss rate is higher in the mifamurtide arm. This amount decreases to approximately £12,000 at 40 years extrapolation beyond trial follow-up, and £7,000 at 60 years, with the main driver of the increase being a

loss of (incremental) QALYs rather than an increase in costs. The omission of a hearing loss rate in the MS decision model will result in an underestimate of variability of the ICER. This has been explored with the ERG PSA (Section 6).

Potential interaction between ifosfamide and mifamurtide treatment is a major issue discussed above. If there is no such interaction, then a high degree of variability is evident in the cost-effectiveness results. As noted in Section 5.5, this is reflected in the results for the groups with and without mifamurtide: ICERs of £724,313 for Regimens A+ versus A, compared with £364,637] for Regimens B+ versus B (Table 9) for the base-case scenario, with corresponding ICERs of £226,372 and £47,589] when extrapolated to 60 years, respectively. Pooling of data for mifamurtide (Regimens A+ and B+) and non-mifamurtide arms (Regimens A and B) yields an ICER of £74,558 at 60 years.

The lack of complete clarity on the number of doses patients received in the INT-0133 trial has been noted (Section 5.5). This variable is a major driver of costs and, in turn, ICERs, which is evident from the sensitivity analysis results.

7.3 Implications for research

- At present it is uncertain whether a more appropriate measure of mifamurtide efficacy for a UK population would be derived from an analysis comparing Regimen A+ with Regimen A or a pooled comparison of Regimens A+ and B+ with Regimens A and B. Further trials would allow a more accurate estimation of the hazard ratio and whether there is an interaction with ifosfamide, if any.

- Further research is needed in other patient groups, namely in individuals with metastatic disease, recurrent disease, older patients and other osteosarcomas.

Appendix 1: Summary of overall - and disease-free - survival using the 2003 and 2006 data set

Table 14: Summary of overall survival using the 2003 and 2006 data set

Interventions (Regimens)[a]	Median follow up (years)	Numbers followed in each group (n)	Event in each group (n)	Hazard Ratio (95% CI; p-value)[b]
2003 data set for overall survival				
A (control)	4.5	174	43 (25%)	-
A+	5.0	167	33 (20%)	-
B	4.6	166	42 (25%)	-
B+	4.8	171	30 (18%)	-
Primary analysis				
A/B combined vs. A+/ B+ combined	4.8	340 vs. 338	85 vs. 63	0.67 (0.48, 0.94; p=0.0183)
Additional analysis requested by the ERG				
A vs. A+	-	174 v 167	43 v 33	0.78 (0.49, 1.24; p=0.2895)
A vs. B	-	174 v 166	43 v 42	1.06 (0.69, 1.63; p=0.7806)
A vs. B+	-	174 v 171	43 v 30	0.69 (0.43, 1.10; p=0.1197)
B vs. A+	-	166 v 167	42 v 33	0.72 (0.45, 1.13; p=0.1546)
A+ vs. B+	-	167 v 171	33 v 30	0.87 (0.53, 1.43; p=0.5770)
B vs. B+	-	166 v 171	42 v 30	0.58 (0.36, 0.93; p=0.0236)
2006 data set for overall survival				
A (control)	7.5	174	51 (29%)	-
A+	7.9	167	37 (22%)	-
B	8.0	166	49 (30%)	-
B+	6.8	171	36 (21%)	-
Primary analysis				
A/B combined vs. A+/ B+ combined	7.7	340 vs. 338	100 vs. 73	0.72 (0.53, 0.98; p=0.0352)
Additional analysis requested by the ERG				
A vs. A+	-	174 vs. 167	51 vs. 37	0.76 (0.50, 1.17; p=0.2172)
A vs. B	-	174 vs. 166	51 vs. 49	0.98 (0.66, 1.45; p=0.9275)
A vs. B+	-	174 vs. 171	51 vs. 36	0.71 (0.46, 1.09; p=0.1190)
B vs. A+	-	166 vs. 167	49 vs. 37	0.75 (0.49, 1.16; p=0.1943)
A+ vs. B+	-	167 vs. 171	37 vs. 36	0.91 (0.57, 1.44; p=0.6868)
B vs. B+	-	166 vs. 171	49 vs. 36	0.68 (0.44, 1.05; p=0.0832)

[a] Regimen A, methotrexate, doxorubicin and cisplatin; Regimen A+, Regimen A and mifamurtide; Regimen B, methotrexate, doxorubicin, cisplatin and ifosfamide; Regimen B+, Regimen B and mifamurtide

[b] p-value from log rank test stratified by ifosfamide use and randomisation strata for Regimens A+ and B+ combined versus Regimens A and B combined; p-value from Cox model stratified by randomisation strata for pair-wise comparisons of A, A+, B, B+

Table 15: Summary of disease-free survival using the 2003 and 2006 data set

Interventions (Regimens)[a]	Median follow up (years)	Numbers followed in each group (n)	Event in each group (n)	Hazard Ratio (95% CI; p-value)[b]
2003 data set for disease-free survival				
A (control)	4.5	174	59 (34%)	-
A+	5.0	167	55 (33%)	-
B	4.6	166	67 (40%)	-
B+	4.8	171	47 (27%)	-
Primary analysis				
A/B combined vs. A+/ B+ combined [c]	4.8	340 vs.338	126 vs. 102	0.74 (0.57, 0.96; p=0.0245)
Additional analysis requested by the ERG				
A vs. A+	-	174 v 167	59 v 55	0.97 (0.67, 1.40; p=0.8622)
A vs. B	-	174 v 166	59 v 67	1.25 (0.88, 1.77; p=0.2207)
A vs. B+	-	174 v 171	59 v 47	0.74 (0.50, 1.09; p=0.1309)
B vs. A+	-	166 v 167	67 v 55	0.76 (0.53, 1.09; p=0.1332)
A+ vs. B+	-	167 v 171	55 v 47	0.77 (0.52, 1.13; p=0.1817)
B vs. B+	-	166 v 171	67 v 47	0.57 (0.39, 0.82; p=0.0029)
2006 data set for disease-free survival				
A (control)	7.5	174	62 (36%)	-
A+	7.9	167	58 (35%)	-
B	8.0	166	71 (43%)	-
B+	6.8	171	49 (29%)	-
Primary analysis				
A/B combined vs. A+/ B+ combined	7.7	340 vs.338	133 vs. 107	0.78 (0.61, 1.01; p=0.0623)
Additional analysis requested by the ERG				
A vs. A+	-	174 vs. 167	62 vs. 58	0.97 (0.68, 1.39; p=0.8763)
A vs. B	-	174 vs. 166	62 vs. 71	1.18 (0.84, 1.66; p=0.3409)
A vs. B+	-	174 vs. 171	62 vs. 49	0.77 (0.53, 1.12; p=0.1651)
B vs. A+	-	166 vs. 167	71 vs. 58	0.81 (0.57, 1.15; p=0.2413)
A+ vs. B+	-	167 vs. 171	58 vs. 49	0.77 (0.53, 1.13; p=0.1850)
B vs. B+	-	166 vs. 171	71 vs. 49	0.63 (0.44, 0.91; p=0.0139)

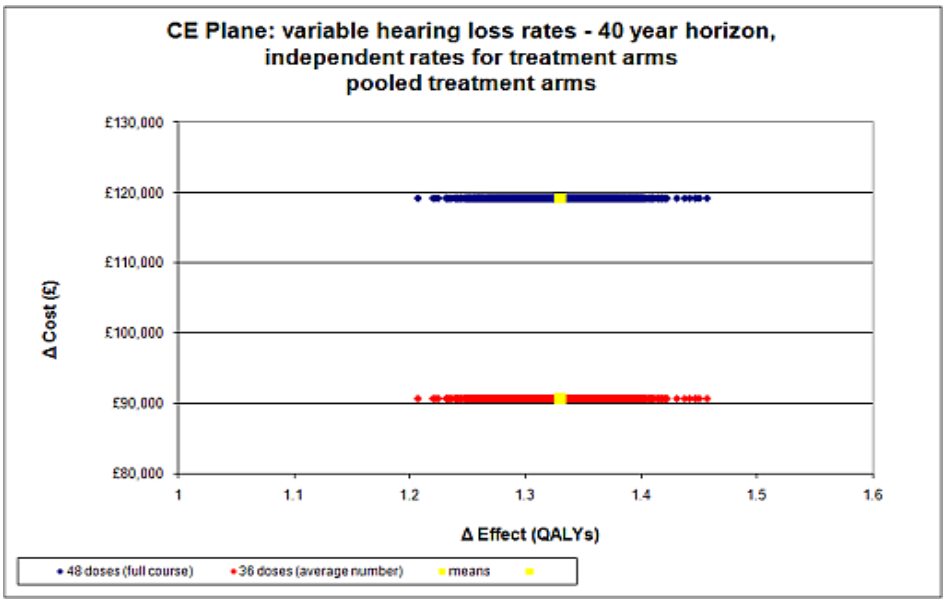
[a] Regimen A, methotrexate, doxorubicin and cisplatin; Regimen A+, Regimen A and mifamurtide; Regimen B, methotrexate, doxorubicin, cisplatin and ifosfamide; Regimen B+, Regimen B and mifamurtide

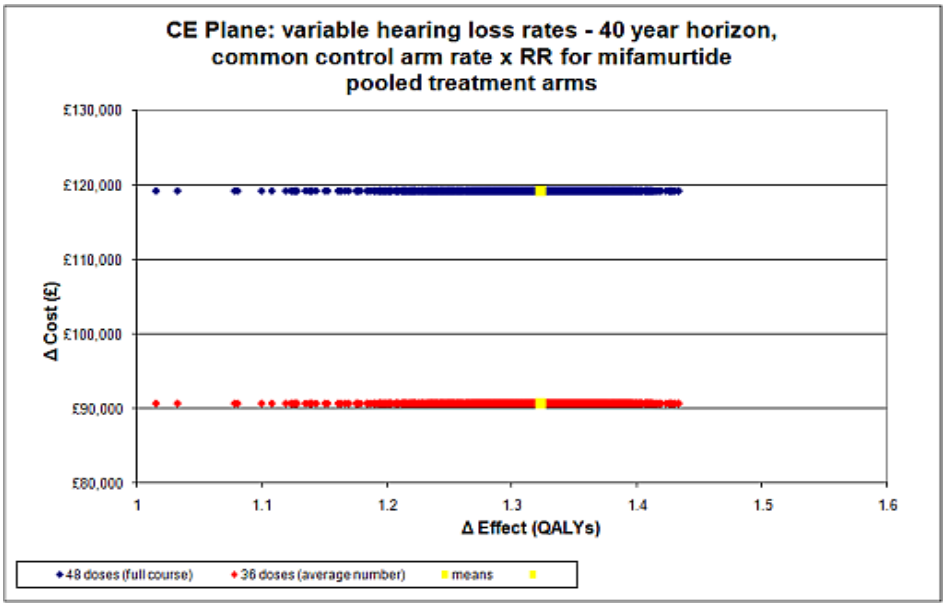
[b] p-value from log rank test stratified by ifosfamide use and randomisation strata for Regimens A+ and B+ combined versus Regimens A and B combined; p-value from Cox model stratified by randomisation strata for pair-wise comparisons of A, A+, B, B+

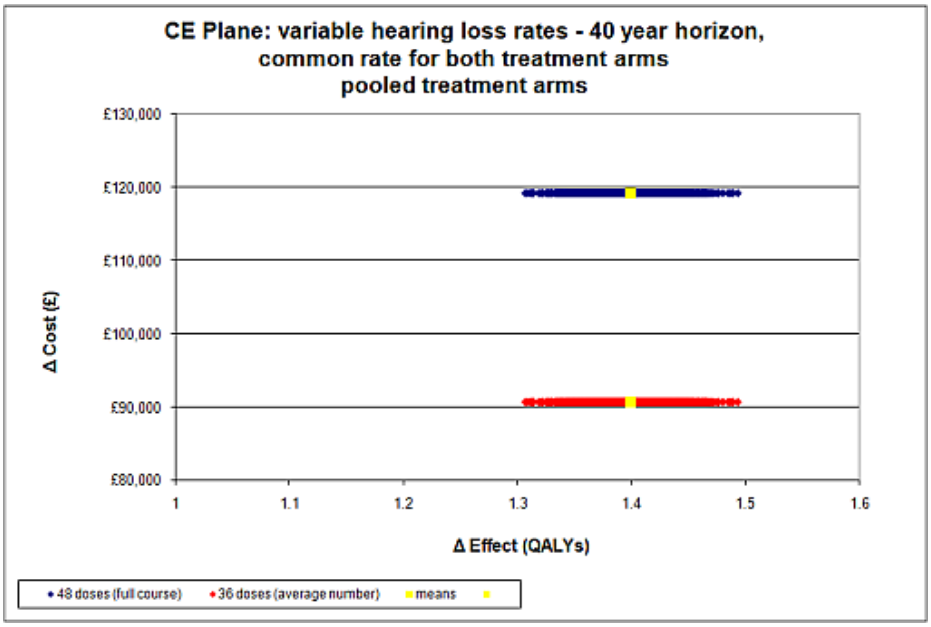
[c] An interaction between the study interventions was observed (p value not reported), therefore the data should not be analysed according to original factorial design (marginal analyses not appropriate) but according to treatment assignments

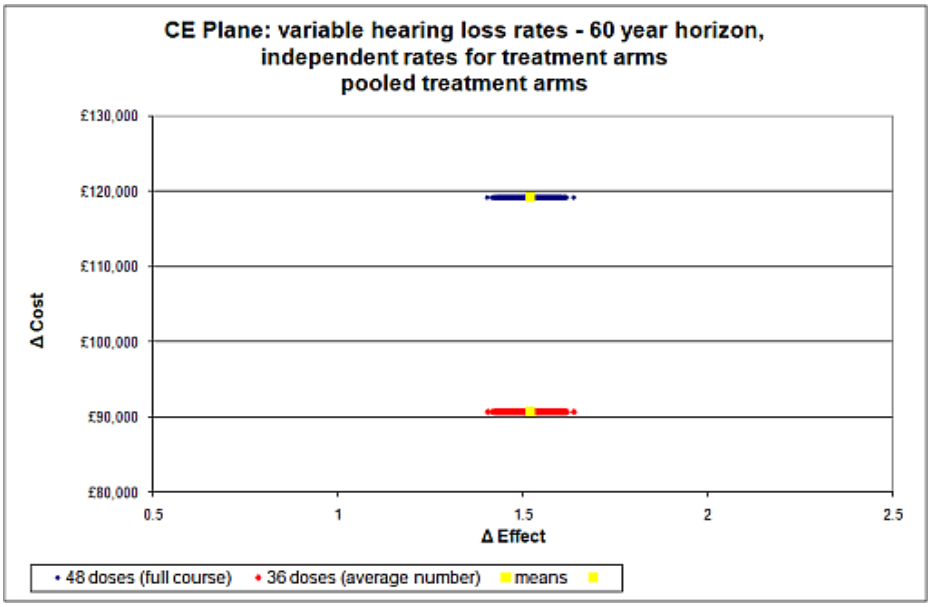
Appendix 2: Cost-effectiveness plane and cost-effectiveness acceptability curves for hearing loss adverse events PSA

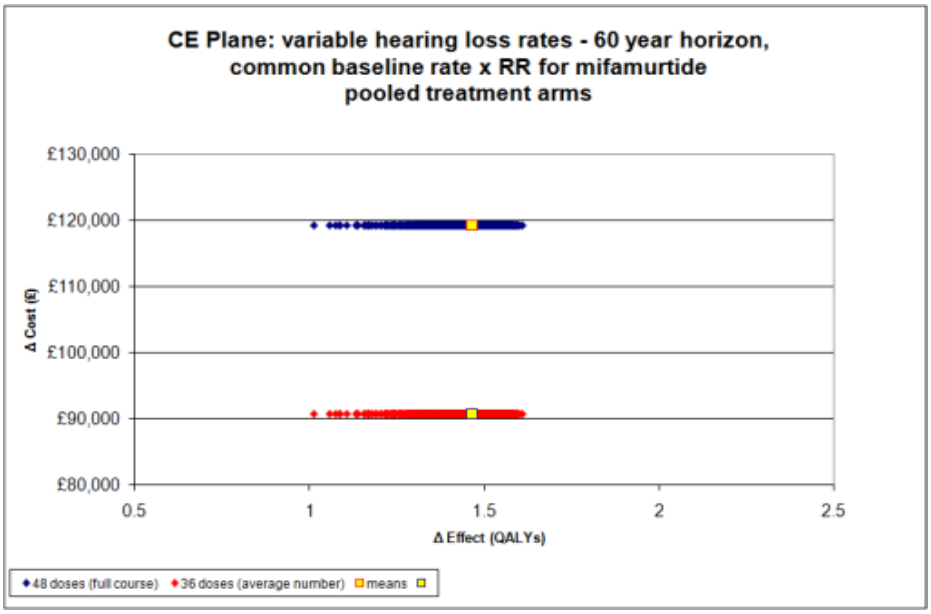
(a) Cost-effectiveness plane plots - pooled treatment arms

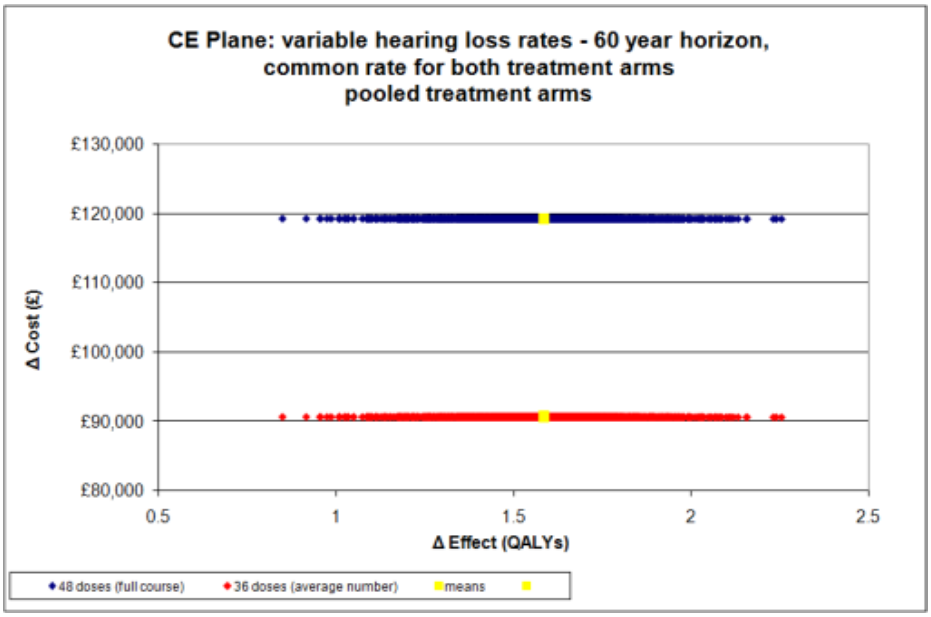




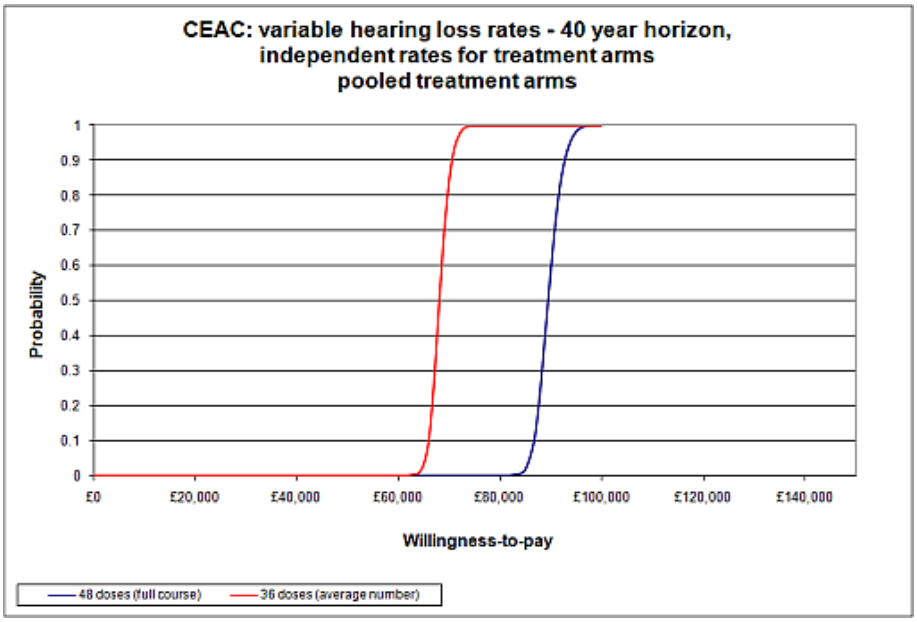

CE Plane: variable hearing loss rates - 40 year horizon,
common rate for both treatment arms
pooled treatment arms
£130,000
£120,000
£110,000
£100,000
£90,000
£80,000
Δ Cost (£)
1
1.1
1.2
1.3
1.4
1.5
1.6
Δ Effect (QALYs)
48 doses (full course)
36 doses (average number)
means

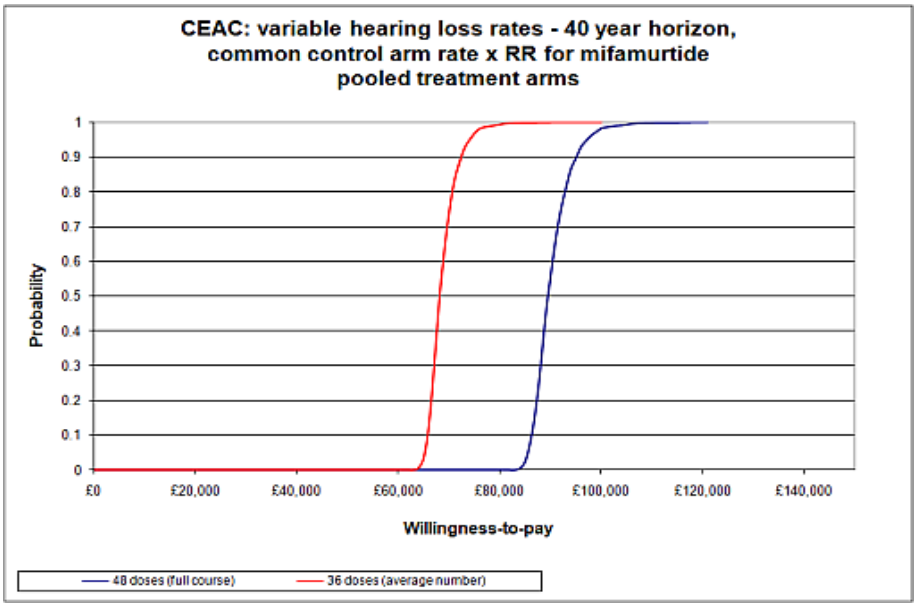

CE Plane: variable hearing loss rates - 60 year horizon,
independent rates for treatment arms
pooled treatment arms
£130,000
£120,000
£110,000
£100,000
£90,000
£80,000
Δ Cost
0.5
1
1.5
2
2.5
Δ Effect
48 doses (full course)
36 doses (average number)
means

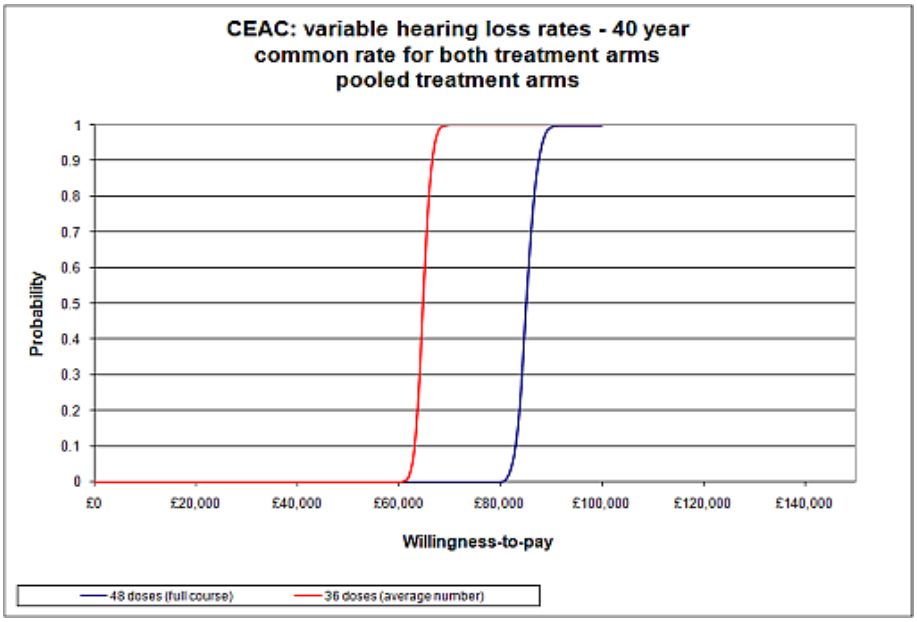

CE Plane: variable hearing loss rates - 60 year horizon,
common baseline rate x RR for mifamurtide
pooled treatment arms
£130,000
£120,000
£110,000
£100,000
£90,000
£80,000
Δ Cost (£)
0.5
1
1.5
2
2.5
Δ Effect (QALYs)
48 doses (full course)
36 doses (average number)
means

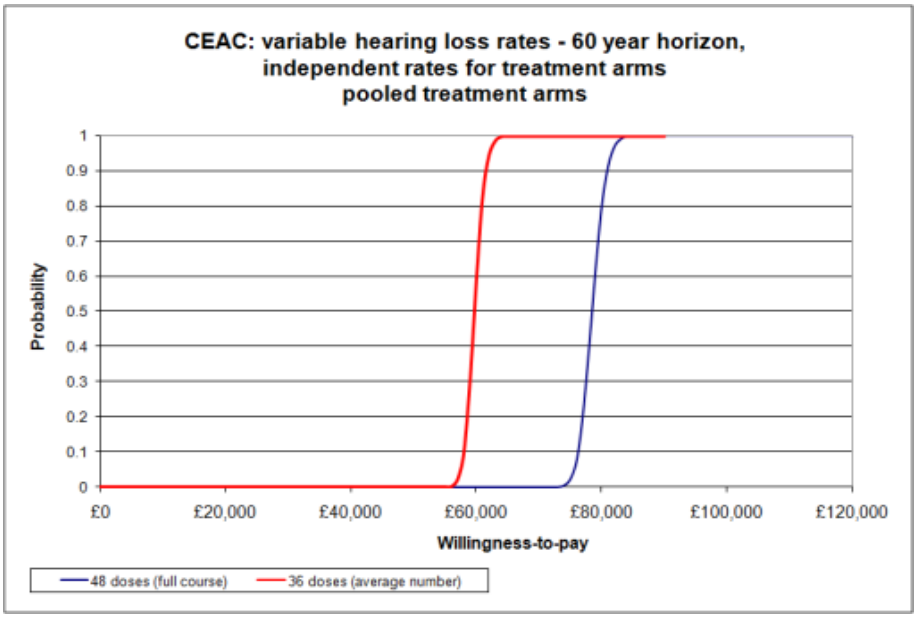


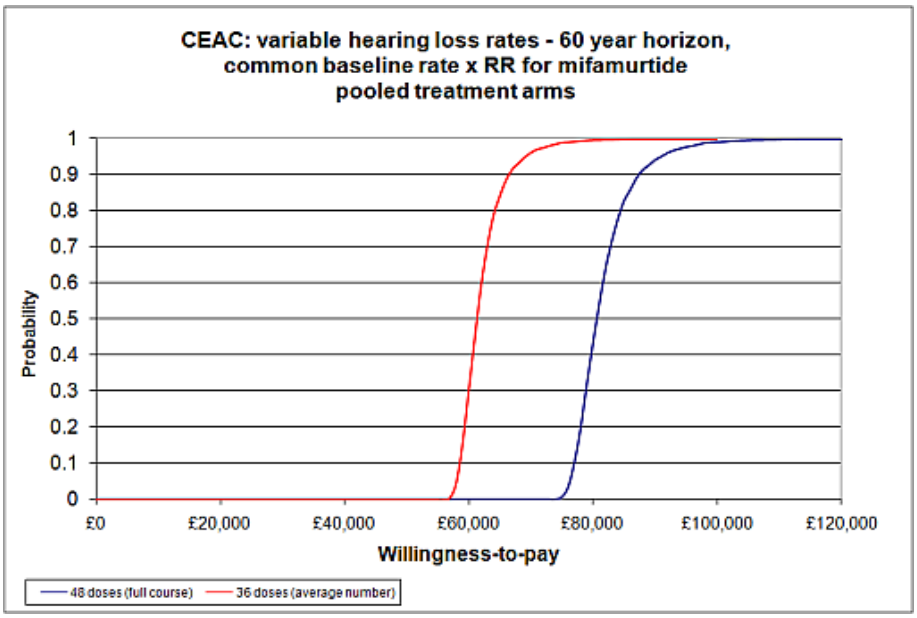
(b) Cost-effectiveness acceptability curve plots – pooled treatment arms

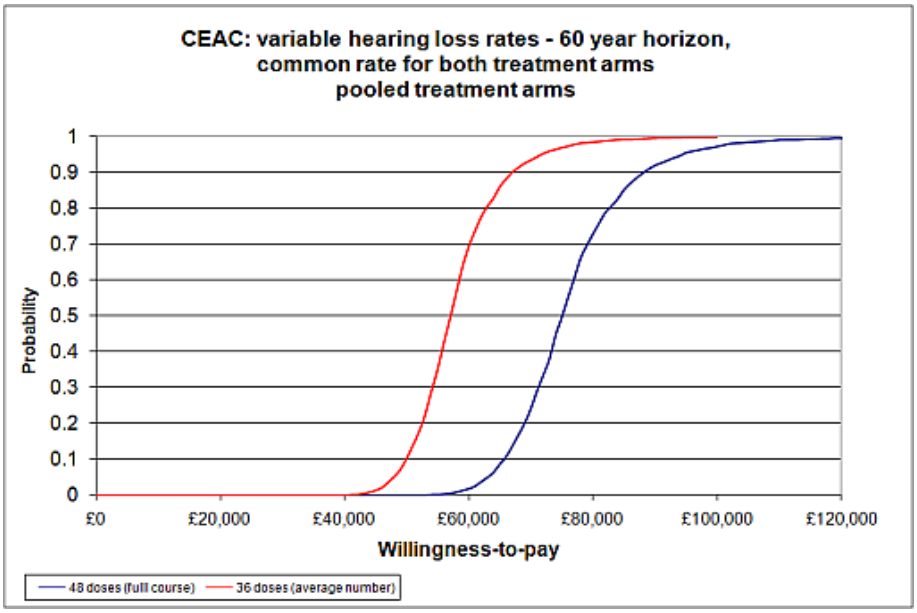



CEAC: variable hearing loss rates - 40 year horizon,
common control arm rate x RR for mifamurtide
pooled treatment arms
Probability
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
£0
£20,000
£40,000
£60,000
£80,000
£100,000
£120,000
£140,000
Willingness-to-pay
48 doses (full course)
36 doses (average number)

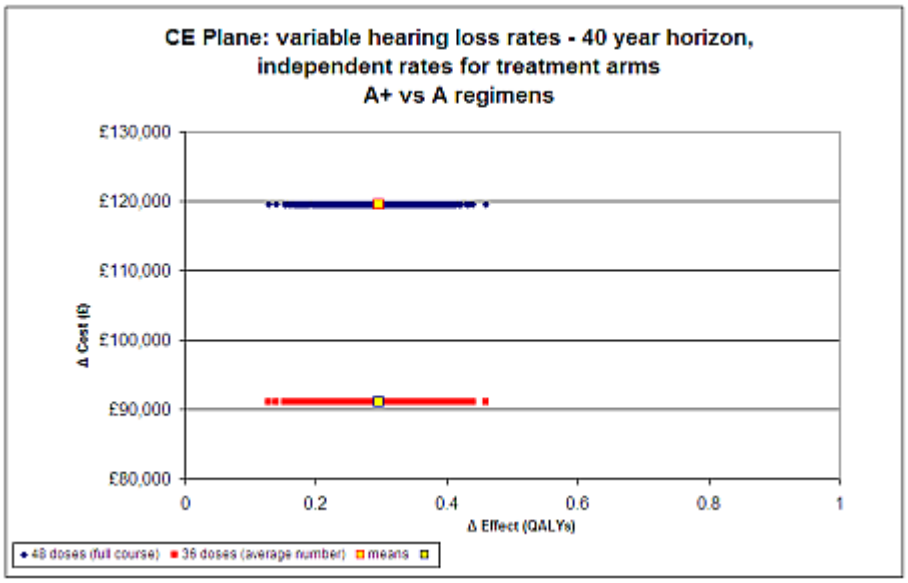

CEAC: variable hearing loss rates - 40 year
common rate for both treatment arms
pooled treatment arms
Probability
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
£0
£20,000
£40,000
£60,000
£80,000
£100,000
£120,000
£140,000
Willingness-to-pay
48 doses (full course)
36 doses (average number)

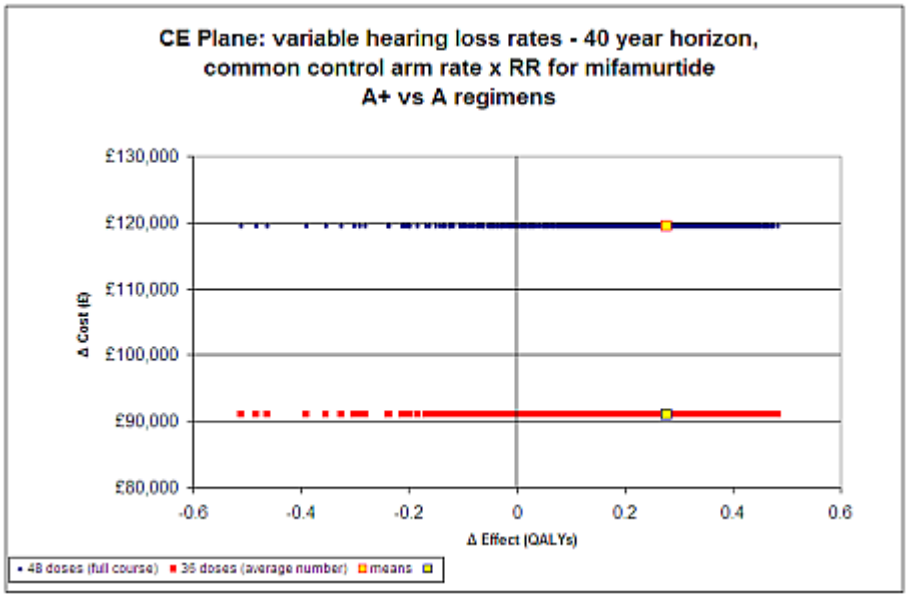

CEAC: variable hearing loss rates - 60 year horizon,
independent rates for treatment arms
pooled treatment arms
Probability
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
£0
£20,000
£40,000
£60,000
£80,000
£100,000
£120,000
Willingness-to-pay
48 doses (full course)
36 doses (average number)

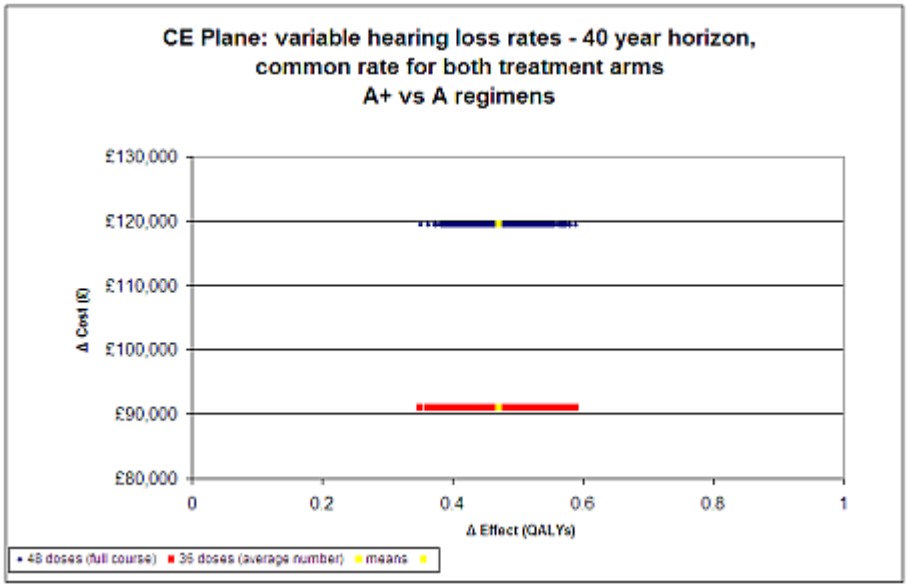


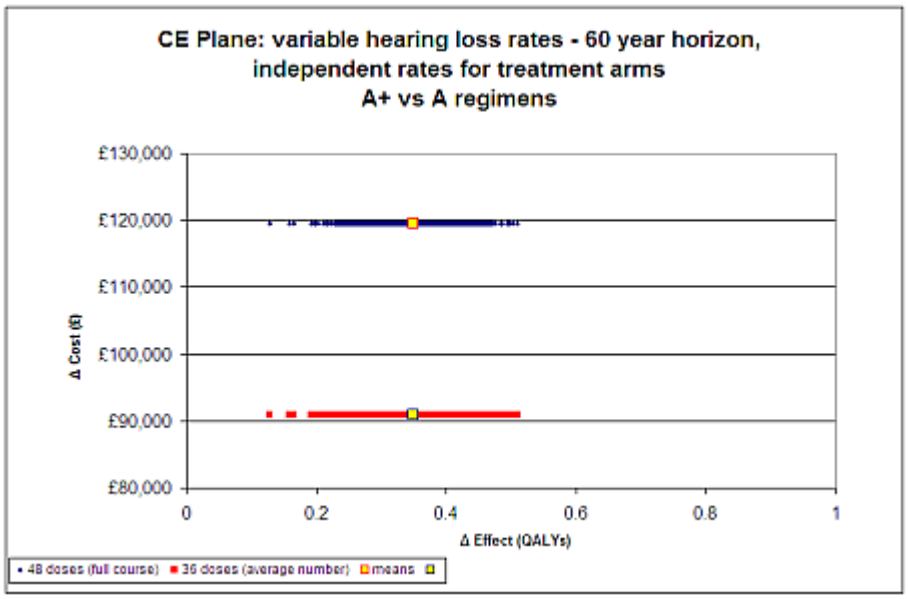


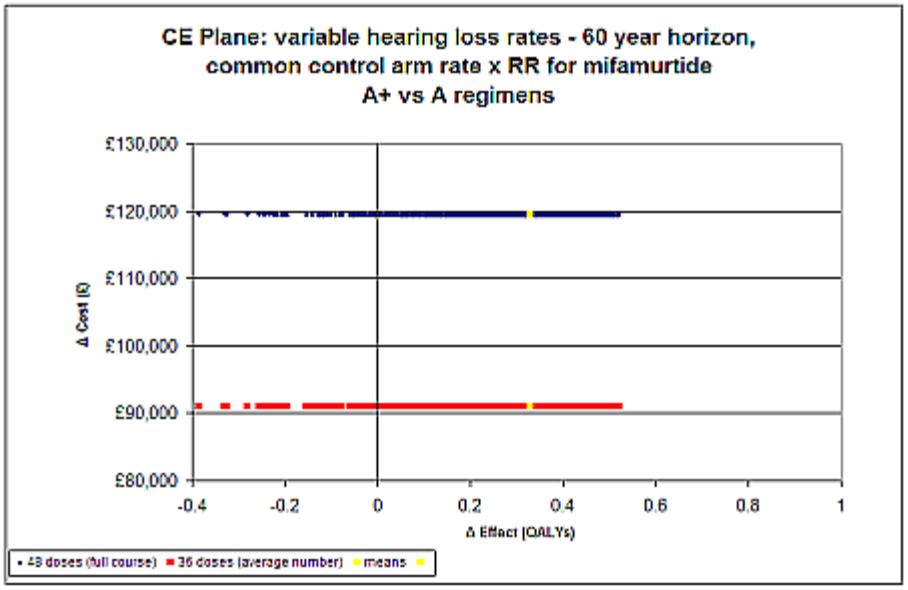
(c) Cost-effectiveness plane plots – Regimens A+ vs. A

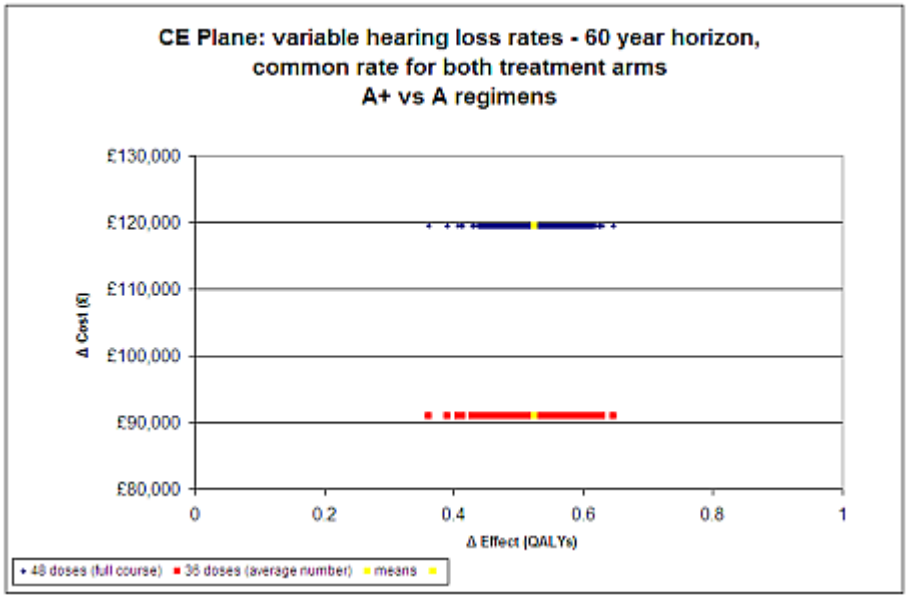

CE Plane: variable hearing loss rates - 40 year horizon,
independent rates for treatment arms
A+ vs A regimens
£130,000
£120,000
£110,000
£100,000
£90,000
£80,000
Δ Cost (£)
0
0.2
0.4
0.6
0.8
1
Δ Effect (QALYs)
48 doses (full course)
36 doses (average number)
means


CE Plane: variable hearing loss rates - 40 year horizon,
common control arm rate x RR for mifamurtide
A+ vs A regimens
£130,000
£120,000
£110,000
£100,000
£90,000
£80,000
Δ Cost (£)
-0.6
-0.4
-0.2
0
0.2
0.4
0.6
Δ Effect (QALYs)
48 doses (full course)
36 doses (average number)
means

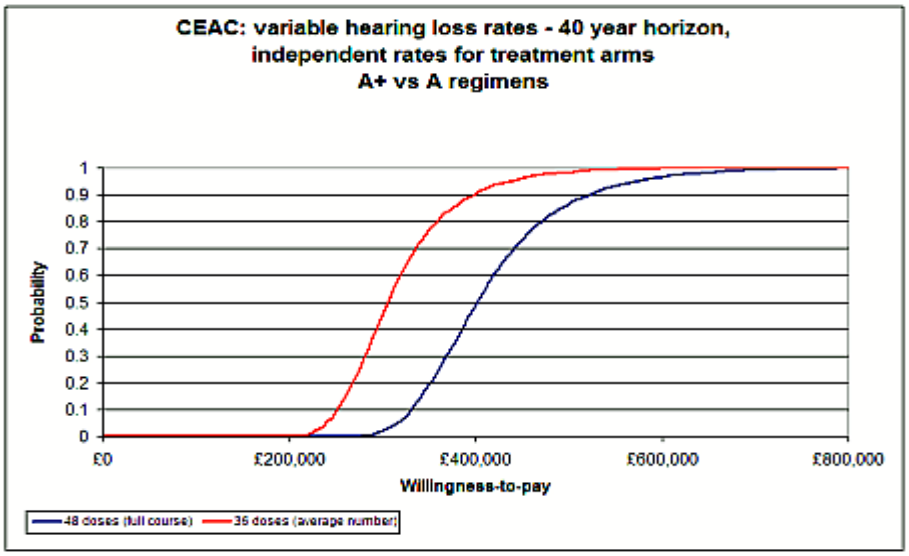

CE Plane: variable hearing loss rates - 40 year horizon,
common rate for both treatment arms
A+ vs A regimens
£130,000
£120,000
£110,000
£100,000
£90,000
£80,000
Δ Cost (£)
0
0.2
0.4
0.6
0.8
1
Δ Effect (QALYs)
48 doses (full course)
36 doses (average number)
means

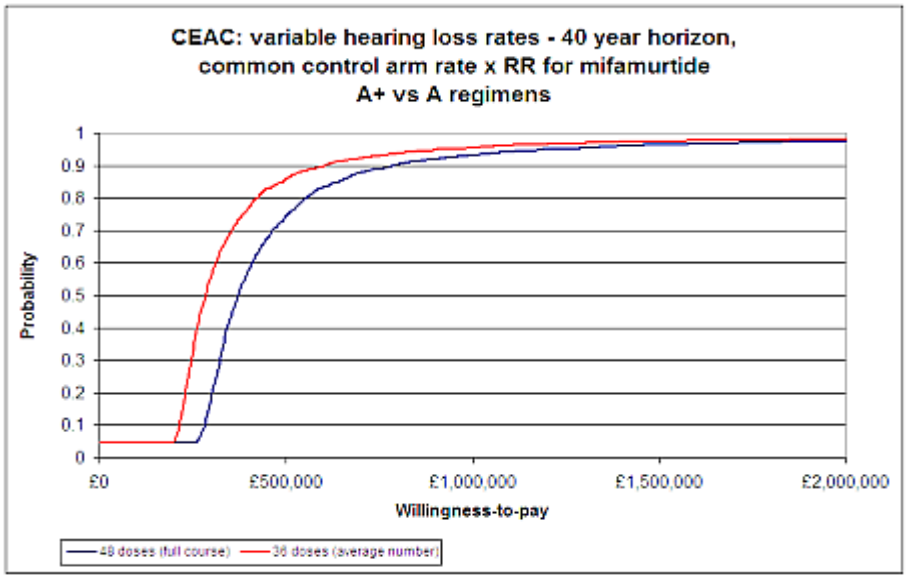

CE Plane: variable hearing loss rates - 60 year horizon,
independent rates for treatment arms
A+ vs A regimens
£130,000
£120,000
£110,000
£100,000
£90,000
£80,000
Δ Cost (£)
0
0.2
0.4
0.6
0.8
1
Δ Effect (QALYs)
48 doses (full course)
36 doses (average number)
means

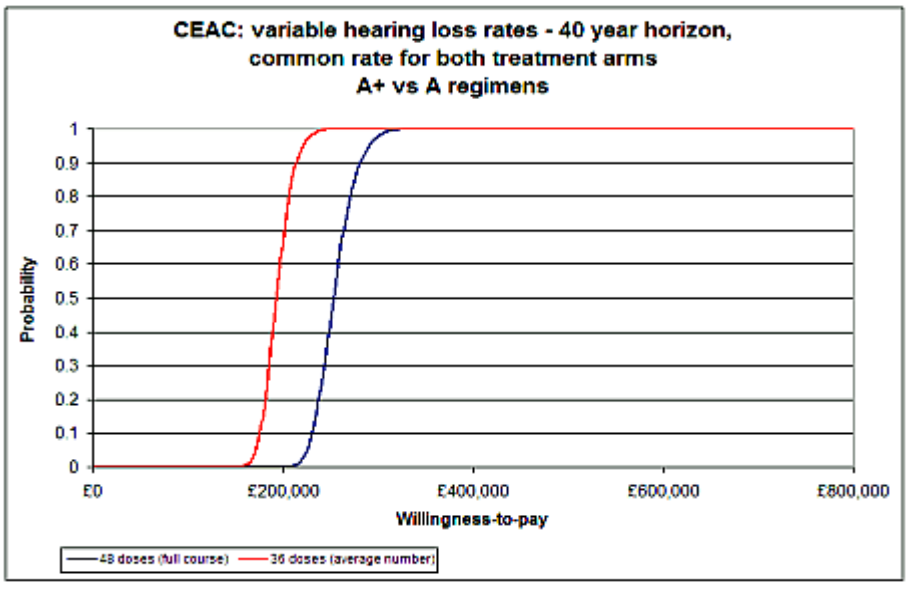

CE Plane: variable hearing loss rates - 60 year horizon,
common control arm rate x RR for mifamurtide
A+ vs A regimens
£130,000
£120,000
£110,000
£100,000
£90,000
£80,000
Δ Cost (£)
-0.4
-0.2
0
0.2
0.4
0.6
0.8
1
Δ Effect (QALYs)
48 doses (full course)
36 doses (average number)
means

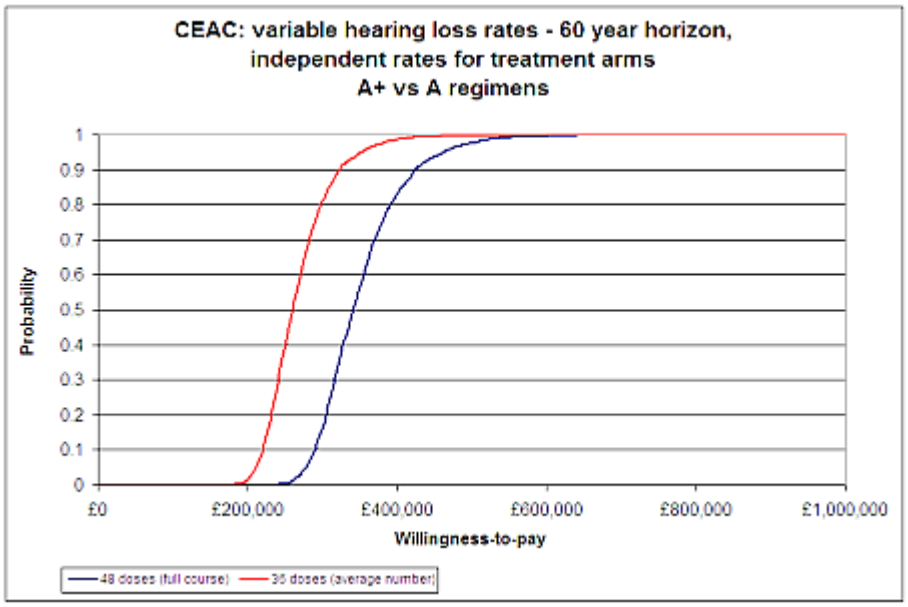

CE Plane: variable hearing loss rates - 60 year horizon,
common rate for both treatment arms
A+ vs A regimens
£130,000
£120,000
£110,000
£100,000
£90,000
£80,000
Δ Cost (£)
0
0.2
0.4
0.6
0.8
1
Δ Effect (QALYs)
48 doses (full course)
36 doses (average number)
means

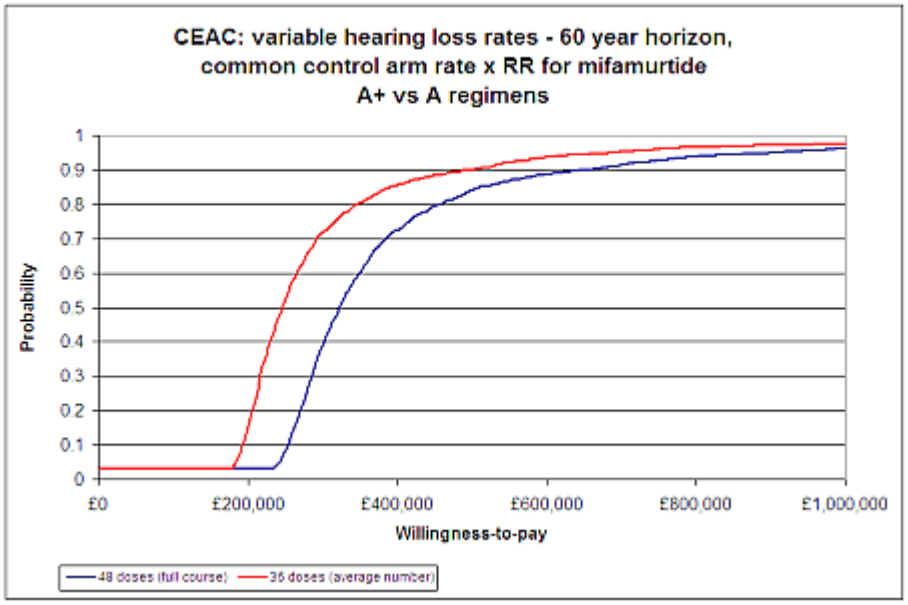
(d) Cost-effectiveness acceptability curve plots – Regimens A+ vs. A

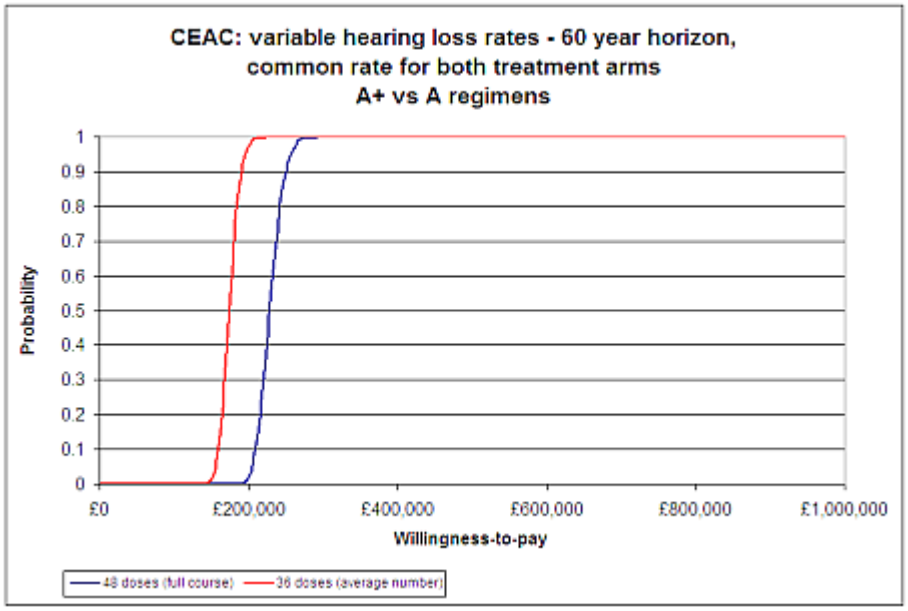







CEAC: variable hearing loss rates - 60 year horizon,
independent rates for treatment arms
A+ vs A regimens
Probability
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
£0
£200,000
£400,000
£600,000
£800,000
£1,000,000
Willingness-to-pay
48 doses (full course)
36 doses (average number)


CEAC: variable hearing loss rates - 60 year horizon,
common control arm rate x RR for mifamurtide
A+ vs A regimens
Probability
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
£0
£200,000
£400,000
£600,000
£800,000
£1,000,000
Willingness-to-pay
48 doses (full course)
36 doses (average number)


CEAC: variable hearing loss rates - 60 year horizon,
common rate for both treatment arms
A+ vs A regimens
Probability
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
£0
£200,000
£400,000
£600,000
£800,000
£1,000,000
Willingness-to-pay
48 doses (full course)
36 doses (average number)

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