NICE Single Technology Appraisal - Mifamurtide for osteosarcoma

On behalf of Takeda UK Ltd, please find our response to questions provided on the 14th January 2010 with regards to the Single Technology Appraisal for Mifamurtide for osteosarcoma.

Questions raised by the Evidence Review Group (School of Health and Related Research [ScHARR], University of Sheffield) and the technical team at NICE are as presented below and answered in this document.

A1 **Priority Question**: Please provide a copy of the PAS as submitted to the Patient Access Scheme Liaison Unit at NICE.
A copy of the Takeda UK Ltd Mepact Patient PAS is enclosed with this clarification response. The enclosed PAS is the original submitted to the Department of Health & the Patient Access Scheme Liaison Unit at NICE (PASLU) on the 16th November 2009. An updated copy of the PAS will be sent week beginning 1st February 2010 after modifications made on the advice of the NICE PASLU team. This will be followed by updated health economics incorporating the modified PAS.
A2 i **Priority Question**: Please clarify the following details of The PAS. At present it appears that in the model a patient would receive unlimited free vials of mifamurtide after completing 38 doses, however in the submission it appears that a patient would receive 10 free vials of mifamurtide after completing the 38 doses. Please clarify the number of free vials of mifamurtide provided through the PAS.
The product licence for mifamurtide states that patients should be given a total of 48 infusions for a complete course treatment. Takeda UK Ltd emphasise that treatment protocols should reflect the product licence to achieve the documented efficacy from the evidence base. The enclosed PAS is the original submitted to the Department of Health & the Patient Access Scheme Liaison Unit at NICE (PASLU) on the 16th November 2009. An updated copy of the PAS will be sent week beginning 1st February 2010 after modifications made on the advice of the NICE PASLU team. This will be followed by updated health economics incorporating the modified PAS.
A2 ii Please confirm that no administration charges for the PAS have been incorporated.
It is correct that no charges for administration of the mifamurtide PAS have been considered in the Cost Effectiveness estimates provided. However the costs for the administration of mifamurtide as a treatment have been incorporated.
A3 **Priority Question**: Clinical advice suggests that often patients who develop complications may be treated at their local hospital which might provide logistical problems in administering the PAS scheme. Please amend the economic model to allow a variable administrative cost per mifamurtide dose to be incorporated.
The administrative cost can be varied by altering the value in cell F22 in sheet “Resource Use” in the latest model. This variable is also analysed in the sensitivity analyses.
A4 Often patients recruited to RCTs are healthier and/or more compliant with medication than those seen in clinical practice. If the patients seen in UK clinical practice were significantly less healthy or less compliant with medication, fewer patients would receive more than 38 doses. This would affect the effect of the PAS scheme on the cost effectiveness. Please comment on this hypothesis and

provide evidence relating the severity of the condition in patients in the trial to that observed in routine practice.

The enclosed PAS is the original submitted to the Department of Health & the Patient Access Scheme Liaison Unit at NICE (PASLU) on the 16th November 2009.

An updated copy of the PAS will be sent week beginning 1st February 2010 after modifications made on the advice of the NICE PASLU team.

This will be followed by updated health economics incorporating the modified PAS.

From November 1993 through November 1997, the Children's Cancer Group (CCG) and the Paediatric Oncology Group (POG) carried out Intergroup Study 0133 (CCG-7921 and POG-9351).

Analysis of the intention to treat population within this trail (662 patients with high-grade resectable non-metastatic osteosarcoma after macroscopically complete surgical resection) was the basis for EMEA approval and the subsequent product licence for mifamurtide in the UK and Europe.

The patient population recruited during the duration of trial INT0133 represented approximately one third of the total US population diagnosed with high-grade resectable non-metastatic osteosarcoma after macroscopically complete surgical resection [iii, iv, v].

Trial INT0133 is representative of current UK clinical practice where the general health of children, adolescents and young adults at diagnosis (aged between 2-30 years) is similar. Osteosarcoma Specialist feedback confirms this position [vi].

Compliance data from the trial is the only available data.

Physicians at the time of treating patients with mifamurtide as part of trial INT0133 were unaware of the outcomes on overall survival.

Feedback from Osteosarcoma Specialist's [vi] suggests that as outcome data for mifamurtide is now in the public domain [iv], it would be the aim to treat patients with a full course of 48 infusions of mifamurtide in line with the product licence & evidence base.

A5 **Priority Question**: There appears to be a discrepancy with the face validity of the model. The base case used in the new submission is associated with a survival rate of 77% without mifamurtide and 83% with mifamurtide; however, the data from the trial give these values to be 70% and 78% respectively. This suggests that the model does not produce the survival rates from the trial that it is simulating. Please provide an explanation as to why this happens in the model and why it may be justifiable.

The 6-year Kaplan-Meier (KM) estimate of the survival rate in the mifamurtide arm is 78% and 70% in the arm without mifamurtide based on all 678 patients. It is important to note that this rate is different than the rate observed in patients who entered the adjuvant treatment phase of the INT-0133 trial. Alike to the previous Cost Effectiveness model submitted in the previous IDM Pharma Inc submission, the analyses in the Takeda cost effectiveness model is based upon an **analysis of the 604 ITT patients who entered the maintenance phase**. Seventy-four patients in the ITT group who did not enter the adjuvant phase were excluded from this analysis. In this patient population who received adjuvant treatment, the 6-year Kaplan-Meier estimate of the survival rate 80.4% in the mifamurtide arm and 72.9% in the arm without mifamurtide.

The 77% and 83% are derived from the proportion of patients who are not dead after the 23.5 years of the trial {(1 -H46) in ME-MEPACT and ME-No_MEPACT excel sheets}.

The reason why the survival rates are not the same is due to the method by which the survival rates have been derived. The differences are based on the fact that the analysis to derive the transition probabilities for the model cycles events in 6 to 9 month intervals while the Kaplan-Meier method does not.

Additionally, in the trial recurrence was an end point and no follow-up data was ascertained. In the cost effectiveness model patients who have a recurrence have a probability of becoming disease free and hence increase the survival rate compared to the trial data. Also in the model withdrawals are

attributed to other health states dependent on the proportion that moved to the other states. This would increase the proportion of survivors compared to the calculated figures from the trial where patients are censored after withdrawal.

A6 **Priority Question**: The new Excel model does not use relative risks but appears to use raw data (presumably from the relevant trials). It is currently unclear which dataset has been used. Please provide a full description of the data used in the Excel model and its source. This is particularly pertinent to the use of Beta trees where the variables used within the model (S1 to S6) have not been defined.

It is correct that raw data has been used in the new CEA model and this data comes from an analysis of the INT-0133 trial provided by the Children's Oncology Group at Andy Anderson hospital in the US. This can be found in the model under the TP_Mepact and TP_No_Mepact excel sheets of the model.

Please find below a description of the source documentation for the transition probabilities used in the new cost-effectiveness model. The same data was used in the original model also. This description includes an explanation of the input data (TP_Data.csv), a SAS program (cost effectiveness (9month_Takeda.sas)) showing the source of where the transition probabilities were generated f (comma delimited format readable in Excel), and a SAS Macro (TransProbMacro.sas) used to calculate the transition probabilities.

The input data found in file "TP_Data.csv" was derived from multiple original datasets provided by the Children's Oncology Group. The data used for calculating the transition probabilities was the 2007 updated dataset. The file "TP_Data.csv" includes a total of 604 intent-to-treat (ITT) patients who entered the adjuvant phase. Seventy-four patients in the ITT group who did not enter maintenance were excluded from this analysis.

A total of 793 patients were randomised into study INT-0133. The primary analysis group included 678 patients, aged ≤30 with newly diagnosed non-metastatic high-grade resectable osteosarcoma. This was the intent-to-treat population as defined by the study protocol. The study also allowed patients with metastatic or unresectable disease to be enrolled, with the study design stipulating that they be analysed separately. Sixteen of the 793 randomised patients were deemed ineligible by the COG after randomisation. US cooperative groups are required to exclude data from ineligible patients in all analyses and reports, thus the total number of patients reported by COG was 777 and the intent-to-treat group analysed by the COG (in the 2008 publication) comprised 662 patients. A true intent-to-treat analysis includes all randomised patients and IDM Pharma's analysis, therefore, included COG-ineligible patients (giving n=793 in total and n=678 as the intent-to-treat population). However, the study findings and conclusions were the same irrespective of inclusion or exclusion of COG-ineligible patients.

A total of 9 variables are used in the calculation of the transition probabilities and are found in the "TP_Data.csv" file. These data are:

1) nrg0no: Patient id number.
2) Mtppe: mtppe treatment indicator where mtppe=1 if patient received mtppe and mtppe=0 otherwise
3) RG0REGA: Variable taking on values 1, 2, 3, 4 where RG0REGA equal to 1 or 2 indicates the patient received regimen A and RG0REGA equal to 3 or 4 indicates the patient received regimen B.
4) TGDTREG: Telephone registration date.
5) Relapse: Relapse indicator where 1=relapse and 0=no relapse.
6) Relapse date: Date of relapse if relapse=1 or date of last follow-up for relapse if relapse=0.
7) Death: Death indicator where if death=1 indicates the patient died and death=0 indicates the patient did not die.

8) Deathdate: Date of death if death=1 or date of last follow-up for death if death=0.
9) TempMarg: Indicator variable in which TempMarg=1 if patient entered maintenance with evidence of disease and TempMarg=0 if there was no evidence that the patient entered maintenance with evidence of disease. This variable indicates whether there are gross or microscopic positive margins after surgery. In this case these patients are not truly disease free since there is evidence of disease at time of surgery. We use this variable to define 2 initial states (State 1 for patients with residual disease TempMarg=1 and State 2 for patients with no evidence of residual disease TempMarg=0).

Disease States in Transition Probabilities Calculations

- State 1: Initial state for a patient with TempMarg=1 (i.e., Residual Disease)
- State 2: Initial state for a patient with TempMarg=0 (i.e., Disease Free)
- State 3: Transition state for a patient with TempMarg=0 who experiences a relapse. A patient is transitioned into this state if between the start of the current cycle and the end of the current cycle they relapse (Recurrence)
- State 4: Transition state entered from state 3 representing the time between a relapse and death (i.e., Disease Progression after being Disease Free)
- State 5: Death (Absorbing State). A patient enters this state if between the beginning of the current cycle and the end of the current cycle they experience a death (Death)

State 6: Withdrawal (Absorbing State). A patient enters this state if between the beginning of the current cycle and the end of the current cycle they withdraw from the study (Withdrawal).

Alongside the submission are the following attachments::

1) TP_Data.csv: Input data
2) costeffectiveness(9month_Takeda.sas): A SAS program for generating the CSV transition probabilities files
3) TransProbMacro.sas: A SAS Macro used to calculate the transition probabilities.
4) Four CSV files generated by programs above:
   - mtp_plus.csv: Subset of patients receiving mtppe
   - mtp_minus.csv: Subset of patients not receiving mtppe
   - Aplus.csv: Subset of patients receiving Regimen A plus mtppe
   - Aminus.csv: Subset of patients receiving Regimen A without mtppe
   - Bplus.csv: Subset of patients receiving Regimen B plus mtppe
   - Bminus.csv: Subset of patients receiving Regimen B without mtppe

A7 I, II, III **Priority Question**:

- With respect to the Beta Trees, a number of issues have been identified: There appears to be no uncertainty associated with a transition probability where all patients remained in the same state. Ideally an uninformative prior would be used to allow the possibility of transitions to other states. Please consider including an uninformative prior to incorporate the uncertainty in the economic model.
- The modelled population due to reside in S4 from S2 have been reapportioned between disease free and recurrence in the ratio of [those that stay in S2 +those that moved to s5 or S6]: [those that were to have moved to S1 or S3]. This ratio appears subjective. Please provide justification for this ratio and an exploration of its effects.
- Those that have a recurrence but were supposed to move into S4 have been reapportioned between progressed disease and disease free in the ratio of [Recurrence with liver metastases * (1-Surgical Remission with lung metastases) + Recurrence without liver metastases * (1-Surgical Remission without lung metastases): Recurrence with liver metastases * (Surgical Remission with lung metastases) + Recurrence without liver metastases * Surgical Remission without lung

metastases). This ratio appears subjective. Please provide justification for this ratio and an exploration of its effects.
The model has been altered to allow uncertainty associated with a transition probability where the data suggests all patients remain in the same state. An uninformative prior has been added. This reapportionment was already part of the original TreeAge model supplied by IDM Pharma Inc and this has been replicated in the new Takeda CE model. The estimates for recurrence are taken from Ferrari et al[0] and are identical to those utilised in the original submission from IDM Pharma Inc. A description of this can be found on pages 141 – 145 of the original IDM Pharma Inc submission. It is relevant to use Ferrari et al. as this study reports the findings from 162 patients with recurrent osteosarcoma, who received first-line treatment including resection of the primary lesion and adjuvant chemotherapy with methotrexate, doxorubicin, cisplatin and isfosfamide and hence is similar to study INT-0133.
A8 I The following issues have been identified relating to the Excel model: Please update the model with the most recent version of the life tables available.
Model has been updated with latest mortality rates for England & Wales (as more appropriate for NICE).
A8 II Please clarify whether cell E278 of the 'ME-No_Mepact' worksheet j25 should be j27. In addition, please confirm whether the reference to cell BY218 is redundant or is a mistyped cell reference.
It is correct that cell E278 of the 'ME-No_Mepact' worksheet j25 should be J27. This formula has been corrected. Additionally, BY218 is a redundant reference, and has been corrected.
A8 III Please confirm whether the use of j43 in the 'ME-Mepact' worksheet Cells E278 and F278 is now redundant or whether they are mistyped cell references.
It is correct that E278 and F278 are now redundant in the model. These formulas have now been corrected
A8 IV Please confirm that the distributions used in the PSA relate to the uncertainty in the average costs for the procedure rather than the range of individual observations.
The distributions around the cost parameters are either assumed to vary by +/- 25% or are assumed to follow a Gamma distribution. A Gamma distribution was chosen as this distribution is often chosen to represent uncertainty in cost parameters as it is always positive (Briggs, Claxton & Sculpher. Decision Modelling for Health Economic evaluation). To derive the alpha and beta Gamma parameters we assumed that the cost distributions had the same standard error as the mean. As the mean of a Gamma distribution is alpha x Beta and the variance is alpha x beta squared, rearranging these equations gives us alpha = mean squared / variance and Beta = variance / mean. Thus the distributions of the cost parameters had the form Gamma (1, mean). If the +/- 25% option is chosen, a Uniform distribution is assumed and the cost values can vary between +/- 0.5 x the variation parameter (default 25%) selected from the point estimate.

A8 V Please clarify why no uncertainty was assumed around the disutility of hearing loss.
Disutility for the hearing loss adverse event was determined from a literature review where one study reported a disutility factor of -18% for hearing-loss in cancer patients[i]. As only one reference was found for this variable, there was no other credible alternative to use, and hence uncertainty was not assessed. It was felt that to model uncertainty with arbitrary figures would provide meaningless results.
A8 VI The AgeUtil parameter does not appear to be used correctly and it appears to square the utility of a person. Please clarify the purpose of this functionality.
Takeda UK feel that NICE have misunderstood the formula. The utility is not squared when the Age-related utility weights are employed. The Age-related utility weight is squared if Age-related weights are employed but it is also divided by itself. Thus if the Age-related utility weights are not employed the Age-related utility weight becomes 1. Therefore, only an appropriate weight is applied to the current utility value. i.e. If the average age of the cohort is 32, for patients in the Disease-free state the 0.75 utility weight is multiplied by the 25-34 years Age weight (0.93) to produce 0.6975 as the utility weight.
A8 VII Deaths in the Post-Recurrence Disease Free States (Column DA of the 'ME-Mepact' and 'ME-No_Mepact' Worksheets) automatically have a half cycle correction. Please clarify why the remaining parameters have the option for half cycle correction not to be undertaken.
The model has been revised to exclude all "IF" statements related to half-cycle correction and thus half-cycle correction is always employed.
A8 VIII The formula used to calculate the discount factor is incorrect as (cycle number / 2) incorrectly assumes that the duration of the first cycle was 0.5 years rather than 0.75. Please correct the formula in the economic model.
The model has been corrected to take into account the initial 0.75 years cycle length.
A8 IX Please clarify why, in column CV in the 'ME-Mepact' and 'ME-No_Mepact' worksheets, the part of the formulae that deal with half cycle correction is omitted, even though this is contained in the other columns for transitions.
The model has been corrected to take into account the initial 0.75 years cycle length as per our answer to question A8 viii.
A8 X The following questions relate to the 'ME-MEPACT' and 'ME-No_MEPACT' worksheets in the model: a) Please provide the rationale for the inclusion of a transition probability in cells e279 to e301(between Progressed Disease [time t] and Progressed Disease [time t+1]) in the two worksheets b) Please clarify why these particular cells do not contain references to the cost of hearing loss.
a) Please provide the rationale for the inclusion of a transition probability in cells e279 to e301(between Progressed Disease [time t] and Progressed Disease[time t+1]) in the two worksheets The equation was incorrect but now has been corrected. The transition probability was an anomaly. b) Please clarify why these particular cells do not contain references to the cost of hearing loss. The equation was incorrect and has been altered to include hearing loss. Please note that as no patients start the model in Health State S1 (Disease Progression) these errors had no effect on the model results.
A8 XI Please confirm whether cell F39 in the Drug Costs Worksheet should be 38 (as was used in the

model base case).
It is correct that cell F39 in the Drug Costs Worksheet should be 38.
A8 XII Please confirm whether cell D29 in the Mortality Worksheet should be 2 (as was used in the model base case).
It is correct that cell D29 in the Mortality Worksheet should be 2.
A8 XIII Please confirm whether cell D12 in the Utility Worksheet should be 0.85 (as was used in the model base case).
It is correct that cell D12 in the Utility Worksheet should be 0.85.
A8 XIV The maximum and median ICER on the 'PSA Calcs' worksheet is incorrect as 'dominated' values are excluded. Please consider the inclusion of dominated values.
These calculations were part of the model development process and were not formally reported by the model. However, the calculations have been changed to exclude dominated values.
A9 **Priority Question**: Please explain why the 'other model assumptions' contained in 3.9.6 (page 30 of the new submission) are not deemed to be part of the base case analyses.
Other model assumptions were left out of the model base case, for two key reasons. Firstly, they were not considered for inclusion in the original IDM Pharma Inc model and whist this received significant questioning from the ERG it seemed a base case cost per QALY of £74K was accepted using a 60 year time horizon. Secondly, inclusion of these other assumptions could be considered a health economics paradox. The addition of mifamurtide to standard treatment chemotherapy in the treatment of osteosarcoma allows more patients to live; the more patients that live will in the future have other health problems and as well as further care for osteosarcoma related illness incur other health resource utilisation. As a result it was viewed unfair to untowardly penalise mifamurtide in this way when assessing long term cost effectiveness. Additionally, the adverse event for hearing loss was not incorporated in the base case as such events were considered to be an anomaly of the data as hearing loss is associated with cisplatin usage and not mifamurtide. The association between hearing loss and mifamurtide was lost on comparison of the incidence of events in the individual mifamurtide treatment groups; specifically the incidence of auditory problems was lower in patients treated with chemotherapy plus mifamurtide than in those treated with chemotherapy alone. Ototoxicity is commonly associated with cisplatin therapy, and the frequency of hearing loss reported for patients treated with mifamurtide was within the range expected for cisplatin alone. Even when the model is set to include all of the other model assumptions as assessed in section 3.9.6 and then applied together for a super pessimistic scenario, the resulting decrease in cost effectiveness is counteracted when the discount rate is adjusted to 1.5% for outcomes and the mifamurtide PAS is introduced. This analysis validates the base case ICER and demonstrates the general robustness of the base case analyses.
A10 The number of Mepact Doses (Column D of the 'Drug Cost' Worksheet) are all integers. Please confirm whether the raw data was used to calculate these numbers. If not, please provide an explanation.
It is correct that raw data was used to calculate the number of Mepact doses administered.
A11 Please clarify the number of patients who may need more than 1 vial (page 37 of the new

submission). Please also confirm whether this occurrence has been included within the model, and if necessary justify why these additional costs have been excluded.

The model does not consider patients who need more than one vial of mifamurtide. This is because only a small number of patients (<10%) in the phase 3 study underwent mifamurtide dose escalation:

- Twenty-eight patients in the intent-to-treat population received doses exceeding 2 mg/m^2, 11 randomised to Regimen A + MEPACT and 17 randomised to Regimen B + MEPACT.
  - In the Regimen A group, 4 patients had a maximum MEPACT dose of 2 mg/m^2 + 1 mg and 7 patients had a maximum dose of 2 mg/m^2 + 2 mg.
  - In the Regimen B group, 3 patients had a maximum MEPACT dose of 2 mg/m^2 + 1 mg and 14 patients had a maximum dose of 2 mg/m^2 + 2 mg.
- In three instances, the higher dose was due to a dosing or labeling error, as documented in the case report form, and all subsequent doses were administered at 2 mg/m^2.

The small proportion of patients (<10%) who underwent dose escalation supports the observation that 2 mg/m^2 is a biologically active dose of mifamurtide. The SMPC and the CHMP (that essentially forms a basis of the terms of the centralised marketing authorisation) stipulates a fixed MEPACT dose of 2 mg/m^2.

A12 Please clarify whether the multiplication factor of 75/85 used to adjust utility values in Table 3.4 (page 20 of the new submission) is still appropriate given that the utility of the disease-free state has been increased from 0.75 to 0.85. It may be the case that in Table 3.4 the utility for disease progression was initially reduced from 0.44 to 0.39, but now needs to be reset to 0.44.

The INT-0133 study was initiated in the early 1990's and the EQ-5D was not included. Additionally because osteosarcoma is a very rare illness there is no dedicated research to assess quality of life and utilities in this area.

The utilities in the IDM Pharma Inc model were based upon a literature review of other oncology HTA's that reported utilities and these were assimilated for the model. As they were pulled from separate places and other areas of oncology they were not related from one distinct piece of research.

All utility information used in the Takeda CE model is identical to that used by IDM Pharma Inc with the exception of the disease free states (disease free and disease free post recurrence) in which a higher utility of 0.85 was used as opposed to 0.75 in the IDM Pharma Inc model.

As a result the modification of one value does not warrant amendment in another, and it is justifiable to alter one utility without modification of others.

An analysis to assess the impact of modification of the disease progression utilities show the cost per incremental QALY gained hardly changes given this amendment (£58,246 with 0.39, £58,243 with amendment to 0.44).

A13 **Priority Question**: The cost effectiveness of treatment in the probabilistic sensitivity analyses has not been presented as a summary cost per QALY value. Such an estimate is required as it produces a more accurate estimation of mean cost effectiveness in the presence of non-linear models. The calculation of this value in the 'PSA Calcs' worksheet (Cell P8) is incorrect as it uses the mean of the individual ICERs rather than the formula of mean incremental cost / mean incremental QALYs. Please provide the ICER derived from the PSA for all combinations of regimen type.

The calculated ICERS in the 'PSA Calcs' worksheet are items in the model for development purposes and are not intended to present final results.

Hence cell P8 was a development guide rather than an active cell.

The calculation has been altered to correctly report the ICER derived from the PSA for all combinations. As in Table A13 below:

Table A13: PSA statistics.

Median	£56,606
Max	£30,869,805
Mean	£56,486
Min	£20,645

A14 **Priority Question:** Please confirm that the base case results compare regimens A/B with regimens A+/B+.

Yes it is correct that the base case results compare regimens A/B with regimens A+/B+.

A15 **Priority Question:** Please provide estimates for regimen A compared with regimen A+, which may be more representative of UK practice.

See response to A16

The current standard of care in Europe & the UK is for the patient to be entered into a clinical trial, commonly with a backbone of treatment comprising the standard of care chemotherapies: cisplatin, doxorubicin and high dose methotrexate with leucovorin rescue. These along with ifosfamide are considered to be the most active agents.[vii]

Regimens A & B are considered the standard of care within UK clinical practice. The decision to use ifosfamide in addition to cisplatin, doxorubicin and high dose methotrexate (regimen B in preference to regimen A) is dependent on patient status and physician preference.

In addition, many UK patients are entered into the Euramos 1 trail which reflects both Regimen A and B as principle treatment arms.

http://www.ctu.mrc.ac.uk/euramos/euramos_i_trial.asp Accessed 27th January 2010.

There is a documented imbalance in regimen A+ compared to A- [viii] which may have introduced bias into the results, reducing the impact of mifamurtide on survival.

In exploring subgroup analyses, an imbalance in histological response was also noted in patients older than 16. In this group a large proportion of individuals experienced unfavourable responses in the MEPACT arms (Table A22 left panel and response to A25). In the larger group of patients aged less than 16 (Table A22, right panel), a balance in favourable responses was seen between those receiving or not receiving MEPACT.

Randomization occurred before induction chemotherapy pre-surgery, but Mepact was used post surgery, so there is a potential for differences in patient allocation.

The group of patients 16 and older had a marked imbalance in necrosis. This imbalance was completely absent in the patients 15 and younger. Examination of the entire intent to treat cohort did not identify a noticeable imbalance in good and poor necrosis between patients assigned to receive or not to receive Mepact. Examination of the patients aged 16 or older showed that there was an excess of poor necrosis in the patients assigned to receive Mepact. Kaplan-Meier analysis of the 15 and younger cohort demonstrates perfect concordance between EFS and survival and both demonstrate improvement with the addition of Mepact to chemotherapy with no hint of interaction between the two study interventions. However this does not mean to suggest that the benefit of Mepact is limited to the younger cohort of patients. [viii]

A16 Please provide all relevant ICERs for the pooled chemotherapy regimens and the individual regimens included within the model (incorporating the requested amendments contained in this document).

Appendix A16: *Please provide all relevant ICERs for the pooled chemotherapy regimens and the individual regimens included within the model (incorporating the requested amendments contained in this document).*

All relevant ICERs are presented below in Table A16.

It is important to consider the cost effectiveness derived from analysis of the B arms.

It is clear the compromised results presented in the A arms (see response to question A15) severely impact on the overall results from the A & B arms.

Clinical opinion suggests that the efficacy of mifamurtide demonstrated within the B arms is more representative of the efficacy of mifamurtide in clinical practice and provides a reasonable upside assessment of cost effectiveness.

The incremental cost effectiveness is £44,812 per QALY gained and reduced to ££37,938 with the PAS applied.

Table A16: ICERs for all treatment regimens from the INT-0133 trial.

Outcome	A+/B+	A/B	Diff	A+	A-	Diff	B+	B-	Diff
Total costs	£123,852	£31,481	£92,371	£122,604	£29,709	£92,895	£125,121	£33,244	£91,877
Mifamurtide Drug costs	£91,189	–	£91,189	£91,189	–	£91,189	£91,189	–	£91,189
Adjuvant Chemotherapy costs	£26,205	£26,205	–	£24,784	£24,784	–	£27,625	£27,625	–
Resource costs	£6,458	£5,277	£1,181	£6,631	£4,925	£1,706	£6,307	£5,619	£687
QALYs	16.72	15.38	1.34	16.69	16.10	0.59	16.71	14.66	2.05
Incremental Cost-effectiveness Ratios									
Incremental cost per QALY gained	**£68,734**			**£158,435**			**£44,812**		
ICER with PAS	**£58,246**			**£134,396**			**£37,938**		

A17 Please clarify the number of patients who may receive more than 1 vial (page 37 of the new submission) and whether this occurrence has been included within the model.

Please see our response to question A11.

A18 Table 3.1 (page 16 of the new submission) indicates that anomaly 5 strongly favours no mifamurtide whereas anomaly 6 favours mifamurtide. This appears to contradict the results in Table 3.9 (page 24 of the new submission) where the combination of anomaly 5 and anomaly 6 result in an increased ICER. Please explain the reason for this apparent discrepancy.
After assessment of the new submission it's clear that there isn't a discrepancy in the data reported between pages 16 and 22 and this question may have been raised due to confusing language. It is reported in Anomaly 6 that: "Overall this error favours mifamurtide. However in combination with anomaly 5 this strongly favours the No- mifamurtide arm as QALYs gained outweigh costs in the no Mifamurtide arm". It may have been more accurate to say, "in isolation" anomaly 6 favours mifamurtide, but in combination with anomaly 5 this favours the no mifamurtide arm. Hence, it would be expected that on page 22 that the ICER would be improved through amendment of these errors.
A19 For completeness, please add the results for anomaly 2 and anomaly 3 to Table 3.9 (page 24 of the new submission) and disaggregate anomaly 5 and 6.
Unfortunately it is not possible to satisfy this request. The anomalies presented in Table 3.1 of the Takeda UK new submission were found, resolved and functionality was not built into the model to show the impact of anomalies 1 and 2; and to disaggregate anomalies 5 and 6.
A20 Please explain why the 6-month mortality rates quoted on page 17 of the new submission are assumed to apply until the end of the time horizon.
Functionality is built into the model to assess the impact of this assumption. Using the current assumption the ICER (with PAS) is £58,212 and when general population mortality is employed this rises slightly to £63,241.
A21 Please clarify whether it is a coincidence that the values in Tables 3.6 and 3.7 (pages 21 to 22 of the new submission) rise by 5 in both tables as the range of the number of doses is increased (which implies in Table 3.7 that all additional doses of mifamurtide beyond 40 were associated with additional outpatient visits).
It is not coincidental that the values in tables 3.6 and 3.7 rise by 5 in both tables as doses increase. They rise in 5 each time because the data corresponds to mid points and the number of mifamurtide doses given being presented in groups of 5. Table 3.6 shows mifamurtide dosing and compliance rate. The figures in the middle column increase by 5 because this is the midpoint (i.e. Number of doses = 31 – 35, hence midpoint 33). Table 3.7 shows the number of additional outpatient visits required when mifamurtide is given monotherapy after combination chemotherapy has ceased. Table 3.7 shows how doses in excess of the range 31 - 35 require an extra outpatient visit. Hence for patients who receive 36 – 40 doses would require 2 extra visits assuming a midpoint of 38 doses, patients who receive 41 – 45 doses would require 7 extra visits assuming a midpoint of 43 doses; this being 5 more than when 31- 35 doses are given and 7 in total. Hence this increases in 5 again because the range of number of doses is presented as such.

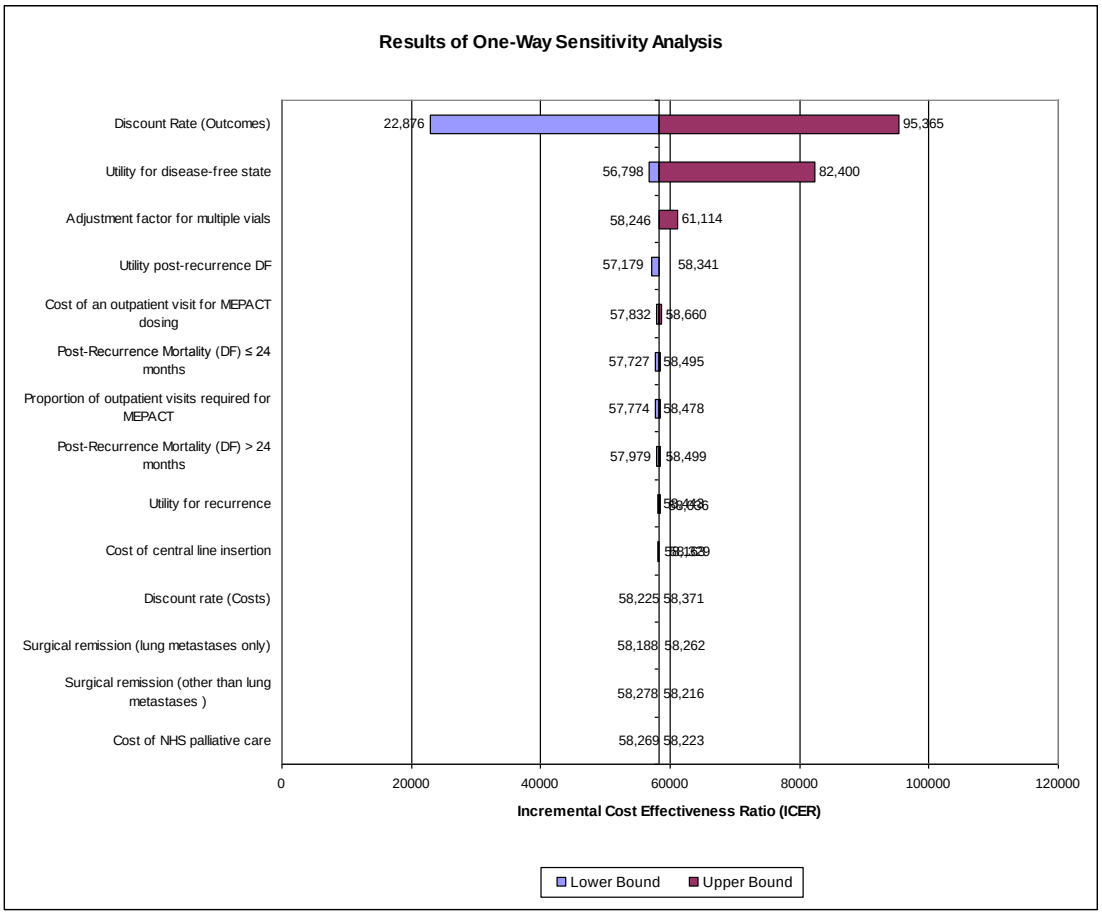
A22 Please clarify whether the raw data from the trial were used in Table 3.7.

No, raw data was not used for the number of additional outpatient visits. Raw data was used to calculate the number of mifamurtide doses given and the number of additional outpatient visits was calculated taking into account this information, and the length of therapy of other chemotherapy medications given in combination to mifmarmurtide.

B1 Please confirm that Figure 3.1 (page 16 of the new submission) is correct. There appears to be a large number of variables where the lower bound is not below the value produced by the deterministic analysis.

This analysis has been rerun and is presented as below in Table B1.

Table B1: Results of reanalysis of One way Sensitivity Analysis.



B2 Please confirm that the values reported in the text of 3.9.3 (page 26 of the addendum) correspond with values in Figure 3.1 (page 16 of the new submission).

There are some discrepancies in the text of 3.9.3 and the figures reported in Figure 3.1. The analyses concerning discounting are correct, however those concerning utilities are incorrect.

This analysis has been rerun as part of the response to question B1.

B3 Please provide the rationale for not incorporating 'other model assumptions' (contained in 3.9.6) within the base case.

Please see our response to question A9

B4 Please clarify why in Table 4.1 (page 35 of the new submission) the potential population falls even though the total UK population is increasing.

There are two reasons why the potential patient population for mifamurtide falls even though the total Uk patient population is increasing.

Firstly, this is caused by rounding. As can be seen in Table x below, the rounded figure comes to a whole number difference, however when this is assessed to two decimal places then the number does not change significantly.

2010	2011	2012	2013	2014
54	54	53	53	53
53.51	53.51	53.43	53.09	53.33

Secondly, Table x below shows how the national population is increasing, the population of those aged 15 – 19 years is decreasing which is the group with the highest incidence of osteosarcoma. Hence, why the target patient population decreases.

POPULATION DATA (millions)	2010	2011	2012	2013	2014	*Notes*
Total UK population	61.5	62	63	63.0	64	
England and Wales population (89% of UK)	54.7	55.2	55.6	56.1	56.5	
Population children (0-14 years)	9.6	9.6	9.7	9.8	9.9	*Office for National Statistics*
Population adolescents (15-19 years)	3.5	3.5	3.4	3.3	3.3	*Office for National Statistics*
Population young adults (20-24 years)	3.8	3.8	3.9	3.9	3.9	*Office for National Statistics*

B5 Please clarify whether the labels on tables 4.1 and 4.2 (page 35 of the new submission) should read ’48 doses’ or ‘38.4 doses’. Please also explain why the values in these tables differ from the previous submission.

The budget impact model works on the assumption of 38.4 doses, so the information reported in section 4.1 is correct. There is no discrepancy with table 4.2 as this doesn’t report number of vials information, although labelling of Table 4.1, “Cost cycle of 48 doses”, is misleading when the model assumes 38.4 doses.

The values in these tables differ from the previous submission because more robust data sources have been used for calculations.

The new budget impact model uses population growth increase estimates, obtained from the Office for National Statistics (ONS) to calculate the projected population size for the next 5 years. To calculate the number of new osteosarcoma cases per year, the model uses incidence rates of subgroups of children populations. The Automated Childhood Cancer Information System has indicated an annual incidence of osteosarcoma in the UK of 7.3 cases/million for adolescents (15-19 years, based on the period 1988-1997 (Stiller et al, 2006)), with a rate of 2.6 cases/million being estimated for children (0-14 years, based on the period 1988-1997 (Stiller et al, 2004)). A study considering the occurrence of osteosarcoma in England estimated incidence rates at 7.7 cases/million for adolescents and 3.3 cases/million for young adults (20-24 years) during the period 1979-1997 (Birch et al, 2003).

B6 It appears that an assumption has been made that all patients have resectable osteosarcoma but no account has been taken for those patients with resectable primary tumours e.g. of the pelvis or vertebra or those with craniofacial tumours, for whom there is no evidence that mifamurtide is appropriate. Please provide the justification for the assumption.

Mifamurtide is indicated for use in children and adults aged between two and thirty years of age for the treatment of high grade resectable non-metastatic osteosarcoma after macroscopically complete surgical resection to remove the tumour. It is used in combination with post-operative multi-agent chemotherapy.

The number of patients presenting with high grade resectable non-metastatic osteosarcoma of the pelvis, vertebrae or craniofacial tumours is small relative to presentation with primary tumours of the limbs. The majority of osteosarcoma patients presenting with such primary tumours are not eligible for surgical resection so out with the product license for mifamurtide.

Table B6 reflects patient characteristics from INT0133.

Primary tumor site	Number of Patients	% of Patients
Femur	374	55
Below knee	185	27
Humerus	73	11
Below elbow	12	2
Leg NOS	2	1
Arm NOS	1	1
Pelvis	12	2
Other Axial	10	2
Not reported	8	-

Meyers PA, Schwartz CL, Krailo Mk et al. Osteosarcoma: A Randomized, Prospective Trial of the Addition of Ifosfamide and/or Muramyl Tripeptide to Cisplatin, Doxorubicin, and High-Dose Methotrexate. J Clin Oncol. 2005;23:2004-2011

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