24th November 2008

National Institute for Health and Clinical Excellence
MidCity Place
71 High Holborn
London
WC1V 6NA

www.nice.org.uk

Dear [redacted]

Single Technology Appraisal – Mifamurtide for the treatment of osteosarcoma.

The Evidence Review Group, (School of Health and Related Research, Sheffield) and the technical team at NICE have now had an opportunity to take a look at submission by IDM Pharma. In general terms they felt that it is well presented and clear. However the ERG and the NICE technical team would like further clarification relating to the clinical and cost effectiveness data.

Both the ERG and the technical team at NICE will be addressing these points in their reports. As there will not be any consultation on the evidence report prior to the Appraisal Committee meeting you may want to the points raised and provide further discussion from your perspective at this stage.

We request you to provide a written response to this letter to the Institute by **17:00, Monday 8 December 2008 (London, UK time)**. Two versions of this written response should be submitted; one with academic/commercial in confidence information clearly marked and one from which this information is removed.

If you present data that is not already reference in the main body of your submission and that data is seen to be academic/commercial in confidence information, please complete the attached checklist for in confidence information.

Yours sincerely

[redacted]
Associate Director – Appraisals
Centre for Health Technology Evaluation

Encl. checklist for in confidence information

Section A. Clarification on effectiveness data

Executive summary.

A1. Please provide justification for the length (36 weeks, 48 infusions) of MEPACT treatment.

Section 6.1.

A2. Please clarify the number of citations identified for clinical effectiveness through MEDLINE. When the ERG reran this search it identified 302 studies. Please explain the discrepency between this figure and the 186 citations reported in your submission.

Section 6.3.1.1.

A3. Please clarify whether outcome assessments were blinded in INT-0333.

Section 6.3.1.2.

A4. Please clarify whether INT-0333 uses the most effective combination (dosage and timing) of high dose methotrexate, doxorubicin and cisplatin. In addition, do the dosage and timings of ifosfamide in the INT-0133 trial reflect current practice in (including in EURAMOS trial) or outside the UK for first and second line therapy?

Section 6.3.1.2 and 6.4.2.

A5. Please provide justification on the protocol amendment to extend MEPACT treatment in the INT-0133 trial from 36 to 48 weeks. In addition, as a result of the amendment, were the numbers of infusions increased? What were the reasons for patients not receiving the full 48 infusions? Do survival rates differ according to the number of doses received? What were the major reasons for patients receiving more than the 48 doses (Table 2, p47)?

Section 6.3.1.2.

A6. Please provide the number of patients in each MEPACT group who had dose escalation to 2mg/m^2 +1mg and then to 2mg/m^2 +2mg. Also provide data on the number of people who exceeded a dose of 2mg/m^2.

Section 6.3.3.

A7. Please clarify the number of patients randomised in the INT-0133 trial, and explain the discrepancies between the manufacturers submission, Meyer et al 2005, and Meyer et al 2008.

Section 6.3.4.

A8. Please confirm the following: Primary endpoint = Disease Free Survival; Secondary endpoints = Overall survival, histological response and adverse events. Please provide precise definitions of the survival outcomes in terms of events and time period.

Section 6.3.5

A9. Please clarify the definition of intention-to-treat (ITT) as being from randomisation (study entry) rather than from receipt of neoadjuvant treatment.

Section 6.3.6.

A10. Please provide a tabulated summary of the suggested critical appraisal criteria as noted in the NICE STA specification guide to manufacturers.

A11. Please provide details on the number of patients (for each of four treatment arms) who did not enter the maintenance phase of INT-0133. In addition, provide details on the number of disease free survival events and death (by treatment arm) in the subset of patients who did not enter the maintenance phase.

A12. Please provide a full breakdown of the number of withdrawals for each treatment group prior to and during the maintenance phase. Please provide details of the reasons for withdrawal (including definition and severity of toxicities etc), broken down by the four treatment arms if possible.

A13. Please provide further details on compliance to study treatments, by each arm, prior to and during the maintenance phase.

A14. Please provide details on rates of discontinuation for each of the four arms, prior to and during the maintenance phase.

Section 6.3.6.4 and section 6.4.2.

A15. Please provide details which summarise, for each of the four arms, what dosage of MEPACT was actually used, and how many cycles of MEPACT were actually administered, during treatment maintenance phase.

Section 6.3.6.6

A16. Please justify why a Gompertz model was preferred. This distribution has a hazard function which increases exponentially with time, which is unlikely to be the case for osteosarcoma. Perhaps a Weibull distribution truncated at the appropriate time may have been more

appropriate, or even a log-normal distribution, which allows for a decrease in hazard after a period of time.

A17. Please clarify whether any tests were undertaken to see if a proportional hazards assumption was appropriate for estimating the treatment effect of MEPACT.

A18. Please provide the p-value for the interaction test for age.

Section 6.4.1.

A19. Please provide distributions for age at diagnosis for each of the four treatment groups.

A20. Please provide details reagarding tumour response (i.e. grades, including definitions) following the neoadjuvant treatment phase, by each of the four regimens.

Section 6.4.3.

A21. Please provide tabulated results (ITT analysis) for each of the treatment groups separately for disease free survival and overall survival time. Ideally data should be reported as follows: median follow up (6 years [2006 data set - published data from Meyer et al 2008] and 7.9 years [unpublished data from 2007 data set], event rates (number of events/total number) for each arm separately (A, A+, B, B+), for each of the 2006 and 2007 data sets. In addition, provide hazard ratios, confidence intervals and p-values for each of the six possible pairs of treatment groups, separately for each of the 2006 and 2007 data sets.

A22. Please explain the disparities between figures 2A and 3A in Meyer et al 2008 relating to event-free survival (EFS) and overall survival (OS). EFS and OS are extremely closely linked in osteosarcoma, and while both sets of survival curves show a large difference between B+ and B, this is not the case with A and A+.

A23. Please provide Kaplan-Meier curves for the four treatment groups for 2006 and 2007 data sets (separately), including numbers at risk at each time point.

A24. Please provide detailed results (including event rates, hazard ratios, confidence intervals and P values) on each subgroup analyses. Were these considered a priori or post hoc (provide evidence to support this)? Please include enough information to support the statement that exploratory findings confirm the robustness and consistency of the findings across the study population.

A25. One subgroup analysis suggests no benefit for MEPACT treatment in patients > 16 years of age. Please explain if this is correct. Is mifamurtide of no benefit to people over 16 years?

Section 6.4.4

A26. Please provide disease recurrence frequencies (Table 5) following adjuvant chemotherapy by each treatment group for the 2007 data set.

Section 6.5.

A27. Please provide further details of the meta-analysis according to the NICE STA specification guide for manufacturers.

Section 6.6

A28. Please clarify and justify why no statistical analysis was carried out for the indirect comparison. Please summarise the relevant data from the six review articles that have been cited.

Section 6.7.

A29. Please provide data on the degree, duration and severity of adverse events (including definitions) in the INT-0133 trial for each of the four treatment groups.

Section B. Clarification on cost-effectiveness data

Section 4.1.2.3.

B1. Please provide rates of limb-salvage and amputations by the four treatment groups.

B2. Please provide results for the reference case, and time horizons of 20, 40 and 60 years, assuming all surviving patients will require appropriate type of revision surgery (i.e., further limb-salvage or prosthetic corrective/replacement) after 10 years. If restructuring the model in this way is not possible please provide estimates based on appropriately discounted costs of an additional surgical intervention based on trial rates.

Section 4.1.2.6.

B3. Please provide results for a 5% recurrence rate after 5 years of follow-up for the reference case, and for time horizons of 20, 40 and 60 years. If restructuring the model in this way is not possible please vary the cost of treating any recurrence by 2% as well as 5%.

Section 7.2.

B4. Please provide results for a modelled time horizon of 60 years as this is considered by the ERG's clinician advisory panel to be a more plausible lifetime in a substantial proportion of cases.

Section 7.2.1.

B5. Please provide results for sensitivity analyses of the reference case model, assuming two vials per cycle instead of one for 5% and for 10% of patients.

Section 7.2.6.7.

B6. Please clarify the justification for not utilising a half cycle. Please confirm that varying cycle length refers to the difference between the 9-month first cycle compared to subsequent 6-month cycles. Please explain why the incremental rewards could not be accommodated under the half-cycle corrected model.

Sections 7.2.7.4 and 10.5.2.4.

B7. Please provide separate results of sensitivity analyses for the reference case model, assuming the following values of hearing-loss rates for the four treatment groups at the end of maintenance therapy.

MEPACT arms (A+, B+)	non-MEPACT arms (A, B)
15%	8%
12.5%	5.0%
19.5%	7.0%
10.5%	9.0%
19.0%	10.0%

Section 7.2.8.2.

B8. Please justify the decision not to adjust utility values for age.

Section 7.2.8.3.

B9. Please justify the use of the utility values without exploring the effect of the following issues:

- recall bias as there is approximately 9 years (on average) between the age at diagnosis and when the EQ5D survey was conducted
- the survey was conducted on survivors only
- the small number surveyed

B10. Please clarify whether utilty values derived for six-month periods were applied to cycle 1? If so please explain the rationale behind this decision.

Section 7.2.11.3.

B11. Please justify and explain how model inputs other than survival probabilities are affected by the way survival data are handled.

B12. Please explore the results using PSA (if possible), and provide results based on a PSA of the reference case model, as well as that for time horizons of 20, 40 and 60 years, for the variables in Tables 12 and 14 (pages 81 and 83, respectively). Please justify any omission from the list of variables in the two tables, and any choice of distribution.

B13. If PSA is used please ensure that correlations between model inputs are appropriately modelled where necessary, rather than using modelling inputs as uncorrelated quantities.

B14. If PSA is not possible, please confirm that all model inputs are estimated mean values on the scale that they are applied. For example, if the distribution of an input is assumed to be normal on a logarithm (log) scale, i.e. log-normal, and the input is applied on the original scale, the required mean is generally not the maximum-likelihood estimate on the log scale, transformed back to the original scale, but the back-transform of the maximum-likelihood estimate plus half the estimated variance (on the log scale).

Section 7.3.

B15. Please provide ICERs comparing each of the six pairs of the four treatment groups, for the reference case and for 20, 40 and 60 year time horizons.

B16. Please provide survival curves for the model output and please compare to the trial results.

B17. Please provide disaggregated costs and QALYs for your base case and for time horizons of 20, 40 and 60 years. The disaggregation should include factors such as QALYs gained from each health state and costs broken down to include drug acquistion costs and administration.

Section 7.6.2.1.

B18. Please cite exact passage(s) of Section 10.5 which is relevant to each item in table 8, in a separate column.

Section 8.1.

B19. Please provide results of the effect on budget impact of an uptake rate of 80%. It appears that until recruitment into EURAMOS I study ceases, the final uptake rate (estimated at 50-60%) is unknown. As this is the only new treatment for osteosarcoma is it possible that the uptake could exceed this estimate?

Section 10.5.9.

B20. Please provide a breakdown of frequency of withdrawals by treatment arm (4 groups) and health status (disease-free, disease-progression, and recurrence) at time of withdrawal.

Section 10.5.9.1.

B21. Please clarify whether the transition from disease-free (DF) status to withdrawal is handled by reallocation to disease-progression (DP) or recurrence, or whether this is handled by reallocation to DP and DF states?

Section 10.5.9.3.

B22. Please provide results for sensitivity analyses of the reference case model when all withdrawals from this state are reallocated to DP and when half are reallocated to DP and half to DF.