NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL (STA)

for MEPACT™ (*Mifamurtide)*

Section A&B

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Section A

Manufacturers and sponsors will be requested to submit section A in advance of the full submission (for details on timelines, see the 'Guide to the single technology appraisal process' – www.nice.org.uk). A (draft) Summary of Product Characteristics (SPC) for pharmaceuticals and a (draft) technical manual for devices should be provided (see appendix 1, section 9.1).

1 Description of technology under assessment

1.1 Give the brand name, approved name and, where appropriate, therapeutic class. For devices please provide details of any different versions of the same device.

Brand Name: MEPACT™ (Liposomal Muramyl Tripeptide Phosphatidyl Ethanolamine [L-MTP-PE])

Approved Name: Mifamurtide

Therapeutic Class: Pharmacotherapeutic group of other cytokines and immunomodulators (ATC Code: L03 AX 15)

1.2 Does the technology have a UK marketing authorisation/CE marking for the indications detailed in this submission? If so, please give the date on which authorisation was received. If not, please state current UK regulatory status, with relevant dates (for example, date of application and/or expected approval dates).

No. The MEPACT Marketing Authorisation Application (MAA) was submitted to the EMEA in November 2006 and is currently under central review. The company expects a final decision from the CHMP in the 4th quarter of 2008 and the European Commission in the Q1 2009.

1.3 What are the (anticipated) indication(s) in the UK? For devices, please provide the (anticipated) CE marking, including the indication for use.

It is anticipated that MEPACT will be indicated (in children, adolescents and adults) for the treatment of high-grade, resectable, non-metastatic

***osteosarcoma following surgical resection. MEPACT is to be used in combination with post-operative multi-agent chemotherapy*.**

1.4 To what extent is the technology currently being used in the NHS for the proposed indication? Include details of use in ongoing clinical trials. If the technology has not been launched, please supply the anticipated date of availability in the UK.

There is no current MEPACT usage in the UK. The date of availability in the UK is dependent in part on the outcome of the central regulatory review.

1.5 Does the technology have regulatory approval outside the UK? If so, please provide details.

MEPACT does not have regulatory approval outside the UK.

1.6 Is the technology subject to any other form of health technology assessment in the UK? If so, what is the timescale for completion?

***The Scottish Medicines Consortium (SMC) requires a technology assessment within 3-months of the date of market authorization*.**

1.7 For pharmaceuticals, what formulation(s) (for example, ampoule, vial, sustained-release tablet, strength(s) and pack size(s) will be available?

MEPACT is available as a powder for suspension for intravenous infusion. Each vial contains 4 mg of mifamurtide with components (a CE marked drug filter) and instructions for reconstitution and administration.

1.8 What is the proposed course of treatment? For pharmaceuticals, list the dose, dosing frequency, length of course and anticipated frequency of repeat courses of treatment.

The proposed dose of MEPACT for all patients is 2 mg/m^2 body surface area. MEPACT is to be administered for 36 weeks as adjuvant therapy following tumour resection as a total of 48 infusions: to be given twice weekly for 12 weeks, with dosing at least 3 days apart; followed by once

weekly treatment for an additional 24 weeks. MEPACT is to be infused intravenously over one hour.

1.9 What is the acquisition cost of the technology (excluding VAT)? For devices, provide the list price and average selling price. If the unit cost of the technology is not yet known, please provide details of the anticipated unit cost, including the range of possible unit costs.

We continue to conduct analysis at this time to determine an appropriate UK and EU acquisition cost for MEPACT. For economic modelling purposes a unit cost of £2375 and range of £1781-£2969 has been assumed for a full course of MEPACT (48 doses).

1.10 What is the setting for the use of the technology?

***The initial setting for MEPACT use is tertiary care e.g. specialised clinics or hospitals delivering oncology services. Prescribing of MEPACT will be initiated and supervised by specialist physicians experienced in the diagnosis and treatment of osteosarcoma. MEPACT can be administered in the out-patient setting*.**

1.11 For patients being treated with this technology, are there any other aspects that need to be taken into account? For example, are there additional tests or investigations needed for selection, or particular administration requirements, or is there a need for monitoring of patients over and above usual clinical practice for this condition? What other therapies, if any, are likely to be administered at the same time as the intervention as part of a course of treatment?

***MEPACT is to be used in combination with post-operative multi-agent chemotherapy and therefore treatments such as doxorubicin, methotrexate, cisplatin and/or ifosamide will be administered at the same time*.**

2 Statement of the decision problem

In this section the manufacturer or sponsor should specify the decision problem that the submission addresses. The decision problem should be derived from the final scope issued by NICE and should state the key parameters that the information in the Evidence Submission will address.

	Final scope issued by NICE	Decision problem addressed in the submission
Population	Individuals with osteosarcoma who have undergone 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 ifosamide***
Comparator(s)	Post-operative multi-agent chemotherapy alone	***Post-operative multi-agent chemotherapy alone***
Outcomes	➢ Overall survival ➢ Disease free survival ➢ Adverse effects of treatment ➢ Health-related quality of life	➢ ***Overall survival*** ➢ ***Disease free survival*** ➢ ***Adverse effects of treatment*** ➢ ***Health-related quality of life***

Economic Analysis	Reference case: Incremental Cost/QALY Horizon: sufficiently long to reflect any differences in costs or outcomes between the technologies being compared Perspective: NHS and Personal Social Services perspective	***Reference case:*** ***Incremental Cost/QALY*** ***Lifetime horizon*** ***Perspective: NHS and Personal Social Services perspective***
Subgroups to be considered	The following subgroups will be considered if included in the marketing authorisation 1) individuals with osteosarcoma related to Paget's disease 2) individuals with metastatic osteosarcoma 3) individuals with relapsed osteosarcoma	***The three subgroups identified are not within the proposed marketing authorisation indication***
Special considerations, including issues related to equity or equality		***None currently identified***

Section B

3 Executive summary

This submission relates to the use of mifamurtide (Brand Name: MEPACT) in patients with osteosarcoma. The MEPACT Marketing Authorisation Application was submitted to the EMEA in November 2006 and is currently under review, with a final decision expected from the European Commission in the fourth quarter of 2008. The active agent in MEPACT (liposomal muramyl tripeptide phosphatidyl ethanolamine) is a stimulator of innate immune processes and activates macrophage tumouricidal activity (Section 4.3). MEPACT represents the first therapeutic advance for the treatment of high-grade resectable, non-metastatic osteosarcoma in over 20 years. This ultra-orphan disease primarily affects children, adolescents and young adults. As patients treated successfully for osteosarcoma rarely experience relapse after 5 years of being disease-free, the survival benefits achieved can allow them to lead full and normal lives.

MEPACT is formulated as a powder for suspension for intravenous infusion. Each vial contains 4mg of mifamurtide to be reconstituted to 0.08mg/ml and further diluted for administration at a fixed dose of 2mg/m^2 body surface area. The single MEPACT treatment course comprises a total of 48 doses; MEPACT treatment is not given as repeated courses. Each MEPACT pack contains one vial of powder containing mifamurtide (for a single dose) and the filter required for administration. The proposed NHS acquisition cost of MEPACT is £2375/dose corresponding to £114,000 for a full course of 48 doses.

MEPACT is indicated for use in children from the age of 2-12 years, adolescents from 12-18 years and adults, for the treatment of high grade resectable non-metastatic osteosarcoma after macroscopically complete surgical resection. It is to be used in combination with post-operative multi-agent chemotherapy. MEPACT treatment is to be administered for 36 weeks as adjuvant therapy following tumour resection: twice weekly at least 3 days

apart for 12 weeks, followed by once weekly treatments for an additional 24 weeks over a total of 48 infusions.

MEPACT will be used as an add-on treatment to 3- or 4-agent adjuvant chemotherapy using high dose methotrexate, doxorubicin and cisplatin with/without ifosfamide. The comparator treatment used for assessment of the decision problem comprises the 3- or 4-agent chemotherapy regimen alone, as this represents the current UK treatment approach (Sections 4.1.2.5 and 6.3.6.3).

The clinical evidence informing on this submission is derived from a large, head-to-head Phase III randomised clinical trial (INT_0133) comparing the use of MEPACT as an add-on to multi-agent chemotherapy versus multi-agent chemotherapy alone (Section 6.3). Analysis of data from the study showed that MEPACT significantly increases overall survival in osteosarcoma patients, achieving a 6-year probability of survival of 77% (95% CI: 72-83%) compared with 66% (95% CI: 59-73%) for patients receiving standard chemotherapy alone (Section 6.4). Long-term follow up of this study allowed survival data to be collected for up to 13 years and demonstrated that survival curves remained apart with extended follow-up. Adverse events (Section 6.7) generally result from the activation of monocytes and macrophages, comprising mild to moderate influenza-type symptoms that are easily managed with paracetamol or acetaminophen. The addition of MEPACT to 3- or 4 agent chemotherapy in study INT-0133 did not exacerbate chemotherapy side effects.

These MEPACT data translate to a reduction in the risk of death of about 30% and a long-term survival benefit for an additional 10 patients of every 100 treated. Such a level of benefit is particularly important given the huge unmet medical need and lack of progress in improving outcome for osteosarcoma patients over the last 20 years.

A cost-effectiveness analysis (Section 7) was performed using a Markov process with six health states, comparing MEPACT as add-on therapy to standard adjuvant chemotherapy compared with standard adjuvant therapy

alone. A 6-month cycle was assumed, except in cycle 1 which represented the maintenance treatment phase of 9-months duration. Outcomes and resource estimates were derived from clinical study INT-0133, expert opinion and published literature. The reference case assumed a 12.25 year model horizon to correspond to the trial follow-up period, but the impact on cost-effectiveness of extending the horizon was explored. An NHS perspective was adopted.

The incremental cost/QALY was found to be sensitive to the model time horizon, and decreased as the follow-up time was increased. For extended follow-up periods the incremental cost/QALY was well within or below the ultra-orphan threshold range proposed by NICE of £200,000 to £300,000 cost/QALY (Section 7.3.3). The reference case used a time horizon of 12.25 years resulting in an ICER of £457,624 (Section 7.3.1). This was based on an incremental effect of 0.26QALYs and an incremental cost of £119,000. Sensitivity analysis demonstrated cost-effectiveness results to be sensitive to the model horizon. MEPACT is considered a cost-effective ultra-orphan drug at its proposed acquisition cost when the model horizon is extended by an additional 20 and 40 years, demonstrating cost/QALY of £92,259 and £68,463, respectively.

The estimated annual budget impact for the NHS in England and Wales was £4.7 million in 2009 rising to £5.8 million in 2013 (Section 8).

4 Context

4.1 Please provide a brief overview of the disease/condition for which the technology is being used. Provide details of the treatment pathway and current treatment options at each stage.

4.1.1 Osteosarcoma

Osteosarcoma is the most common primary bone tumour and usually occurs during childhood and adolescence. Osteosarcoma is characterised by the presence of malignant mesenchymal cells that produce osteoid or immature bone[1]. The disease is most commonly seen in individuals in their second decade, and it is proposed that the development of osteosarcoma is associated with the adolescent growth spurt[2]. Lesions are usually seen in the long bones and are highly aggressive, with a propensity to metastasise particularly to the lung in the early disease stages. If left untreated the primary lesion will undergo local and systemic progression leading to death within a matter of months, usually as a result of respiratory failure[3].

The incidence of bone cancer has been estimated as being in the region of 9 cases/million of the population per year in the UK, with a total of 472 cases being reported in England and Wales in 2000[4]. Osteosarcoma is estimated to occur with an incidence of 3 cases/million per year[5]. As osteosarcoma is most commonly seen in children or adolescents, country-specific incidence rates are usually considered in terms of the occurrence in these age groups. 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[6]), with a rate of 2.6 cases/million being estimated for children (0-14 years, based on the period 1988-1997[7]). 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[8]. Osteosarcoma incidence rates have not changed notably since the late 1970s[6].

These data indicate the number of osteosarcoma cases per year to be: 30 for children (aged 0-14, based on 1980-1994 data[9] and 1986-1995 data[7]), 31 for adolescents (aged 15-19, based on 1980-1994 data[9]) and 12 for young adults (aged 20-24, based on 1979-1997 data for England[8]). Of these, about 80% of patients are likely to have non-metastatic disease[2,10,11]. The term 'ultra-orphan' is used to describe very rare diseases and to draw a distinction with the 'commoner' orphan diseases. The National Institute for Health and Clinical Excellence (NICE) defines a disease as ultra-orphan it has a UK prevalence of less than 1 in 50,000 and if there are less than 1000 cases per year. The data informing on osteosarcoma indicate that approximately 73 children, adolescents and young adults present with osteosarcoma per year in England/the UK, with 58 having high-grade non-metastatic disease.

4.1.2 Osteosarcoma treatment

Most patients diagnosed with osteosarcoma present with a localised primary lesion, with only 15-20% showing radiographic evidence of metastases[11,3]. Until the 1970s the standard therapy for osteosarcoma involved surgical resection of the primary lesion and/or radiotherapy[2]. However clinical outcomes were poor, with survival rates of 15-20%[12], leading to the presumption that most patients with localised disease also have subclinical microscopic metastases[10,3,5,13] . If untreated these micro-metastases result in very rapid disease progression despite aggressive resection of the primary lesion. As a result, a number of clinical trials in the 1970s considered the efficacy of single-agent and combination chemotherapy regimens in patients with osteosarcoma[10]. These studies showed that chemotherapy has the potential to increase disease-free survival rates and delay metastatic spread. The good activity profile seen with certain agents, led to the development of multi-modal osteosarcoma management protocols that utilise neoadjuvant chemotherapy, followed by local tumour resection, with an adjuvant chemotherapy regimen to eliminate remaining metastatic disease foci.

4.1.2.1 Osteosarcoma presentation and diagnosis

Patients presenting with osteosarcoma usually show pain and swelling around the area of the primary lesion. In children and adolescents the primary tumour usually occurs in the long tubular bones, and is particularly associated with the metaphysis of the femur, tibia and humerus[14,10,5]. Radiographic evaluation usually shows bone lesions but is also key to identifying metastatic spread to the lung. Bone imaging usually by computed tomography (CT) or magnetic resonance imaging (MRI) allows determination of the extent of tumour involvement in the surrounding tissues, to inform on the most suitable surgical procedure[10,2,5]. A definitive diagnosis of osteosarcoma requires tumour biopsy, which also facilitates histological typing[10].

4.1.2.2 Neoadjuvant chemotherapy

Pre-surgical chemotherapy is now routinely used for the management of osteosarcoma. It reduces pain symptoms[15], targets micro-metastases and results in fibrotic and necrotic changes in the primary lesion[16] facilitating its demarcation from normal tissue and improving the quality and adequacy of the surgical margin[1,10,17]. After resection, the primary lesion is histologically assessed to determine its degree of responsiveness to the chemotherapeutic agents administered. The tumour response to neoadjuvant therapy is graded to identify a poor histological tumour response as >5-10% viable tumour cells remaining[18,19]. Numerous studies have shown that both an inadequate surgical margin and a poor histological response to neoadjuvant chemotherapy are associated with a higher incidence of local disease recurrence and metastatic spread, and poor prognosis[14,1]. Such studies have led to estimates of 5-year event-free survival rates at around 35-45% for poor responders, compared with 70-80% for good responders[13]. However, knowledge of a poor histological response can be used to direct subsequent therapy, indicating a potential benefit of adding agents to the adjuvant chemotherapy regimen[20,10,2].

4.1.2.3 Surgery

After about 10 weeks of neoadjuvant chemotherapy osteosarcoma patients undergo surgical resection to remove the primary tumour[20]. A major factor in

optimising treatment outcome is achieving complete surgical resection of the primary lesion. Prior to the use of neoadjuvant chemotherapy, amputation was the usual surgical treatment option for children diagnosed with osteosarcoma. The ability of pre-surgical chemotherapy to shrink and delineate the primary tumour allows the surgeon to resect closer to the lesion. In combination with better imaging techniques, improvements in surgical procedures and advances in biomedical engineering, this allows a proportion of patients to undergo limb-salvage surgery rather than amputation[15,21]. Limb-salvage surgery aims to preserve a functioning limb, by replacing resected bone. In the UK endoprosthetic implants represent the limb-salvage methodology of choice, with allo- or autografts, distraction osteogenesis and rotationoplasty being used infrequently[22,17]. Though limb-salvage procedures necessitate the surgeon performing the resection closer to the primary lesion, this is not associated with poorer prognosis[22,23]. However the risk of local tumour recurrence is directly associated with inadequate resection margins[24,21,25].

The choice between amputation and limb-salvage surgery needs to take into account numerous factors in addition to optimising the likelihood of cure[21]: The cosmetic and psychological implications of amputation versus limb-salvage require consideration, and the greater acceptability of the latter option has probably driven uptake in about 85% of cases[10,21,2,17]. However, children undergoing amputation often adjust well to their situation and experience good functional results. In the UK setting amputation is used more than in other countries, with 75% of patients undergoing limb-salvage[26].

Achieving the best functional outcome for the child is key to optimising quality of life in either the short- or long-term. Endoprosthetic reconstruction can allow the patient to return rapidly to functional activities[27], whereas adaptation to using a prosthetic limb takes longer; However as the typical osteosarcoma patient has not yet completed growth, both prosthetic limbs and endoprostheses will need to adapt with the developing patient and be able to withstand the long-term demands of an active daily life. An advantage of external prosthesis that they are readily replaced as the child grows.

Though modern endoprostheses have been developed that are extendable without surgical intervention[28,17], they remain susceptible to loosening, wear and mechanical failure[29]. Current 10-year failure rates are estimated at 50% for all osteosarcoma patients[30] and at around 30% for those with endoprostheses of the distal femur[27]. Other factors requiring consideration include the substantially higher potential for infectious complications (estimated at 12% over 10 years) with implants and the risk of delayed amputation (estimated at 15% over 10 years) as a result of endoprosthesis failure or infection[31,21,27].

4.1.2.4 Adjuvant chemotherapy

Following surgery, current osteosarcoma management programmes include additional post-operative chemotherapy. Adjuvant chemotherapy is usually administered over about 20 weeks[20].The specific treatment agents are usually comparable to those administered in the neoadjuvant setting, however patients experiencing a poor response to neoadjuvant chemotherapy may receive a modified post-operative regimen[32,33].

4.1.2.5 Current chemotherapy options

A standard chemotherapy regimen for treating osteosarcoma has not been defined, though many treatment options have been considered since the 1970s. Early studies using single-agent chemotherapy showed that a number of agents with activity against other solid childhood neoplasms have limited efficacy against osteosarcoma[20,10]. However, cisplatin, doxorubicin and high-dose methotrexate showed 20-40% response rates during single-agent use[3]. Some improvement in treatment response rates was achieved when the efficacy of combination chemotherapy regimens was investigated. However disease-free survival rates in the region of 60-70% were only seen consistently when 3-agent regimens began to be used, in both neoadjuvant and adjuvant settings[10].

Since the 1980s a 3-agent chemotherapy regimen (neoadjuvant and adjuvant) combining high-dose methotrexate, doxorubicin and cisplatin has achieved a degree of acceptance and has been used in numerous osteosarcoma clinical trials over the last decade[34,14,35,33,2,5,13]. In addition ifosfamide has shown

efficacy in some studies, and has been used as add-on therapy to the 3-agent combination of high-dose methotrexate/ doxorubicin/cisplatin[32]. As yet it is not clear whether the addition of ifosfamide offers a notable clinical advantage over the 3-agent regimen[31,1,20,5]; some data have indicated that addition of ifosfamide to adjuvant chemotherapy may represent a suitable salvage option for patients achieving a poor histological response with neoadjuvant treatment[32,33].

Some groups have investigated the efficacy of alternative 3- or 4-agent combination regimens, often based on ifosfamide and/or etoposide; while alternative regimens may not improve treatment effect, some are less toxic and therefore easier to use[36,37]. The addition of agents on top of the 3- or 4-agent regimen has not shown convincing clinical benefit and can add to side effects[2,3].

In the UK most osteosarcoma patients undergo high-dose methotrexate/ doxorubicin/cisplatin treatment without the addition of ifosfamide. Currently patients diagnosed with osteosarcoma are likely to be enrolled into the European and American Osteosarcoma (EURAMOS) 1 trial[20]. This trial aims to consider the use of additional agents that might improve on the clinical benefits achieved with high-dose methotrexate/ doxorubicin/cisplatin. All patients receive this 3-agent neoadjuvant regimen and post-resection: patients with a good histological response are randomised to receive/not receive additional interferon-α; patients with a poor histological response are randomised to receive/not receive additional ifosfamide and etoposide[1].

4.1.2.6 Treatment outcome

The development of a multi-modal treatment approach incorporating multi-agent neoadjuvant chemotherapy, local surgical resection of the primary lesion and multi-agent adjuvant chemotherapy has resulted in a dramatic increase in survival rates for osteosarcoma patients[8,9]. It is generally accepted that 10-year overall survival can be achieved in up to 70% of osteosarcoma patients with non-metastatic resectable disease[38,33]. UK data for children and adolescents presenting with osteosarcoma from 1988-1997 estimate 5-year survival at 53% and 62%, respectively[39]. A more recent study of cancer

survival in adolescents/young adults in England reported a 5-year survival rate of 49% for osteosarcoma patients diagnosed from 1996-2001[8].

Patients who do not achieve long-term clinical benefit may undergo: local recurrence of the primary lesion (~1%), metastatic recurrence (~33%) with lesions usually developing in the lung; or local and metastatic recurrence (~5%)[24,32,40,41]. The highest recurrence and mortality risk for patients with osteosarcoma occurs in the 1-2 years post-diagnosis, though substantial risk persists through 5 years post-diagnosis[42,43]. Ferrari et al.[44] estimated that 53% of patients relapse within 2 years of surgery, 26% relapse in the third year, 12% in the fourth year and a further 4% in the fifth year. Only 1-2% of osteosarcoma patients undergo disease recurrence 5 years or more after their initial treatment[45].

4.1.3 The osteosarcoma patient care pathway

4.1.3.1 First-line therapy

On confirmation of a diagnosis of high-grade, resectable, non-metastatic osteosarcoma, patients in the UK usually begin a course of neoadjuvant chemotherapy. Most experience some tumour response, though a small proportion (<5%) are identified as early non-responders and rapidly undergo disease progression. Optimal surgery to remove the entire primary tumour renders the patient disease-free, with a subsequent course of adjuvant chemotherapy being administered to target micro-metastases.

4.1.3.2 Second-line therapy

A proportion of patients undergoing multi-modal therapy remain disease-free. However, for those experiencing disease recurrence there is no standard treatment[44,42,41].

Whether repeat surgery is performed following recurrence depends on the feasibility of the procedure and the likelihood of achieving surgical remission. Patients presenting with a single pulmonary lesion (about 10%) are often treated with surgery alone. Those with multiple pulmonary lesions are likely to undergo second-line chemotherapy followed by surgery where feasible;

pulmonary metastases are excised in about 50% of patients[24]. If surgery is not performed the patient cannot achieve disease-free status and prognosis is very poor[44,41]. Some patients undergo radiotherapy as a second-line/palliative management option[24,42]. Patients presenting with bone metastases have a particularly poor prognosis[44], and most will receive palliative chemotherapy without further surgery.

Patients may receive second-line chemotherapy for recurrent osteosarcoma, however there is no regimen of choice[41]. In one UK treatment centre about 40% of patients were reported to receive additional chemotherapy for local recurrence or metastatic disease[42]. If relapse occurs more than 2 years after initial treatment the tumour is assumed to be sensitive to the first-line agents, which are administered again; If relapse occurs within 2 years of initial therapy the tumour is assumed to show a degree of resistance to first-line agents[10,42], and the patient will ideally be enrolled into a clinical trial to receive a novel therapy. A number of chemotherapeutic agents have or are being considered in the metastatic setting including ifosfamide, etoposide and biological agents such as interferon-α[14,40]. However, clear benefit for a particular second-line agent or combination therapy has not been demonstrated[42], particularly in patients for whom complete tumour resection is not feasible[44].

The proportion of patients achieving disease-free status following osteosarcoma recurrence is considerably lower than that seen with primary disease. Various reports have estimated that 20-30% of patients achieve long-term disease-free status after relapse[29,24,31,44,40,41]. The presence of metastases in conjunction with local recurrence is likely to be associated with a significantly worse prognosis than local progression alone[42]. Those undergoing repeated relapse may receive additional rounds of treatment, but the likelihood of a patient achieving disease-free status is dependent on the ability to remove all lesions[1].

4.1.3.3 Other patient management requirements and follow up

In addition to the osteosarcoma treatment itself, disease management needs to optimise the long-term functioning of patients[10]. A patient will require intensive physiotherapy and rehabilitation for about 4-6 months post-surgery

to allow for adaptation to using their endoprosthesis or prosthetic limb. The need for such support will gradually reduce after this time.

Though modern extendable endoprostheses do not require surgical procedures to lengthen the implant and allow for growth, many patients will require additional revision surgery for maintenance, or following mechanical failure or infection associated with the implant[29,27,46]. In some instances failure of the endoprosthesis can only be managed by subsequent amputation[27], which is associated with additional clinical requirements for the patient. Prosthetic limbs are more readily replaced following growth or failure.

The potential for local and/or metastatic recurrence of osteosarcoma necessitates regular patient surveillance. Follow-up in UK treatment centres may be as often as every 1-3 months in the first year post-treatment, 3-monthly over the second year, 6-monthly for the next 3-5 years, with subsequent annual monitoring[47].

The potential for toxicity to be associated with any chemotherapy regimen needs to be monitored and managed, in both the short and long-term. Acute toxicities associated with osteosarcoma chemotherapy include myelotoxic and gastrointestinal side effects[35]. Severe, acute myelotoxicity events, even with prophylactic granulocyte colony-stimulating factor support, can necessitate patient hospitalisation and red blood cell and platelet transfusion[34].

Long-term side effects are associated with various osteosarcoma chemotherapy components: cisplatin is ototoxic, causing permanent high-tone hearing loss in 10-20% of patients[33]. Hearing problems result in the need for a hearing-aid in some, and is particularly problematical for younger patients who have not yet attained speech or for those attending school. Other neurological toxicities such as peripheral neuropathy are also associated with cisplatin[2]. Doxorubicin is associated with both early and late cardiotoxicity[35,33,48]. Cardiotoxicity needs to be considered in terms of the potential for subclinical damage to both limit cardiac growth and worsen with time, raising concerns over the occurrence of late cardiac failure in osteosarcoma survivors[33,48]. Longhi et al.[48] reported severe late-onset, symptomatic cardiotoxicity in about

2% of surviving osteosarcoma patients that led to death or required heart transplant in a notable proportion (46% and 23% respectively); Both cisplatin and ifosfamide are associated with kidney toxicity and there have been suggestions that concomitant administration may exacerbate renal effects[49]. Standard treatment regimens specify the use of mesna to protect the bladder and kidneys. Severe renal toxicity is rarely seen during treatment but can develop years after finishing chemotherapy. In addition, long-term problems with fertility and the health of offspring can be associated with chemotherapy[50,40].

The potential for long-term disease-free survival of osteosarcoma patients also raises the potential that secondary malignancies may develop, which may be associated with chemotherapy or other factors[12,51]. Some reports have suggested that the risk of developing a second malignancy may be higher for survivors of bone cancers. The incidence of second malignancy was estimated at 3-6%[29,12,2] for osteosarcoma patients, however in the study by Gaffney et al.[12] this equated to 31% of long-term survivors with the time to second malignancy ranging from 17-62 years.

Given the potential for long-term survivors of osteosarcoma to experience late chemotherapy side effects, second malignancies and late relapse, prolonged follow up is a vital aspect of care. In addition, maintenance of prostheses and management of the sequelae of chemotherapy toxicities are integral components of long-term care.

4.1.4 Quality of life impact of osteosarcoma

4.1.4.1 Background

With 60-70% of patients achieving long-term survival following osteosarcoma, increasing importance can be placed on the impact of treatment on the functioning and quality of life of survivors, through childhood and adolescence and into adulthood.

The use of surgery in the treatment of osteosarcoma in the UK is standard practice, with 75% of patients having limb-salvage surgery[26]. However due to risks of infection, cancer recurrence and failure of endoprostheses, the use of

amputation retains a place in the clinical decision making process. Because of the central place of surgery for osteosarcoma patients the main focus of the quality of life literature has been to assess the impact of the different surgical approaches.

4.1.4.2 Quality of life in osteosarcoma survivors post-treatment

Quality of life after cancer treatment is associated with: physical complications due to the disease and lasting side effects of chemotherapy, psychological concerns over relapse or recurrence, and long-term impact on employment and other socioeconomic parameters. For patients treated for osteosarcoma there may be additional factors impacting on quality of life primarily related to the young age of patients, including mobility limitations, ongoing pain and stigma associated with amputation or other surgery[52].

Despite the obvious physical and social limitations imposed by osteosarcoma treatment in children, the conclusion from studies conducted since 1990 in several countries is that survivors of osteosarcoma/lower extremity tumours generally adjust well over time. However, this is not a universal finding and some studies have reported compromised quality of life.

A UK study conducted semi-structured interviews with 12 mothers of patients aged 6-22 treated for osteosarcoma or Ewing's sarcoma, and found that ability to participate in physical activities such as sport or social life was restricted in the 6 months post-diagnosis[53]. However, by 12-18 months post-diagnosis patients had generally adjusted to the physical and social limitations of their condition and the main focus was on emotional coping strategies[53]. A further UK study using the generic SF 36 quality of life questionnaire reported less positive outcomes for 41 young lower extremity tumour patients who underwent limb-salvage surgery[54]. Mean scores on each SF 36 sub-scale (physical functioning, physical role, performance, pain, general health and social functioning) were significantly below population norms, although this is maybe not surprising given the condition and young age of patients.

Studies in other countries have reported generally positive patient quality of life/functional outcomes post-treatment. In an early US observational study

Chang, et al.[55] assessed changes in psychosocial functioning and quality of life in 88 patients, of whom 65 were treated with limb-sparing surgery to the lower extremity. Socioeconomic status, sexual functioning, pain and functional outcomes were assessed using the McGill Pain Questionnaire and the Functional Living Index-Cancer over the 42 month study period. Significant improvements were found across most domains including employment status, sexual functioning, pain and global quality of life. A further US study in osteosarcoma patients, with a mean of 12 years post-diagnosis, rated psychopathology using a battery of measures and found no significant difference from a general population control[56]. In an Austrian study, only minor long-term psychological quality of life problems were reported in 80% of osteosarcoma or Ewing's sarcoma patients about 8 years after multi-modal treatment[57].

More recent European studies have reported generally positive outcomes for long-term physical and emotional functioning. A Dutch study administered generic child quality of life questionnaires and an adolescent coping questionnaire to 20 children who had received surgery (13 with osteosarcoma) at 3 and 8 years post-surgery[58]. At 3 years follow-up patients reported significantly lower scores for motor functioning and autonomy compared with a healthy control group, whilst at 8 years patients actually achieved higher scores for motor functioning, autonomy, cognitive functioning, social contact and negative emotions. A French study of osteosarcoma and Ewing sarcoma patients also reported good post-treatment health outcomes using a generic Child Health questionnaire[59]. The authors concluded that whilst physical function outcomes were good at 4 years post-diagnosis, there were quality of life issues relating to lower self-esteem in patients with endoprostheses, with family activity limitations and pain reported by patients who had relapsed.

A number of non-UK based studies have also considered the impact of treatment for bone tumours on long-term socioeconomic circumstances. These found that several years post-treatment, patients in young adulthood reported limited or no differences compared with healthy controls in education

status or income; however they may be less likely to be married, have children or live independently and were likely to have experienced school absences[54,57,60,61].

4.1.4.3 Type of surgery impact on quality of life outcomes

Two studies in the 1980's suggested no significant long-term difference in physical and social functioning and quality of life outcomes associated with amputation versus limb-salvage surgery for children with bone sarcomas[62,63]. Since these reports much attention has been given to addressing this issue. Subsequent observational studies have examined functional outcomes using validated instruments, typically the Musculoskeletal Tumour Society (MSTS) scoring system[64] and/or the Toronto Extremity Survival Score (TESS)[65]. Health-related quality of life has been assessed using the generic SF 36, cancer specific questionnaires and visual analogue scales.

A number of recent studies have shown differences in long-term outcome between bone tumour patients receiving amputation and limb-salvage surgery, using the validated functional outcome measures. Limb-salvage surgery patients were found to experience improved physical and social functioning compared with based on TESS and MSTS scores, especially if amputation occurred above knee[66,67,68,69].

There is less evidence of long-term differences for psychosocial outcomes or key socioeconomic indicators such as employment status and income[70,22,60,46]. Postma et al.[71] used a variety of assessment measures in survivors of lower limb bone tumours and showed some reduction in self-esteem for amputation patients, but similar quality of life and psychosocial outcomes.

Potential functional ability benefits in limb-salvage patients do not translate clearly into a long-term quality of life benefits. A number of studies found no significant differences in most generic SF 36 health status domains for limb-salvage surgery patients versus those with amputation[72,67,73]. Yonomoto et al.[69] showed a significant difference in social functioning but not in other domains. A larger Scandanavian study in 118 patients who had undergone

amputation or limb-sparing surgery found that amputees had significantly lower SF 36 scores for physical functioning and pain sub-scales[66]. Typically, patients with above knee amputations experienced lower functional status and generic quality of life outcomes[73 67]. Studies using other quality of life measures including the EORTC QLQ C30 cancer specific quality of life questionnaire[74], or the Quality of Life for Cancer Survivors instrument (Qol-CS)[75] also reported similar quality of life outcomes for amputees versus limb-salvage patients.

These studies demonstrated that a relatively high level of long-term functioning and quality of life is achieved for many bone tumour survivors, regardless of type of surgery. In contrast a UK study[54] and a recent Japanese study[69] showed SF36 scores in some domains to be significantly lower for bone tumour survivors than for the national population. However, several other studies have demonstrated higher SF 36 scores for long-term survivors[66,67]. MSTS or TESS scores for bone tumour survivors are also reported at about 80% of those for healthy individuals[66,67,21,76,75,77].

4.2 What was the rationale for the development of the new technology?

Though bone tumours are very rare, they have the fourth highest mortality rate of all adolescent malignant diseases seen in England and Wales[78]. Further, mortality rates for bone tumours have not fallen substantially in the last 25 years.

Currently 60-70% of patients diagnosed with high-grade, non-metastatic osteosarcoma achieve long-term disease-free survival following 3- or 4-agent neoadjuvant and adjuvant chemotherapy regimens combining methotrexate, doxorubicin and cisplatin with or without ifosfamide[38,33]. Various studies have been conducted in an attempt to improve on these survival rates by: dose intensification of chemotherapeutic agents[34,38,40,79,26]; treatment intensification treatment at the loco-regional level using intra-arterial rather than intravenous dosing[32,33]; and using novel agents such as taxanes, gemcitabine, topotecan and trabectedin[2,13]. Overall these approaches have proved disappointing. As a result it is generally assumed that the clinical benefits associated with

conventional chemotherapy have reached a plateau, leading to calls for new strategic approaches to the management of osteosarcoma[35].

Further, osteosarcoma patients with a poor response to neoadjuvant chemotherapy still have a dire prognosis[80,10,13]. It is postulated that a poor histological response may indicate an underlying resistance of tumour cells to chemotherapeutic agents; if so alternative agents added to the adjuvant treatment may also be susceptible to multi-drug resistance pathways[10]. Despite attempts to identify treatment modifications that improve efficacy, novel post-operative salvage regimens for patients with a poor histological response have not substantially improved prognosis[15,80].

Various authors have suggested that the combination of multi-agent chemotherapy with biological response modifiers/immune activators may achieve additional treatment benefits[80,10,2,81,13]. The development of MEPACT has focused on targeting the potent immunostimulatory activity of the active component to tumour cells, both in the primary lesion and in micro-metastases. The active agent in MEPACT is muramyl tripeptide phosphatidylethanolamine (MTP-PE) and comprises a synthetic lipophilic analogue of muramyl dipeptide, a component of Gram-positive and Gram-negative bacterial cell walls[82,83]. MTP-PE is a potent stimulator of innate immune processes and has been incorporated into liposomes to promote biodistribution to tumour lesions.

4.3 What is the principal mechanism of action of the technology?

The particle size and the proportion of negatively charged lipids in MEPACT liposomes means that they preferentially distribute to organs such as the liver, spleen, lungs and bone marrow. Following distribution to tissues MEPACT liposomes are phagocytosed by macrophages and monocytes. After internalisation the macrophage gradually metabolises the liposome layers, leading to a slow intracellular release of MTP. MTP binds to intracellular NOD2 receptors to activate the downstream NF-κB inflammatory signalling pathway and stimulate innate immune defences[81]. This culminates in the release of cytokines and inflammatory molecules, which produce a constellation of symptoms typically referred to as ‘cytokine flu’. Within hours of

administration, cytokines (tumour necrosis factor-α, interleukins 6 and 12) and/or other indicators of immune stimulation (neopterin, C-reactive protein, interferon-γ) are detectable in serum[82,84,85]. MTP also up-regulates the production of macrophage/monocyte surface adhesion molecules, thereby promoting interaction with tumour cells[81].

These properties result in the activation of regional macrophages that directly target tumour killing, via the production of tumour necrosis factor-α. In addition, the production of cytokines promotes the secondary activation of other immune effectors such as NK cells, granulocytes, dendritic cells and T cells[81]. These processes induce peripheral fibrosis, inflammatory cell infiltration and neovascularisation of osteosarcoma lesions[86].

4.4 What is the suggested place for this technology with respect to treatments currently available for managing the disease/condition?

MEPACT will be used as an add-on treatment to adjuvant chemotherapy. The activity of MEPACT is not affected by concomitant chemotherapy[82].

4.5 Describe any issues relating to current clinical practice, including any variations or uncertainty about best practice.

As a result of the uncertainties surrounding optimal treatment, the standard of care for UK osteosarcoma patients recommends enrolment into a clinical trial. This currently this involves entering the ongoing EURAMOS 1 trial (www.ctu.mrc.ac.uk/euramos/euramos_i_trial.asp)[20].

4.6 Provide details of any relevant guidelines or protocols.

The NICE guidance on Cancer Services 'Improving outcomes for people with sarcoma' published in 2006 is relevant to the use of MEPACT in children, adolescents and young adults with osteosarcoma (www.nice.org.uk/Guidance/CSGSarcoma). These guidance documents recommend that patients with bone sarcomas: are treated by a multi-disciplinary sarcoma team, with direct referral for diagnostic procedures to a specialist bone treatment centre, and diagnostic review being performed by a

specialist sarcoma pathologist/radiologist. Treatment for sarcoma should involve: definitive tumour resection by a specialist surgeon, chemotherapy to be carried out at designated centres by specialist clinicians, and the option for enrolment into relevant clinical trials. The guidance document informs on supportive care to be provided following treatment including the provision of prostheses, access to rehabilitation services and follow up.

Information on the ongoing EURAMOS 1 trial (ISRCTN trial number 67613327) can be found at www.ctu.mrc.ac.uk/euramos/euramos_i_trial.asp.

5 Equity and equality

5.1 Identification of equity and equalities issues

5.1.1 Are there any issues relating to equity or equalities?

A major issue concerning equality of care for osteosarcoma patients is associated with whether or not they are treated at a specialist centre. Stiller et al.[9] showed that patients with osteosarcoma achieve better survival rates if they receive therapy at a specialist paediatric or bone tumour treatment centre. The complex nature of both the surgical resection and chemotherapy regimens used for osteosarcoma patients, has led a number of authors to advocate that treatment should only be performed by highly specialised multi-disciplinary teams[87,31,17]. Only specialist centres are able to offer the patients the full spectrum of care with the opportunity to enter ongoing clinical trials[1].

The NICE guidance on Cancer Services 'Improving outcomes for people with sarcoma' (www.nice.org.uk/Guidance/CSGSarcoma) recently identified the important role of specialist, multi-disciplinary treatment for patients with osteosarcoma. Analysis of current service provision indicated that most patients with bone sarcoma are currently treated at specialist centres.

5.1.2 How has the analysis addressed these issues?

The intended place of use for MEPACT is within highly-specialised tertiary care centres in conjunction with other aspects of osteosarcoma treatment. As such, the use of MEPACT is consistent with NICE guidance recommending that this patient group is treated by a multi-disciplinary specialist team. However, the option to enter into a clinical trial is recommended for patients with osteosarcoma and how this would balance against the uptake of MEPACT as a new recommended treatment is unclear.

6 Clinical evidence

6.1 Identification of studies

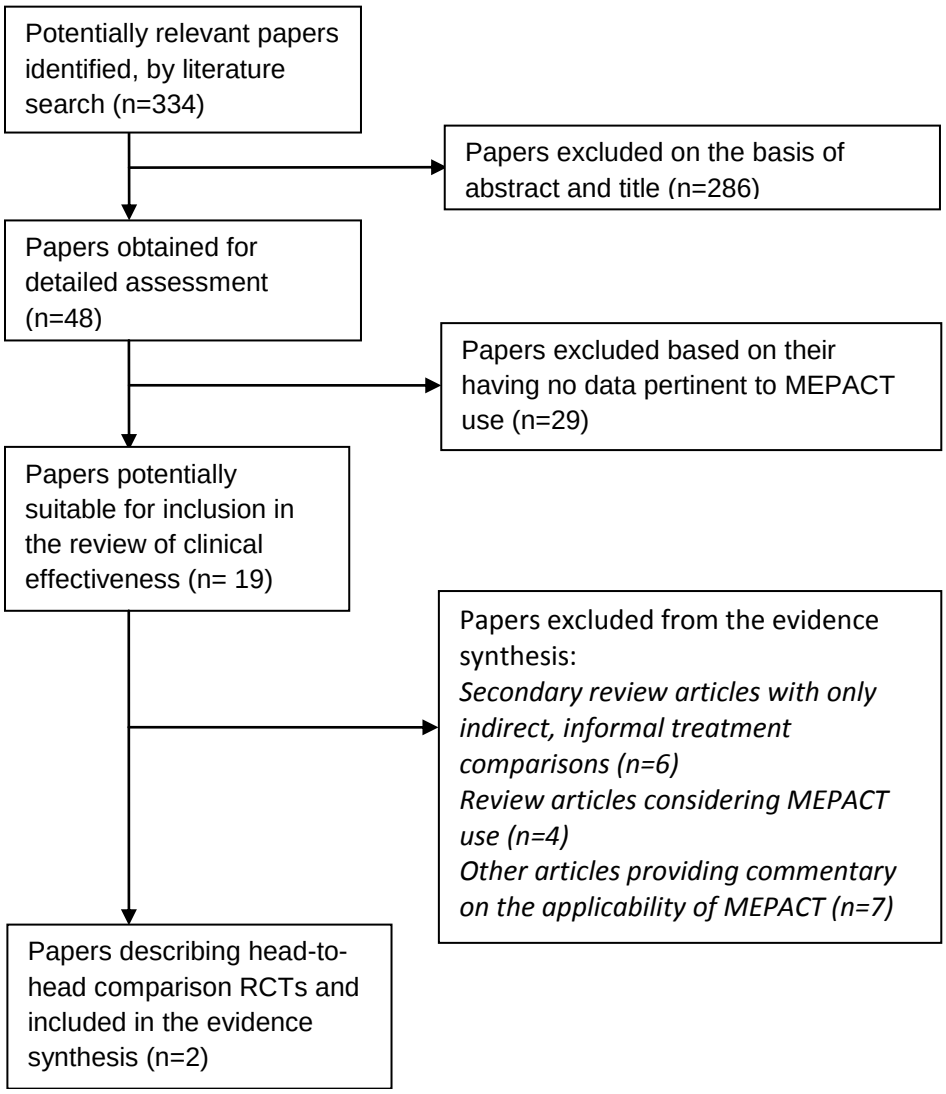
A comprehensive systematic literature search was conducted on 10 September 2008 to identify articles relevant to osteosarcoma (including terms of osteogenic, bone, osteoid and osteolytic sarcoma) and MEPACT (including terms of mifamurtide, muramyl-tripeptide, muramyl tripeptide, CGP 19835, L-MTP-PE, MTP-PE, MLV 19835A, phosphatidyl ethanolamine and Junovan). Details of the strategy used to search the Medline are presented in Section 10.2, Appendix 2; this strategy was modified to search other databases and relevant websites. Literature was also identified by citation searching on key papers, and from scanning the bibliographies of retrieved items.

Unpublished clinical trial data was provided by IDM to inform on Section 6.4.

6.2 Study selection

A total of 334 articles were identified based on the search criteria. Two researchers independently screened titles and abstracts to ensure the relevance and consistency of the literature selection. Any discrepancies in the perceived relevance of specific papers were resolved by consensus. The relevance of each study was assessed according to the PICO (Population, Intervention, Comparison, Outcome) criteria. The literature selection process is summarised in Figure 1.

Figure 1: Flow chart of literature selection for MEPACT clinical effectiveness



Two reports of one randomised clinical trial considering MEPACT use in osteosarcoma patients were identified[83,88]. In addition, six papers comprised secondary review articles considering MEPACT clinical trial data[14,10,35,2,85,13], seven provided additional commentary on the use of MEPACT[36,87,20,3,89,90,91,92] and four provided general information[93,82,94,81]; these papers were used to inform on Section 4 of this document.

6.2.1 Complete list of RCTs

One Phase III randomised clinical trial (INT-0133) considering the use of MEPACT as an add-on to multi-agent chemotherapy in children, adolescents and young adults with osteosarcoma was identified from the systematic literature review. This trial was the subject of two research papers:

- Meyers, Schwartz and Krailo et al. (2008) Osteosarcoma: the addition of muramyl tripeptide to chemotherapy improves overall survival - a report from the Children's Oncology Group. J Clin Oncol; 26(4): 633-8[88].
- Meyers, Schwartz, and Krailo et al. (2005) Osteosarcoma: a randomized, prospective trial of the addition of ifosfamide and/or muramyl tripeptide to cisplatin, doxorubicin, and high-dose methotrexate. J Clin Oncol; 23(9): 2004-11[83].

6.2.2 Inclusion and exclusion criteria

Studies were selected according to the PICO stratagem: The study population comprised children, adolescents and young adults diagnosed with high-grade, non-metastatic osteosarcoma. The intervention comprised neoadjuvant chemotherapy with high-dose methotrexate, doxorubicin and cisplatin with/without ifosfamide followed by adjuvant therapy with the same regimen plus MEPACT. The comparator comprised neoadjuvant and adjuvant chemotherapy with high-dose methotrexate, doxorubicin and cisplatin with/without ifosfamide. Outcome measures comprised overall survival, disease-free survival, quality of life and safety.

6.2.3 List of relevant RCTs

One Phase III randomised clinical trial (INT-0133) directly comparing the use of MEPACT as an add-on to multi-agent chemotherapy versus multi-agent chemotherapy alone was identified by systematic review of the literature. This trial was the subject of two research papers[83,88]:

- Meyers, Schwartz and Krailo et al. (2008) Osteosarcoma: the addition of muramyl tripeptide to chemotherapy improves overall survival - a report from the Children's Oncology Group. J Clin Oncol; 26(4): 633-8[88].
- Meyers, Schwartz, and Krailo et al. (2005) Osteosarcoma: a randomized, prospective trial of the addition of ifosfamide and/or muramyl tripeptide to cisplatin, doxorubicin, and high-dose methotrexate. J Clin Oncol; 23(9): 2004-11[83].

The 2008 paper supersedes that published in 2005, presenting updated analyses based on the full dataset.

6.2.4 List of relevant non-randomised controlled trials

Two additional non-randomised trials using MEPACT in osteosarcoma patients were identified. Studies considering MEPACT use in osteosarcoma patients are summarised in Section 10.4, Table 20. Information from these studies was used to inform on safety considerations (Section 6.7).

6.2.5 Ongoing studies

MEPACT is currently being used to treat osteosarcoma patients as part of a compassionate-use programme (Section 10.4, Table 20); however this study will not report additional data over the next 12 months.

6.3 Summary of methodology of relevant RCTs

The study was initiated in recognition that 30-40% of patients with high-grade non-metastatic osteosarcoma do not achieve long-term survival benefits, despite aggressive surgical resection of the primary lesion and the use of multi-agent noeadjuvant and adjuvant chemotherapy. Earlier Phase II studies had provided histological evidence that MEPACT is able to induce fibrotic changes, immune cell infiltration and neovascularisation in metastatic pulmonary osteosarcoma lesions[86] and prolong the interval to disease relapse[95]. These preliminary data, therefore, indicated that MEPACT may be a beneficial treatment in patients treated surgically for non-metastatic disease, as a result of its potential activity against microscopic lesions.

6.3.1 Methods

The RCT INT-0133 was a multi-centre, randomised, open-label Phase III study entitled ‘Trial of doxorubicin, cisplatin, and methotrexate with and without ifosfamide and with and without muramyl tripeptide phosphatidyl ethanolamine (MTP-PE) for treatment of osteogenic sarcoma [in patients with non-metastatic and resectable disease]’. The study was conducted at 178 sites primarily in the US and recruited patients from November 1993-November 1997. Follow-up data were collected until March 2007.

6.3.1.1 Randomisation and blinding

Patients were randomised on enrolment into the study. Prior to the start of the study, a randomisation assignment sheet was constructed with treatments assigned using a block size of 4. Assignments were generated using the Children's Cancer Group-developed program RANDTAB. Patients were enrolled into the study when the investigator phoned the operations office of either the Children's Cancer Group or the Pediatric Oncology Group, where the registrar provided the randomised treatment assignment.

Randomisation was stratified with an algorithm to minimise between-arm allocation imbalances by: lactate dehydrogenase level above/below the institutional upper limit of normal, the involvement/non-involvement of disease above the knee or elbow, and prior amputation/no amputation.

This was an open-label study and did not attempt to blind treatment for a number of reasons: As the preparation of MEPACT requires the use of filters and extends the treatment period, conducting a blinded study was considered unfeasible and unethical. It is difficult to justify exposing a child or adolescent to 48 additional infusions solely to ensure maintenance of a treatment blind. In addition, escalation of MEPACT dosing to a biologically effective level is dependent upon the observation of a clinical effect that would be likely to compromise the blind.

6.3.1.2 The intervention

Neoadjuvant/induction therapy

Patients with a new diagnosis of high-grade non-metastatic resectable osteosarcoma, were randomly assigned to one of four treatment groups. They then received 10 weeks of neoadjuvant induction therapy with one of two chemotherapy regimens:

- Regimen A induction therapy consisted of 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).

- Regimen B induction therapy consisted of two doses of doxorubicin (25mg/m^2/day over 72 hours), two courses of ifosfamide (1.8g/m^2/day x 5 days) and four doses of methotrexate (12g/m^2).

Tumour resection

Definitive surgery was performed during Weeks 10-11, while the patient was not receiving chemotherapy. Following resection the pathologist assigned a Huvos score, based on the patient's response to neoadjuvant therapy as judged by necrosis in the resected tumour tissue.

Adjuvant/maintenance therapy

Maintenance therapy was scheduled to begin at Week 12: Patients in Regimen A received their induction chemotherapy regimen with (A+) or without (A-) addition of MEPACT. Patients in Regimen B received their induction therapy plus cisplatin, and with (B+) or without (B-) addition of MEPACT. The total doses of methotrexate, cisplatin and doxorubicin administered during induction and maintenance were identical in Regimens A and B.

- Regimen A maintenance therapy 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).
- Regimen B maintenance therapy consisted of four doses of doxorubicin (25mg/m^2/day over 72 hours), four doses of cisplatin (120 mg/m^2), three courses of ifosfamide (1.8g/m^2/day x 5 days) and eight doses of methotrexate (12g/m^2).

The timings of the study treatments during the maintenance phase are summarised in Figure 2.

Figure 2: Trial INT-0133 dosing schema

	Week of maintenance phase treatment																										
	12	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28**	**29**	**30**	**31**	**32**	**33**	**34**	**35**	**36**	**37**	**38**	**39-48**
A	C, 3D			MX	MX	C, 3D			MX	MX	3D			MX	MX	3D			MX	MX								
A+	C, 3D, 2M	2M	2M	MX, 2M	MX, 2M	C, 3D, 2M	2M	2M	MX, 2M	MX, 2M	3D, 2M	2M	M	MX, M	MX, M	3D, M	M	M	MX, M	MX, M	M	M	M	M	M	M	M	M
B	C, 3D			MX	MX	5I, 3D			MX	MX	C, 3D			MX	MX	5I, 3D			MX	MX	C			5I			C	
B+	C, 3D, 2M	2M	2M	MX, 2M	MX, 2M	5I, 3D, 2M	2M	2M	MX, 2M	MX, 2M	C, 3D, 2M	2M	M	MX, M	MX, M	5I, 3D, M	M	M	MX, M	MX, M	C, M	M	M	5I, M	M	M	C, M	M

MX – single dose methotrexate, 3D – 3 days dosing with doxorubicin (given over 72 hours), C – single dose cisplatin, 2M – 2 days dosing with MEPACT at least 3 days apart, M – 1 day dosing with MEPACT, 5I – 5 days dosing with ifosfamide

Patients assigned to receive MEPACT in the maintenance phase received twice-weekly intravenous infusion for 12 weeks followed by once weekly intravenous infusion for an additional 24 weeks, as a total of 48 infusions over 36 weeks. A protocol amendment specified that MEPACT treatment should be extended by an additional 12 weeks (to 48 weeks); the treatment of all patients was compliant with this amendment. The starting dose of MEPACT was 2mg/m^2, which could be dose-escalated to 2 mg/m^2 + 1mg and then to 2mg/m^2 + 2mg until biological activity was seen as defined by: an elevation of oral body temperature to at least 38.1°C within 24 hours of beginning drug administration, the presence of visible Grade 2 rigors lasting 30 minutes, or a significant elevation in C-reactive protein (>2x baseline) 24 hours post-dose.

Additional therapies

Leucovorin was administered to counteract methotrexate toxicity. Leucovorin administration began exactly 20 hours after the end of methotrexate infusion, with at least 10 doses being given to achieve a methotrexate level below 0.1µM.

Mesna was used to prevent haemorrhagic cystitis in patients receiving ifosfamide. An initial mesna dose of 360mg/m^2 was administered 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 was also specified for 4-24 hours after the start of ifosfamide dosing.

Granulocyte colony-stimulating factor and erythropoietin were specified management options for haematological toxicity.

6.3.2 Participants

Patients with newly diagnosed fully malignant high-grade osteosarcoma of bone, with no more than 1 month since diagnostic biopsy, were eligible for the study. At the time of study entry, tissue blocks or diagnostic hematoxylin and eosin stained sections from the biopsy were submitted with appropriate information identifying the biopsy sites. Diagnostic evidence was reviewed by two independent pathologists.

Inclusion criteria specified that patients:

- Were to be less than 30 years of age.
- Were to have normal renal, hepatic and cardiac function.
- (Or the patient's legally authorised guardian) were to provide informed consent.

If primary ablative surgery had already been performed, inclusion was allowed but patients were not evaluable for histological response.

Patients were not eligible for the study if they had:

- Metastatic disease or unresectable primary disease. (Patients with metastatic disease were eligible at some study sites but were not to be included in the intention-to-treat analysis and are not considered in the evidence presented here.)
- Low grade osteosarcoma, parosteal/periosteal sarcoma, radiation induced sarcoma or osteosarcoma arising in pre-malignant bony lesions.
- A history of pericarditis or myocarditis.
- Undergone prior chemo- or radiation therapy.
- Previously received treatment for another malignancy.

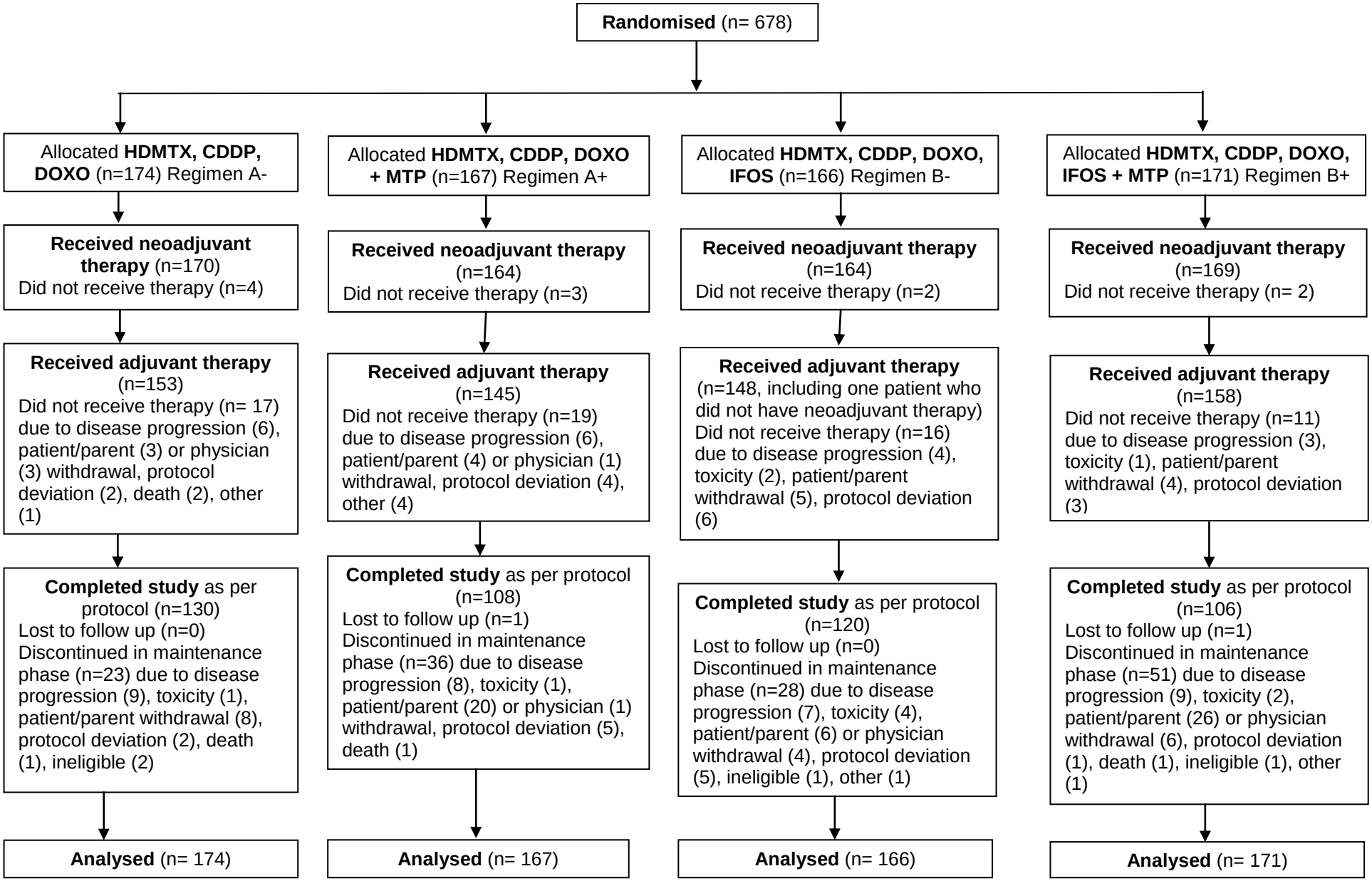
Patients could only be enrolled into the study at sites that had received Institutional Review Board approval for the study protocol.

6.3.3 Patient numbers

The numbers of patients entering the RCT, and who were randomised and allocated to each treatment arm are summarised in Figure 3, with details of the treatments specified as:

- **Regimen A-** high-dose methotrexate, cisplatin, doxorubicin (HDMTX, CDDP, DOXO).
- **Regimen A+** high-dose methotrexate, cisplatin, doxorubicin plus MEPACT (HDMTX, CDDP, DOXO + MTP).
- **Regimen B-** high-dose methotrexate, cisplatin, doxorubicin, ifosfamide (HDMTX, CDDP, DOXO, IFOS).
- **Regimen B+** high-dose methotrexate, cisplatin, doxorubicin, ifosfamide plus MEPACT (HDMTX, CDDP, DOXO, IFOS + MTP).

Figure 3: Flow chart of trial INT-0133



The reasons for not receiving neoadjuvant chemotherapy varied, but typically included patient/parent decision to undergo treatment elsewhere or lack of the appropriate insurance. Specific reasons for patients not receiving neoadjuvant therapy according to treatment regimen are not available, however these patients were included in the data analysis populations.

Information concerning the reasons for patients being lost to follow up are not available.

It should be noted that the analysis groups presented here differ slightly from those reported in the publications based on the study[83,88]. This difference arises because the Children's Oncology Group by mandate and convention does not include ineligible patients in their analyses.

6.3.4 Outcomes

6.3.4.1 Study objectives

The primary objectives of study INT-0133 related to MEPACT were:

- To determine if the addition of MEPACT to cisplatin, doxorubicin and methotrexate, with or without ifosfamide, enhanced overall survival.
- To determine if the addition of MEPACT to cisplatin, doxorubicin and methotrexate, with or without ifosfamide, enhanced disease-free survival as an intermediate endpoint for overall survival.

The choice of these endpoints followed a review of the National Cancer Institute, Cancer Cooperative Group System practices.

The stated aim of the study was to improve the survival of patients with osteogenic sarcoma. However the study was sized for the first planned analysis of the intermediate endpoint disease-free survival[96], a recognised surrogate indicator of overall survival in cancer patients that assesses survival from the time of treatment randomisation to the time of osteosarcoma relapse or death.

Additional study objectives not related to the investigational agent also assessed the impact of: ifosfamide treatment on overall and disease-free

survival, the predictive capacity of a good histological response to neoadjuvant therapy for disease-free survival benefit and whether p-glycoprotein can act as a prognostic indicator of treatment benefit.

6.3.4.2 Study outcomes

Efficacy was assessed by monitoring survival and disease status. Disease status was assessed using a combination of clinical and diagnostic tests, imaging studies of affected bone (X-ray, CT, MRI), imaging studies of the chest to assess for metastatic disease (X-ray, CT), and bone scan with radiographic examination of positive areas. Safety was assessed by monitoring toxicities and adverse events, clinical laboratory measurements, echocardiograms and audiograms.

Disease status was assessed at the end of each treatment course. Post-treatment follow up continued at 3-monthly intervals in the year after treatment, then every 6 months for 2 years, then yearly and at relapse. Long-term follow up was planned for all patients. The study protocol specified a number of instances under which patients were to be removed from per-protocol therapy (progressive disease, completion of all therapy courses) or considered off-study (death, lost to follow-up, entry into another study).

Patients undergoing disease recurrence received a variety of treatment options according to the clinician's judgement.

6.3.5 Statistical analysis and definition of study groups

The relevant study hypothesis was that: MEPACT, which has demonstrated the ability to enhance macrophage tumoricidal activity against osteogenic sarcoma *in vitro* and which prolongs survival in dogs with spontaneous osteogenic sarcoma, would enhance the killing of minimal residual disease in patients with osteogenic sarcoma after surgery.

6.3.5.1 Planned sample size

Many paediatric cancers have the potential of complete cure, seen as a flattening of the Kaplan-Meier survival plots above zero. This flattening results from two phenomena: if a patient, particularly a child, is cured then the hazard

of death becomes very small because competing risks of death are small in the young population; patients who are not cured have events and/or die relatively quickly. As a result, paediatric study groups tend to emphasise the use of survival distribution models based on the possibility of observing cure. Study INT-0133 was planned based on the use of the Gompertz survival distribution.

Sample size calculations were based on the assumption that there would be 60% long-term disease-free survival in patients receiving neither ifosfamide nor MEPACT, and that the study would be able to detect a difference of 60% vs. 72% in this outcome measure with two-sided significance level of 0.05, power of 80% and 2-years follow up. This assumes that 50% of treatment failures occur within 1.3 years, a value derived from prior experience. Using these assumptions, the study planned for 585 patients with non-metastatic resectable disease over 3.9 years accrual.

The planned sample size for the study was 585 patients. However, a specialist filter required for reconstitution and administration of MEPACT was unavailable from 15 June 1995 to 15 January 1996. To allow sufficient patients to receive MEPACT therapy according to the protocol, accrual was extended to allow randomisation of an additional 60 patients following a protocol amendment.

6.3.5.2 Interim analysis

During the time study INT-0133 was enrolling, the National Cancer Institute implemented more rigorous requirements for data monitoring committees, specifying the need for formal interim analyses. As a result a protocol amendment specified that interim data analyses be conducted, these were performed in September 1996, February 1997 and January 1998. The analyses were performed at predetermined intervals to assess futility or the presence of highly significant treatment differences that might justify early study completion. None of the analyses demonstrated results that crossed a monitoring boundary for chemotherapy, MEPACT or the interaction between chemotherapy and MEPACT.

A detailed statistical analysis performed to address concerns about the potential impact of interim analyses, concluded that the type I error probability for the analysis of disease-free survival was not markedly increased. There was no impact on the analysis of overall survival, since it was not assessed in the interim analyses.

6.3.5.3 Analysis groups

All randomised patients were included in the intention-to-treat analysis, including those patients whose treatment was affected by the lack of availability of filters for MEPACT administration. Survival analysis allowed inclusion of patients who dropped out of the study or were lost to follow up as 'censored' observations.

6.3.5.4 Planned statistical methods

The study analysis specified a 2 x 2 factorial design with two factors: the chemotherapy factor (randomisation to one of two different chemotherapy regimens) and MEPACT (randomisation to receive MEPACT or not). Only the MEPACT aspect is pertinent to this submission. The primary endpoint analysis comprised a stratified log-rank test of the MEPACT factor, with stratification by the randomisation stratification factors and the chemotherapy factor. 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.

Differences in the incidence of adverse events between treatment groups were assessed using Fischer's exact test

6.3.5.5 Additional post-hoc analysis

Additional analyses considering event-free survival (defined as the time from study entry to disease progression, death from any cause, occurrence of a second malignant neoplasm or last follow up) were performed independently by the Children's Oncology Group. Assessment of this endpoint is historically based, as it is the intermediate endpoint typically used in osteosarcoma cooperative group study. Thus event-free survival was analysed by the

Children's Oncology Group for publication purposes, so that the outcome could be compared with those from other studies.

Subset and sensitivity analyses were conducted on the intention-to-treat population to support the robustness of conclusions from the primary analyses.

6.3.6 Critical appraisal of relevant RCTs

The RCT described is a long-term study conducted over 14 years and has had to adapt to certain logistical problems and to changes in the requirements of advisory bodies. However the methodological quality of the RCT is consistent with current standards, with some limitations.

6.3.6.1 Study conduct

The randomisation of treatment assignment was concealed by the schedule being held at the central operations offices for the Children's Cancer Group (now Children's Oncology Group). However, it was not considered feasible or appropriate to conduct a blinded study: given the additional treatment requirements associated with MEPACT dosing, the ethical constraints on placebo dosing in paediatric cancer patients; and the need to demonstrate MEPACT side effects to confirm a biological effect. As a result the study was open-label in nature. However the potential for bias was minimised by the use of survival parameters as the key efficacy endpoints.

The first aim of the pivotal study INT-0133 was to improve survival, as indicated on the first page of the study protocol. The convention at the time the protocol was written was to justify in the document the number of patients to be enrolled and the time at which the initial analysis would be available. For INT-0133, the first planned analysis considered an intermediate endpoint (disease-free survival) and the study was sized for that endpoint. Assessment of disease-free survival as a surrogate for overall survival was the accepted convention for paediatric oncology studies when this trial began; however overall survival is considered a more robust endpoint, having less potential for bias and being the ultimate treatment goal.

Due to logistical problems with availability of the filters required for MEPACT administration, a protocol amendment specified that an extra 60 patients could be recruited into the study. During that time 43 of 51 patients randomised to a MEPACT arm did receive MEPACT and all randomised patients were included in the intention-to-treat population.

This was a four-arm parallel-group factorial design (2x2) study, as is appropriate for investigating treatment efficacy in a disease with a progressive course such as osteosarcoma. The prospectively defined analysis was to compare patients randomised to MEPACT (Regimen A+MEPACT and Regimen B+MEPACT combined) to patients randomised to no-MEPACT (Regimens A and B combined).

The Children's Oncology Group study sites underwent FDA and EMEA inspections to confirm that study INT-0133 had been conducted according to GCP standards. There were no critical findings at inspected sites or at the Children's Oncology Group data management centre, with no finding of systematic bias in favour of one treatment arm. The data were reported to be acceptable to support a marketing application by EMEA inspectors.

6.3.6.2 Follow up

The final follow-up period for this study was up to 12.5 years with a median follow-up of 7.9 years, and 75% of patients alive at last contact with least 5.3 years of follow up. Extended follow-up periods are important for accurately assessing survival parameters in diseases such as high-grade osteosarcoma, where >98% of patients who relapse do so within 5 years of treatment[45] and where survival at this point can equate to long-term cure. Follow up was stopped 14 years after study initiation based on a new Children's Oncology Group policy to close long-term follow up of clinical studies after 10 years. To prevent bias, efforts to minimise lost-to-follow up were applied uniformly to all treatment arms. Consistent with standard rules of setting censoring times, patients were censored on the date of last patient contact. There is no reason to believe that the methods of follow-up or application of censoring in these analyses led to any bias in the study conclusions.

Long-term follow-up data were not available for some patients withdrawing from the study. A slightly higher incidence of withdrawal from therapy was apparent for the MEPACT dosing groups. Most of these withdrawals were not due to toxicities that required significant intervention, were life-threatening, or necessitated truncation of MEPACT therapy; rather they were voluntary decisions to not participate further in an investigational study. The investigators considered it likely that early withdrawals from MEPACT treatment arms during the study were largely due to the use of an investigational agent of unproven benefit that may be uncomfortable or inconvenient when added to the fairly heavy burden of combination chemotherapy. It is considered likely that, with proven survival benefit, treatment compliance would improve. It is also recognised that in trials comparing treatments where one is significantly longer than the other, patients are more likely to cease therapy earlier than planned in the 'longer' arm[90].

Relapse of osteosarcoma typically occurs within 2-3 years of diagnosis. Relapse or death beyond 5 years is rare; in this study 75% of patients who died did so before 4.5 years and 90% of patients who died did so before 6 years. In the final 2007 dataset, close to 95% of patients were accounted for at 3 years and more than 80% were accounted for beyond 5 years. Sensitivity analyses employing complete case analysis and imputation of missing values support the reduction in risk of death demonstrated by the intention-to-treat analysis (hazard ratio = 0.72).

While most patients with osteosarcoma survive long-term, a subpopulation of patients withdrew from the Phase III study due to treatment failure, i.e., relapse of osteosarcoma or second malignancy. In these patients death is a likely outcome within 5 years of treatment failure. This is consistent with the natural history of osteosarcoma, with the data on survival after relapse from both the Phase III study and the published literature indicating 20-45% 5-year survival in patients with complete resection of metastatic disease after relapse[44]. Consistently poor outcomes (0% survival at 5 years) are reported for patients not achieving a second complete remission[44]. The worst possible value for treatment outcome was assigned to patients censored for a negative

reason; for these analyses, patients who had less than the specified follow up (1, 3 or 5 years) after a report of osteosarcoma relapse or second malignancy were considered to have died. These analyses resulted in consistent treatment effects favouring MEPACT, with hazard ratios of 0.74-0.75.

Another approach to sensitivity analysis is to compare the results of the full analysis set to those of the complete case analysis. This involves ignoring incomplete data and performing the statistical analysis with complete data only as a secondary supportive analysis, to illustrate the robustness of conclusions. Complete case analysis was performed on the Phase III study intention-to-treat data excluding cases that were censored before 1, 3 or 5 years. These resulted in favourable hazard ratios (0.72-0.73) and significant p-values that are consistent with the primary analysis.

The results of the intention-to-treat and sensitivity analyses involving subgroups of the Phase III population (Section 6.4.3) were consistent with the primary analysis and led to similar estimates of treatment effect. This provides assurance that censoring of information had no impact on the overall study conclusions.

6.3.6.3 Study location

The RCT was conducted at 178 study centres, mainly in the US. The treatment regimens and practices used in the study are broadly consistent with those used within the UK. The 3-arm chemotherapy regimen specified is routinely used in the UK; the use of ifosfamide as part of a 4-arm chemotherapy regimen is not used. However, ifosfamide as part of the adjuvant regimen for patients experiencing a poor histological response to neoadjuvant therapy is an option in the ongoing osteosarcoma trial (www.ctu.mrc.ac.uk/euramos/euramos_i_trial.asp).

The RCT participants are likely to be highly comparable to patients who would receive the intervention in the UK, given the consistent demographic profiles, prognostic factors and disease characteristics seen in osteosarcoma patients from diverse geographical locations[20,39]. In addition treatment outcomes in osteosarcoma patients are similar across geographical regions[97,43]. The

patient population used in this study is also comparable to that in the population-based SEER (Surveillance, Epidemiology and End Results) program[26].

6.3.6.4 Investigational agent

The MEPACT dosing regimen used in the RCT is consistent with that detailed in the Summary of Product Characteristics (Section 10.1, Appendix 1), though the latter does not specify the option for dose-escalation. That the Summary of Product Characteristics does not specify dose-escalation is consistent with the findings of the RCT, where only 28 of 293 patients who received at least one dose of MEPACT (<10%) underwent a planned dose-increase due to a lack of biological activity at the starting dose.

6.3.6.5 Study participants

The characteristics of the patients in the different RCT treatment arms were comparable in terms of demographic profile, disease location and the specified stratification factors (Section 6.4.1).

6.3.6.6 Study analysis and confounding factors

The Gompertz model is particularly suited to this paediatric patient population. Such a model assumes that for most patients the risk of disease recurrence is highest during the first few years post-treatment; after this point the survival curve tends to flatten because there are few other competing events in a young population. The study data were shown to fit the Gompertz model well.

The analysis of both efficacy and safety parameters used the intention-to-treat population. However the protocol allowed recruitment of patients with metastatic or unresectable osteosarcoma at some study sites. Patients with metastatic or non-resectable disease were excluded from the intention-to treat population used for the study analyses; the exclusion of such patients from the principal study endpoint analysis was specified in the study protocol.

The statistical analysis plan specified a 2 x 2 factorial analysis to assess for the effects of both MEPACT and ifosfamide use. The effect of ifosfamide is not relevant to this discussion. The Cox proportional hazards regression

model was used to estimate the treatment effect of MEPACT[98] and the Kaplan-Meier[99] product-limit estimator was used to estimate survival curves. The log-rank test using standard censoring rules comprised the prospectively defined analysis and was the approach used for the intention-to-treat efficacy analysis. These methodologies were appropriate, pre-planned, conservative and standard to a study with censored survival data.

Publication of the independent analysis of the intermediate endpoint by the Children's Oncology Group suggested that an interaction precluded the planned analysis by factorial design[83]. However in their reanalysis of the survival data published in 2008[88], they concluded that there was no evidence of interaction and that the marginal analysis is appropriate.

To further examine the potential for interaction, the method of Gail and Simon[100] was used to formally test for qualitative interaction within each of the treatment/demographic groups (i.e., age, gender, race, and chemotherapy). This methodology assesses qualitative interactions in which one treatment may be superior for some patient subsets, while the alternative treatment may be superior for other subsets. A likelihood ratio test is used to test for these qualitative interactions. Statistical analyses of qualitative interactions ruled out important interactions between MEPACT and other variables including gender (p=1.0), race (p=1.0) and chemotherapy (p=1.0).

6.4 Results of the relevant comparative RCTs

The intention-to-treat population was used for all efficacy analyses. The initial clinical study report presented data accrued to June 2003 and August 2006; an addendum subsequently provided the updated findings based on data to March 2007. Following an EMEA inspection of the Children's Oncology Group data centre in April 2008, the inspectors reported that the 2007 dataset provides the most up-to-date and comprehensive data and can be reliably used for benefit/risk assessment.

6.4.1 Demographic characteristics

The demographic characteristics of patients in the study INT-0133 intention-to-treat population are summarised in Table 1. Patient demographic

characteristics were similar across treatment groups, with a median age of about 14 years and with most patients being white and having a primary lesion of the femur or tibia. The distribution of stratification factors was also comparable across treatment groups.

Table 1: Demographic characteristics (ITT population)

	Regimen A (N=174)	**Regimen A+** (N=167)	**Regimen B** (N=166)	**Regimen B+** (N=171)
Gender				
Male	85	95	87	105
Female	89	72	79	66
Age (years)				
Mean	13.8	14.0	13.5	13.8
Median	13.3	14.3	13.6	13.9
Range	4.0 – 30.1	4.9 – 29.2	4.2 – 30.6	1.4 – 30.4
Race				
White	116	109	120	105
Hispanic	20	27	16	22
Black	26	19	25	27
Oriental	4	4	0	6
Filipino	1	3	1	2
Other	7	5	4	9
Primary Tumour				
Arm –	18	21	16	21
Arm – Radius	2	0	4	5
Arm – Ulna	0	1	1	0
Arm	0	0	1	0
Leg – Femur	91	91	96	91
Leg – Tibia	40	45	38	45
Leg – Fibula	7	3	2	3
Leg	1	0	1	0
Other	8	5	7	4
Unknown	7	1	0	2

6.4.2 MEPACT dosing

The number of MEPACT doses received by patients entering the maintenance treatment phase of study INT-0133 is presented in Table 2. Those patients receiving more than 48 doses of MEPACT underwent dose-escalation based on the rules specified in the protocol.

Table 2: MEPACT dosing for patients receiving adjuvant therapy

Dosing	MTP (N=303)
0 doses	12 (4%)
1 to ≤12 doses	25 (8%)
13 to ≤24 doses	26 (9%)
25 to ≤36 doses	38 (13%)
37 to ≤48 doses	141 (47%)
>48 doses	61 (20%)

6.4.3 Survival

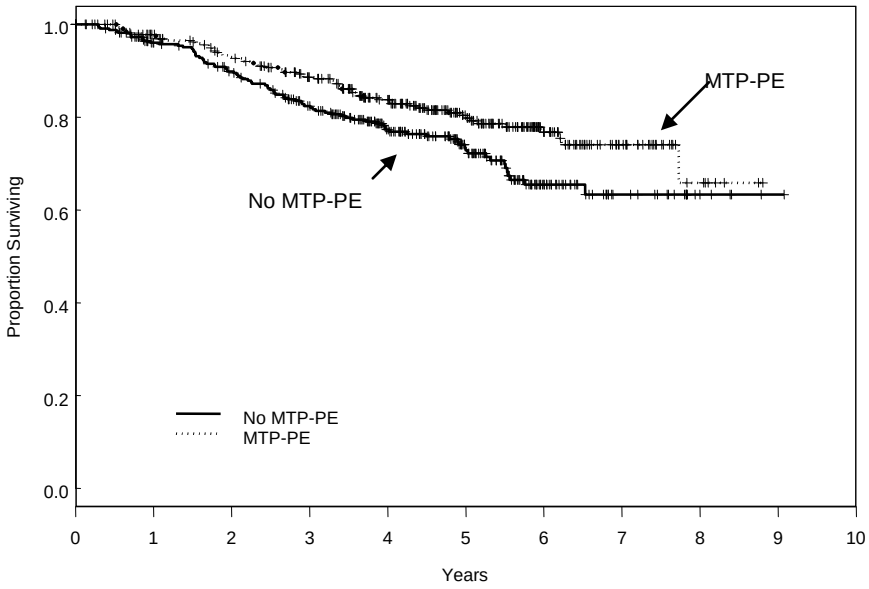
In the initial analysis of the 2003 data showed that MEPACT significantly increased overall survival in patients with non-metastatic resectable osteosarcoma, achieving a 6-year probability of survival of 77% (95% CI: 72-83%) compared with 66% (95% CI: 59-73%) for patients receiving standard chemotherapy (Table 3 and Figure 4).

Table 3: Summary of survival analyses (ITT population, 2003 dataset)

Variable	Patients (events)	P-value	Hazard Ratio	95% CI for HR
Overall Survival				
No MEPACT (A/B)	340 (85)	---	1.00	---
MEPACT (A+/B+)	338 (63)	0.0183[1]	0.68	(0.49, 0.95)
Disease-Free Survival				
No MEPACT (A/B)	340 (126)	---	1.00	---
MEPACT (A+/B+)	338 (102)	0.0245[1]	0.76	(0.58, 0.98)

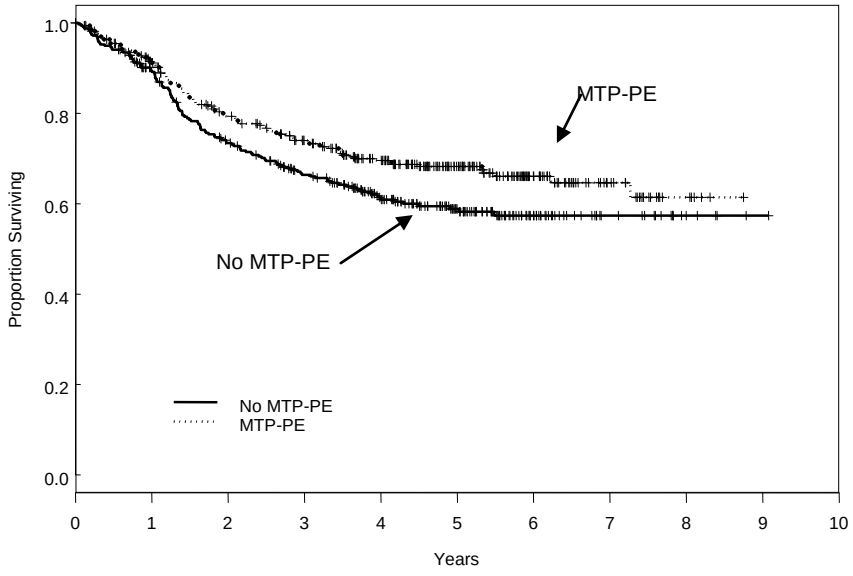
[1]from log-rank test stratified by ifosfamide use and randomisation strata.

Figure 4: Overall survival ± MEPACT (ITT population, 2003 dataset)



Similarly the addition of MEPACT to chemotherapy in the maintenance phase significantly increased disease-free survival, achieving a 6-year probability of surviving without osteosarcoma relapse of 66% (95% CI: 61-72) compared with 57% (95% CI: 52-64%) for patients receiving chemotherapy alone (Table 3 and Figure 5).

Figure 5: Disease-free survival ± MEPACT (ITT population, 2003 dataset)



An addendum to the main clinical study report was produced in July 2008 assessed follow-up data to March 2007. The overall survival and disease-free survival data from 2006 and 2007 demonstrated that the survival curves remained apart with extended follow-up, confirming the conclusions of the 2003 data. The comparability of the overall survival analysis data for the 2006 and 2007 dataset findings are summarised in Table 4. In the final 2007 dataset, the median survival of patients alive at last follow up was 7.9 years. The consistency of the early findings with those in the mature dataset, confirm that a sustainable survival benefit is associated with MEPACT treatment.

Table 4: Summary of overall survival analyses for the 2006 and 2007 datasets (ITT population)

Variable	Patients (events)	P-value	Hazard Ratio	95% CI for HR
2006 dataset				
No MEPACT (A/B)	340 (100)	---	1.00	---
MEPACT (A+/B+)	338 (73)	0.0352[1]	0.72	(0.53, 0.98)
2007 dataset				
No MEPACT (A/B)	340 (100)	---	1.00	---
MEPACT (A+/B+)	338 (73)	0.0313[1]	0.72	(0.53, 0.97)

[1]from log-rank test stratified by ifosfamide use and randomisation strata.

In subgroup analyses of survival based on the intention-to-treat population, hazard ratios for subgroups based on gender, age, ethnicity, study site, geographic location, tumour size, lactate dehydrogenase/alkaline phosphatase level, cooperative study group (Children's Cancer Group or Pediatric Oncology Group) and background chemotherapy (3 or 4-agent) favoured MEPACT treatment (<1.0). These exploratory findings confirm the robustness and consistency of the findings across the study population. Only one subgroup of patients (>16 years) did not show a benefit for MEPACT treatment.

6.4.4 Study events

At the time of the final dataset (March 2007), 73 patients in the MEPACT group had died compared with 100 patients in the no MEPACT group.

The numbers of patients undergoing disease recurrence following adjuvant chemotherapy with or without MEPACT, detailing site of recurrence, are summarised in Table 5. Most patients in both treatment groups experienced disease recurrence at pulmonary and other (pleural, regional, radiation field, mediastinal, lymph node) sites.

Table 5: Summary of site of disease recurrence following adjuvant therapy (ITT population, 2007 dataset)

Site of recurrence	No MEPACT (N=303) n (%)	MEPACT (N=301) n (%)
Number of patients with disease recurrence	100	78
New pulmonary metastases	47 (47)	41 (53)
New bone metastases	7 (7)	8 (10)
Primary disease site	12 (12)	3 (4)
Other	37 (37)	26 (33)

6.5 Meta-analysis

The data from the group of patients with metastatic or non-resectable disease (non-intention-to-treat) further supports the efficacy findings for MEPACT, and the two groups have been analysed together for comparison with population-based data. There is a consistent, favourable survival benefit across patient groups (non-metastatic, metastatic, all patients) with a reduction in the risk of death of about 30%.

6.6 Indirect/mixed treatment comparisons

Data from the head-to-head RCT was used for the reference-case analysis. Informal (without statistical analysis), indirect comparison of osteosarcoma treatment regimens was identified in six review articles[14,10,2,85,13,35,2]. These reports do not add to the data and are not discussed further.

6.7 Safety

6.7.1 MEPACT alone

Adverse events at all severity grades were recorded in numerous Phase I and II studies. As a result MEPACT has been extensively investigated in over 700

patients and is generally well tolerated. Clinical effects resulting from the MEPACT induced activation of monocytes and macrophages are mild to moderate and similar to those seen with naturally occurring infection. The most frequent adverse events reported in patients and healthy subjects treated with MEPACT alone were fever, chills, fatigue, headache, nausea/vomiting, myalgia and tachycardia, hypotension, hypertension and dyspnoea. During Phase I and II monotherapy studies chills occurred in 89% of patients and fever in 85%; in the Phase II osteosarcoma study chills occurred in 96% of patients and pyrexia in 98%. Such events are typically mild to moderate and easily managed with paracetamol or acetaminophen, without compromising treatment efficacy. They were typically reported minutes to hours following infusion, were transient and did not require medical intervention. The maximum tolerated dose for MEPACT was defined as 4-6mg/m^2, to ensure that such events did not exceed Grade 2 severity.

6.7.2 MEPACT in conjunction with chemotherapy

The toxicity profile of MEPACT when administered in conjunction with 3- or 4-arm chemotherapy was considered in study INT-0133. Only Grade 3 and 4 severity events were recorded, this being consistent with paediatric cooperative group practices, published studies and the intent to administer MEPACT at below the maximum tolerated dose. Overall, the addition of MEPACT to 3- or 4-agent chemotherapy in study INT-0133 did not result in a detectable exaggeration of chemotherapy side effects.

To enable MEPACT-associated side effects to be distinguished from those attributable to chemotherapy components, the difference in the incidence of adverse events was compared between patients who received MEPACT and those who did not. Grade 3 and 4 adverse events where the addition of MEPACT to chemotherapy significantly increased incidence comprised objective (11.5% with MEPACT vs. 7.1% without, p=0.047) and subjective (3.6% vs. 0.6%, p=0.007) hearing loss. However the association between hearing loss and the study treatment was lost on comparison of the incidence of events in the individual MEPACT treatment groups; specifically the incidence of auditory problems was lower in patients treated with 4-arm

chemotherapy plus MEPACT than in those treated with 4-arm chemotherapy alone. Ototoxicity is commonly associated with cisplatin therapy, and the frequency of hearing loss reported for patients treated with MEPACT was within the range expected for cisplatin alone. Other toxicities associated with chemotherapy components did not occur at a notably higher incidence in patients receiving add-on MEPACT dosing.

In contrast patients receiving MEPACT were significantly less likely to experience a Grade 3 or 4 reduction in creatinine clearance rate (0.6% vs. 4.1% of patients not receiving the study drug, p=0.004). In addition, though MEPACT administration is known to be associated with hypotension the incidence of Grade 3 or 4 hypotension was lower in patients receiving MEPACT (0.3% vs. 2.1%) though the difference did not achieve statistical significance (p=0.069).

Pleural and pericardial effusions were identified in two patients in study INT-0133. Pleural effusion is also seen in chronic autoimmune disease and could be associated with the immune stimulation cause by MEPACT. Occasional reports of breathing difficulty, chest pain, chest discomfort and/or abnormal radiologic findings may be related phenomena. In patients with microscopic pulmonary lesions, sudden macrophage and monocyte activation could cause oedema in the lesion and surrounding pulmonary vascular bed leading to cough, dyspnoea and chest discomfort. The constellation of such symptoms should be recognised as a moderately rare but potentially significant adverse event associated with MEPACT. Abnormal radiological signs are consistent with the earlier findings of fibrosis and immune infiltrates in areas of metastatic osteosarcoma following MEPACT administration.

Allergic reaction, primarily skin rash, occurred in a few patients. These were typically not life-threatening; one instance of Grade 4 allergic reaction was recorded but appears to have been transient Grade 4 hypertension. It may be difficult to distinguish true allergic reactions from exaggerated inflammatory responses.

6.8 Non-RCT evidence

Non-RCT evidence was not assessed for this evidence submission.

6.9 Interpretation of clinical evidence

6.9.1 Provide a brief statement of the relevance of the evidence base to the decision problem. Include discussion of the relevance of the outcomes assessed in clinical trials to the clinical benefits experienced by patients in practice.

The data from study INT-0133 demonstrate that patients with newly diagnosed non-metastatic high-grade resectable osteosarcoma experience improved outcomes when MEPACT is added to a 3- or 4-agent chemotherapy. The 6-year survival probability was 77% in patients who received MEPACT compared with 66% in patients who did not. This translates to a long-term survival benefit for 10 additional patients of every 100 treated. Such a level of benefit is particularly important given the huge unmet medical need and the lack of progress in improving outcome for osteosarcoma patients over the last 20 years.

The first analysis of intermediate endpoints, showed improved outcome for patients receiving MEPACT in terms of both overall survival (p=0.018) and disease-free survival (p=0.025). In subsequent follow-up analyses, using the final and complete 2007 data, the survival benefit continued to be significant and consistent. The most important evidence for the efficacy of MEPACT in osteosarcoma patients is prolongation of survival. An improvement in overall survival is the gold-standard endpoint for a new osteosarcoma drug, showing unquestionable clinical benefit for the paediatric patient.

6.9.2 Identify factors that may influence the applicability of study results to patients in routine clinical practice; for example, how the technology was used in the trial, issues relating to the conduct of the trial compared with clinical practice, or the choice of eligible patients. State any criteria that would be used in clinical practice to select suitable patients based on the evidence submitted. What proportion of the evidence

base is for the dose(s) given in the Summary of Product Characteristics?

MEPACT administration in the RCT was as add-on therapy to currently favoured 3- and 4-arm chemotherapy regimens. The chemotherapy regimens used in the trial are comparable to those being studied in the ongoing EURAMOS trial. The MEPACT dosing regimen used in the study is consistent with that specified in the Summary of Product Characteristics.

The clinical trial data supporting this submission relate to the use of MEPACT in patients with high-grade, non-metastatic, resectable osteosarcoma. Survival benefit has been demonstrated for all such patients with the greatest benefit being seen in patients treated with the 4-arm chemotherapy regimen plus MEPACT. Some pre-clinical findings have suggested a mechanism by which MEPACT and ifosfamide might act synergistically against osteosarcoma lesions: MEPACT activates the production of the cytokine interleukin 12, which in turn induces expression of the cell surface molecule Fas on osteosarcoma cells; Alkylating agents such as ifosfamide up-regulate the expression of Fas ligand on osteosarcoma cells. The concurrent up-regulation of both cell surface Fas and Fas ligand enhances their interaction, which activates apoptotic pathways leading to cell death[2,81]. As ifosfamide is proposed as a potential dose-intensification agent for adjuvant therapy in patients with a poor histological response to neoadjuvant therapy, co-administration of MEPACT may help to increase treatment benefits for these patients.

7 Cost effectiveness

7.1 Published cost-effectiveness evaluations

7.1.1 Identification of studies

A systematic review was undertaken to identify any existing published cost-effectiveness evaluations for this ultra-orphan disease indication. No economic evidence was identified. Details of the search strategy used are presented in Section 10.3.

An additional search of Medline for English language studies assessing quality of life and/or functional outcomes in osteosarcoma, lower extremity bone tumours or bone sarcomas published between 1990-2008 was conducted. This was supplemented by identification of papers cited in relevant studies. In addition, the York NHS EED and HTA database (accessed via the CRD website), the Tufts University Register of cost-effectiveness analyses and NICE website were also searched to identify utility studies (Section 10.3.6).

7.1.2 Description of identified studies

No studies were identified that addressed the cost-effectiveness of interventions for osteosarcoma or other lower extremity cancers in children. Utility is a key cost-effectiveness outcome measure for UK health technology assessments. However, there are also no published assessments of utility outcomes for osteosarcoma or lower extremity cancer health states or treatments.

No evidence was found for disease specific quality of life outcomes associated with osteosarcoma disease states such as recurrence or disease progression. The evidence for quality of life outcomes has focussed on long-term outcomes for osteosarcoma survivors akin to the off-treatment disease-free state, accounting for the impact of surgery. The evidence suggests that amputation or other surgery may be associated with a small detrimental impact on quality of life initially but that amputation does not necessarily mean significantly reduced overall quality of life. The conclusion is that survivors of

osteosarcoma can lead relatively normal lives across all aspects, including employment, home and social affairs. This means that there is support for a scenario in which the health utility is not considered lower for patients with amputation versus limb-salvage surgery, especially in the long-term (Section 7.2.8).

7.2 De novo economic evaluation(s)

An economic evaluation was undertaken to assess the cost-effectiveness of adding MEPACT to 3 and 4-agent chemotherapy regimens combining cisplatin, doxorubicin and methotrexate with or without ifosfamide. The reference case is described in Table 6.

Table 6: Description of the reference case

Aspect of Reference Case	Description
Technology MEPACT	MEPACT is to be given concomitantly in combination with 3- or 4-agent chemotherapy (combining high-dose methotrexate, doxorubicin and cisplatin) with or without ifosfamide.
Population	Newly diagnosed, resectable, non-metastatic osteosarcoma in children, adolescents and young adults.
Model horizon	A 12.25 years model horizon has been chosen. Cost-effectiveness could be considered within a framework of certainty as the results of the clinical trial could be used. However this is considered a highly conservative approach, as a differential mortality effect between the MEPACT and comparator arm persists at the end of 12.25 years. Thus, although costs are mostly incurred in the short term, the full-life gain and utility benefits have not been realised.
Comparator	Combination with 3- or 4-agent chemotherapy (high-dose methotrexate, doxorubicin and cisplatin with or without ifosfamide). The 3-agent regimen is most commonly used in the UK and both regimens are used in the EURAMOS 1 trial (Section 4.5).
Dosing schedule	A total of 48 infusions given; twice weekly for 12 weeks, with dosing at least 3 days apart, followed by once weekly for an additional 24 weeks.
Outcome	Incremental Cost/QALY
Discounting	3.5% for costs and benefits
Perspective	NHS

The reference case considers a time horizon of 12.25 years, which is the follow-up duration for study INT-0133 from commencement of the maintenance phase. The INT-0133 clinical trial data has been used in the economic model to support the estimates of cost-effectiveness. For cancer treatments to assess the impact on survival, a lifetime horizon could be

adopted to take full account of the differential mortality effect between intervention and comparator. However a shorter time horizon was chosen for the reference case, so that cost-effectiveness was assessed based only on observed clinical trial data. This has the effect of decreasing uncertainty but produces cost-effectiveness estimates for MEPACT that are conservative. Therefore, cost-effectiveness results are also presented for two longer-term horizons (20 and 40 years) as scenario analyses.

7.2.1 Technology

7.2.1.1 How is the technology used within the economic evaluation? For example, give indications, and list concomitant treatments, doses, frequency and duration of use.

The proposed dose of MEPACT for all patients is 2mg/m^2. MEPACT is to be administered for 36 weeks as add-on treatment to adjuvant chemotherapy following tumour resection. A total of 48 infusions are to be given; twice weekly for 12 weeks, with dosing at least 3 days apart, followed by once weekly treatment for an additional 24 weeks. MEPACT is to be infused intravenously over 1 hour. MEPACT is to be given concomitantly in combination with 3- or 4-agent chemotherapy (combining high-dose methotrexate, doxorubicin and cisplatin with or without ifosfamide).

The indication for MEPACT is for the treatment of newly diagnosed, resectable, non-metastatic osteosarcoma in children, adolescents and young adults.

7.2.1.2 Has a treatment continuation rule been assumed? Where the rule is not stated in the SmPC this should be presented as a separate scenario, by considering it as an additional treatment strategy alongside the base-case interventions and comparators.

No treatment continuation rule has been assumed. MEPACT therapy is to be terminated after a maximum of 48 doses.

7.2.2 Patients

7.2.2.1 What group of patients is included in the economic evaluation? Do

they reflect the licensed indication? If not, how and why are there differences? What are the implications of this for the relevance of the evidence base to the specification of the decision problem?

The osteosarcoma patients included in the economic evaluation are ≤30 years, reflecting the licensed indication.

7.2.2.2 Was the analysis carried out for any subgroups of patients? If so, how were these subgroups identified? If subgroups are based on differences in relative treatment effect, what clinical information is there to support the biological plausibility of this approach? For subgroups based on differences in baseline risk of specific outcomes, how were the data to quantify this identified? How was the statistical analysis undertaken?

No subgroup analyses were carried out.

7.2.2.3 Were any obvious subgroups not considered? If so, which ones, and why were they not considered? Refer to the subgroups identified in the scope.

The three subgroups identified in the scoping document were not considered in this submission, as they are not within the proposed marketing authorisation. The subgroups comprise:

- Individuals with osteosarcoma related to Paget's disease.
- Individuals with metastatic osteosarcoma.
- Individuals with relapsed osteosarcoma.

7.2.2.4 At what points do patients 'enter' and 'exit' the evaluation? Do these points differ between treatment regimens? If so, how and why?

Patients enter the evaluation on commencement of adjuvant chemotherapy, i.e. after neoadjuvant treatment and surgical resection. For the reference case, patients exit the evaluation either at the time of death or 12.25 years after follow-up. The evaluation entry and exit points do not differ between treatment regimens. Patients are also evaluated for 20 and 40 years extended follow up.

7.2.3 Comparator technology

What comparators were used and why were they chosen?

The comparator was post-operative 3-agent chemotherapy (including methotrexate, doxorubin, cisplatin) with or without ifosfamide. This treatment regimen is currently used in the UK.

7.2.4 Study perspective

The study employs an NHS perspective.

7.2.5 Time horizon

What time horizon was used in the analysis, and what was the justification for this choice?

The time horizon chosen was 12.25 years corresponding to the follow-up duration of study INT-0133, to allow cost-effectiveness to be assessed on observed data only. However, this is a conservative approach, as a differential mortality effect between MEPACT and the comparator will persists beyond 12.25 years. Thus although costs are mostly incurred in the short term, the full-life gain and utility benefits have not been realised. As MEPACT is indicated for children, adolescents and young adults with the potential for a long life expectancy, clinical experts considered it important to consider longer time horizons. Therefore, the economic evaluation also considers additional time horizons of 20 and 40 years as scenario analyses.

7.2.6 Framework

a) Model-based evaluations

7.2.6.1 Please provide the following.

- A description of the model type.
- A schematic of the model. For models based on health states, direction(s) of travel should be indicated on the schematic on all transition pathways.
- A list of all variables that includes their value, range (distribution) and source.
- A separate list of all assumptions and a justification for each assumption.

The economic model built in TreeAge Pro 2008 software is based on a Markov process with six health states. The first cycle length is of 9-months duration to reflect the maintenance phase, where all patients receive adjuvant chemotherapy with or without MEPACT. The cycles thereafter are of 6-months duration. The Disease-Free and Disease-Progression health states are starting health states and cycle 1 in these health states represents the maintenance phase. Most patients start in the Disease-Free health state (Section 10.5, Table 29). Figure 6 represents a schematic of the model indicating the possible transition pathways between health states, with descriptions of the states presented in Table 7.

Figure 6 Health states used for economic modelling

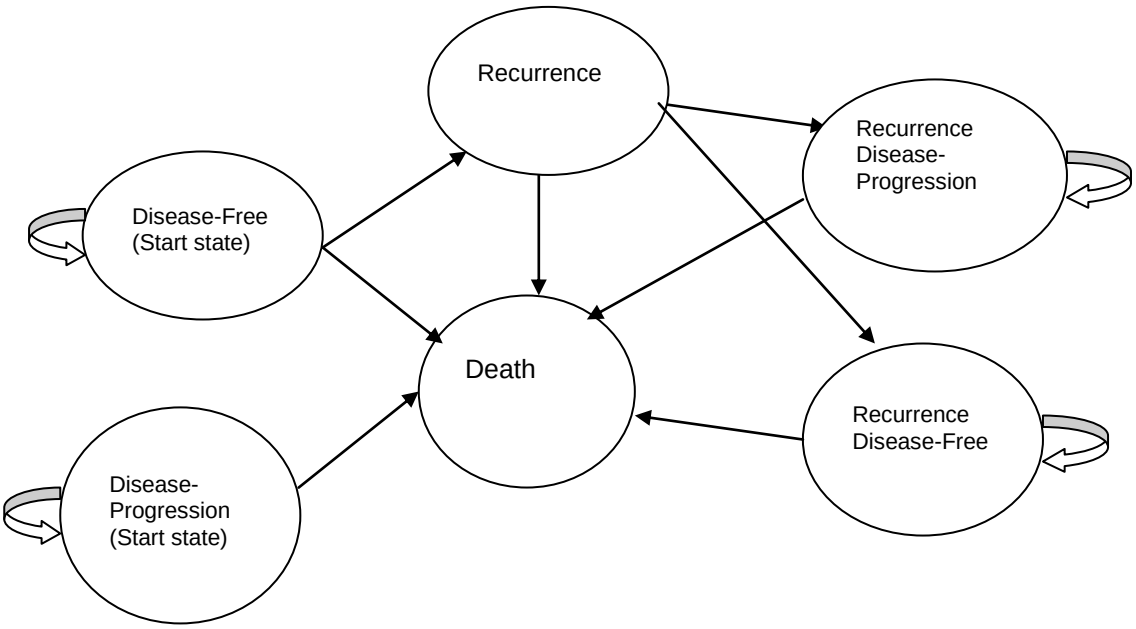


Table 7: Description of the health states used for modelling

State	State Description
Disease-Progression (starting state)	Cycle 1: Evidence of disease via post-surgical pathological assessment i.e. not free of gross or microscopic disease. Cycle 1 corresponds to the maintenance phase where patients receive adjuvant chemotherapy with or without MEPACT. All other cycles: Evidence of disease via routine monitoring or when monitoring was clinically indicated.
Disease-Free (starting state)	Cycle 1: No evidence of disease via post-surgical pathological assessment i.e. free of gross or microscopic disease. Cycle 1 corresponds to the maintenance phase where patients receive adjuvant chemotherapy with or without MEPACT. All other cycles: No evidence of disease via routine monitoring of disease status or when monitoring was clinically indicated.
Death	Death of patient.
Recurrence	A relapse of osteosarcoma, conditional on a patient having no evidence of disease prior to recurrence. Patients remain in this health state for 1-cycle.
Recurrence: Disease-Free	No evidence of disease post-recurrence. (Note, this information is based on literature estimates, as disease status post-recurrence was not collected in INT-0133) This state is set up as a tunnel state with 23 temporary states to accommodate cycle dependent monitoring costs
Recurrence: Disease-Progression	Evidence of disease post-recurrence. (Note, this information is based on literature estimates, as disease status post-recurrence was not collected in INT-0133 This state is set up as a tunnel state with three temporary states.

Table 8 lists variables used in the model. Assumptions regarding resource utilisation and unit costs can be found in the Section 10.5.

Table 8: Variables used in the model

Variable Name	Description	Value	Range
C_2nd_chemo_cycle	Cost of second-line chemotherapy cycle	1636	
C_AE_hearing	Cost of hearing AE (cycle 1)	50	
C_AE_infus	Cost of infusion reaction AE (cycle 1)	1.91	
C_catheter	Cost of central line insertion	2281	
C_chemo_A	Cost of adjuvant chemotherapy regimen A	26832	
C_chemo_B	Cost of adjuvant chemo regimen B	31181	
C_ct_scan	Cost of CT scan	100	
C_isotope_scan	Cost of bone isotope scan	183	
C_mepact_dose	Cost of a MEPACT dose	2375	
C_mepact_outvisit	Cost of an outpatient visit for MEPACT dosing	189	
C_MRI	Cost of MRI scan	278	
C_NHS_palliative_care	Cost of NHS palliative care	3403	
C_other_pulm_surg	Cost of other non-pulmonary surgery only	6168	
C_outpat	Cost of outpatient visit - no treatment	189	
C_palliative_care	Cost of all palliative care (33% added) for hospice care provided by voluntary/charity	5105	
C_pharm_time	Cost of pharmacy time to prepare a MEPACT dose	50	
C_pulm_surg	Cost of pulmonary surgery	5426	
du_hearing_loss	Disutility associated with hearing loss	0.18	
du_hearing_loss_mainten	Disutility for hearing loss in maintenance phase	0	
du_limb_salvage	Disutility associated with limb-salvage	0	
initial_lifegain	Life gain in first cycle of 9 months	0.75	
Lifegain	Life gain for cycle 2 onwards 6 months	0.5	
no_2nd_chemo_cycles	Number of second-line chemotherapy cycles	5	4-10
no_mepact_doses	Number of MEPACT doses	48	36-48
P_AE_hearing_MEPACT	Probability of hearing loss AE MEPACT	0.15	
P_AE_hearing_NOMEPACT	Probability of hearing AE NOMEPACT	0.8	
P_AE_infus_MEPACT	Probability of infusion AE MEPACT	0.98	
p_AE_infus_NOMEPACT	Probability of an infusion AE No MEPACT	0	
p_limbsalvage	Proportion of patients in UK with limb-salvage	0.75	
p_mepact_outvisit	Proportion of outpatient visits required for MEPACT	0.3	0-0.3
p_recur_lungmets	Probability of recurrence with lung metastases	0.5	0.75
p_startdiseasefree_MEPACT	Proportion of patients starting in DF state	0.983498	
p_startdiseasefree_NOMEPACT	Proportion starting in DF No MEPACT	0.993355	
p_startdisease_MEPACT	Proportion of patients starting in DP state	0.016502	
p_startdisease_NOMEPACT	Proportion starting in DP with NO MEPACT	0.006645	
u_death	Utility for death	0	
u_disease	Utility for disease-progression	0.39	0.22
u_diseasefree	Utility for disease-free state	0.75	
u_maintain	Utility for maintenance phase (cycle 1)	0	0.20
u_postrecurr_disease	Utility post-recurrence disease-progression	0.39	0.22
u_postrecurr_disease_free	Utility post-recurrence DF	0.75	
u_recurrence	Utility for recurrence	0.61	0.22

7.2.6.2 Why was this particular type of model used?

A Markov process was used to represent the important changing and recurring events for osteosarcoma patients over time, and to accommodate the change in utilities associated with the different health states.

7.2.6.3 What was the justification for the chosen structure? How was the course of the disease/condition represented? Please state why any possible other structures were rejected.

The chosen states: Disease-Progression, Disease-Free, Death, Recurrence, Recurrence: Disease-Free and Recurrence: Disease-Progression were considered to best represent the disease pathway and to differentiate disease stages in terms of costs, clinical effect and patient utility. The clinical data supported the computation of transition probabilities between the relevant states.

The initial plan to include five states in the model was rejected, as the clinical data did not support an estimation of Recurrence $\rightarrow$ Disease-Progression and Recurrence $\rightarrow$ Disease-Free. Patients who experienced a recurrence in study INT-0133 were not routinely followed up for disease status but only for death and withdrawal from study. The clinical literature reports that the risk of survival post-recurrence is dependent on the site of recurrence, and that site is a determinant for achievement of disease-free status and survival post-recurrence. In study INT-0133 patients experiencing recurrence who were lost to follow up were reported as withdrawals. As the literature indicates the risk of death post-recurrence to be different for patients achieving disease-free or non-disease free status, it was considered important to factor literature findings into the model. Therefore, two additional states were added to the model Recurrence: Disease-Free and Recurrence: Disease-Progression

7.2.6.4 What were the sources of information used to develop and inform the structure of the model?

The clinical estimates (the transition probabilities) were derived from study INT-0133 and the post-recurrence estimates were most derived from the literature, except in the case where death was recorded as an event post

recurrence. The utility estimates were taken from an EQ 5D survey of UK patients with osteosarcoma, supplemented by utility estimates for other oncology indications. Resource utilisation was derived from a combination of sources: Information pertaining to the model assumptions and resource utilisation is presented in Section 10.5.

7.2.6.5 Does the model structure reflect all essential features of the condition that are relevant to the decision problem? If not, why not?

Cost-effectiveness is considered within a framework of certainty based on observed results from clinical trial. However this is considered a conservative approach, as a differential mortality effect between the MEPACT and comparator arm is still seen at the end of 12.25 years. Thus, although costs are mostly incurred in the short term, the full-life gain and utility benefits have not been realised. Hence, results based on this time horizon provide an estimate of the minimum cost-effectiveness outcome potential for MEPACT.

7.2.6.6 For discrete time models, what was the model's cycle length, and why was this length chosen? Does this length reflect a minimum time over which the pathology or symptoms of a disease could differ? If not, why not?

A 6-month cycle length was chosen as this was judged to be of clinical relevance and to reflect a time period over which the pathology of the disease could differ.

7.2.6.7 Was a half-cycle correction used in the model? If not, why not?

No. The functionality within TreeAge PRO to perform half-cycle correction was not considered appropriate, as it neither accommodates incremental rewards, which vary by cycle, nor varying cycle lengths. Discussions with TreeAge Pro (personal communication Andrew Munzer) confirmed that it would be inappropriate to use the functionality in this case and to attempt manual programming could lead to flaws and errors in the model. It is acknowledged that the consequence of not being able to implement this would lead to an overestimate of total costs, as the majority of costs are incurred in the first cycle.

7.2.6.8 Are costs and clinical outcomes extrapolated beyond the trial follow-up periods? If so, what are the assumptions that underpin this extrapolation and how are they justified? In particular, what assumption was used about the longer-term difference in effectiveness between the technology and its comparator?

For the reference case using a 12.25 year time horizon, costs and clinical outcomes are not extrapolated but are only taken from study INT-0133. For the 20 and 40 year extended time horizons, the reference case model was used and patients remaining in the disease-free health-state at the end of 12.25 years were assumed to remain in the that state for a further 20 and 40 years. Expert opinion advised that if patients are disease-free after 5-6 years it is likely that they will remain disease-free for the duration of their lifetime.

b) Non-model-based economic evaluations

7.2.6.9 Was the evaluation based on patient-level economic data from a clinical trial or trials?

Yes, the evaluation is based on patient-level clinical data from trial INT-0133 which follows patients for 12.25 years post-commencement of maintenance treatment.

7.2.6.10 Provide details of the clinical trial, including the rationale for its selection.

Details of the clinical trial can be found in Section 6. The trial was a head-to-head, randomised study comparing add-on MEPACT to 3- or 4-agent adjuvant therapy versus adjuvant chemotherapy alone. The trial was conducted in the US and included 30% of all possible osteosarcoma patients diagnosed.

7.2.6.11 Were data complete for all patients included in the trial? If not, what were the methods employed for dealing with missing data for costs and health outcomes?

Data were not complete for those patients who withdrew from the study. Patients who withdrew in the Disease-Progression state were assumed to remain in this state. Patients who withdrew in the Disease-Free state were

assumed to be reallocated to either the Disease-Free state or the Recurrence state (as described in Section 10.5.9).

Section 10.5, Table 34 presents an overview of patient status for each 6-month cycle (cycle 1 of 9-months duration) from the commencement of maintenance therapy. For patients who withdrew after recurrence, literature estimates were used to model overall survival and disease-free patterns as described in Section 10.5.9.

7.2.6.12 Were all relevant economic data collected for all patients in the trial? If some data (for example, resource-use or health-related utility data) were collected for a subgroup of patients in the trial, was this subgroup prespecified and how was it identified? How do the baseline characteristics and effectiveness results of the subgroup differ from those of the full trial population? How were the data extrapolated to a full trial sample?

No. Utility data and resource use data were not collected in the trial. UK resource use was advised by clinical experts. Utility data was collected from a subgroup of UK patients, who were survivors of osteosarcoma from a single centre in the UK and the methodology is described in Section 7.2.8.3. This patient group was assumed to adequately represent the trial population.

7.2.6.13 Are costs and clinical outcomes extrapolated beyond the trial follow-up period? If so, what are the assumptions that underpin this extrapolation and how are they justified? In particular, what assumption was used about any longer-term differences in effectiveness between the technology and its comparator?

Costs and clinical outcomes are not extrapolated beyond the trial follow-up periods for the reference case. For the analyses assessing 20 and 40 year follow-up horizons the costs and utilities for the Disease-Free state, in which patients were assumed to remain, were computed based on the time dependent cycle costs and utilities for the reference case. Costs and outcomes were discounted over the relevant time horizon.

7.2.7 Clinical evidence

7.2.7.1 How was the baseline risk of disease progression estimated? Also state which treatment strategy represents the baseline.

The baseline risk was assessed by considering the evidence of disease via post-surgical pathologic assessment, i.e. free/not free of gross or microscopic disease prior to MEPACT administration. Starting states reflected whether or not patients had evidence of disease prior to MEPACT administration, however few patients commenced treatment in the Disease-Progression state.

7.2.7.2 How were the relative risks of disease progression estimated?

Disease progression was assessed based on the clinical data for each 6-month cycle for the MEPACT and no-MEPACT treatment groups. State transition probabilities were then computed and used in the model to assess disease progression for each treatment group.

7.2.7.3 Were intermediate outcome measures linked to final outcomes (such as patient survival and quality-adjusted life years [QALYs])? If so, how was this relationship estimated, what sources of evidence were used, and what evidence is there to support it?

Yes. A 6-month life gain was assumed when a patient entered the Disease-Free, Disease-Progression, Recurrence, Recurrence: Disease-Free, or Recurrence: Disease-Progression state. Utilities were computed for each health state and additionally at cycle 1 for the two starting health states. QALYs were then computed for each cycle spent in a particular state and accumulated over the model horizon, and were discounted at a rate of 3.5%. Information regarding the estimation and collection of the utilities for each state are outlined in Section 7.2.8.

7.2.7.4 Were the health effects or adverse effects associated with the technology included in the economic evaluation? If not, would their inclusion increase or decrease the estimated cost effectiveness of this technology?

Adverse events considered clinically relevant and with a higher incidence in the MEPACT arm were included in the reference case. Such events included Grade 1 and 2 infusion reactions such as fevers and chills.

Clinical expert opinion considered the higher incidence of hearing loss in the MEPACT group as a data anomaly, as hearing loss is associated with cisplatin use and the rates in the trial were consistent with those reported for cisplatin. Hearing loss has, therefore, not been included in the reference case but is explored in a sensitivity analysis (as hearing loss objective or subjective: MEPACT 15%, No-MEPACT 8% [INT-0133]).

7.2.7.5 Was expert opinion used to estimate any clinical parameters? If so, how were the experts identified, to which variables did this apply, and what was the method of elicitation used?

Yes, expert opinion was used to assess resource utilisation and the handling of follow up. As osteosarcoma is an ultra-orphan disease the number of UK experts is limited. Experts were identified from interactions with the CHMP, with Dr. Ian Lewis acting as the key advisor on this submission (Dr. Ian Lewis, Deputy Medical Director, Leeds Teaching Hospitals NHS Trust and Clinical Lead for Children)

7.2.7.6 What remaining assumptions regarding clinical evidence were made? Why are they considered to be reasonable?

It was assumed that patients receiving MEPACT would not always receive the full treatment course. Table 2 suggests that patients on average receive approximately 36-40 doses, and the use of 36-48 doses was explored in a sensitivity analysis.

To explore the impact of using a longer term horizon than that defined for the reference case, a sensitivity analysis was undertaken to assess the cost-effectiveness of 20-year and 40-year extended horizons. It was assumed that

patients who remained in the Disease-Free state at the end of the reference time horizon (12.25 years) would remain disease-free in the long-term. The same annual monitoring costs and utilities were assumed for the disease-free state and both costs and QALYs were discounted over the 20- and 40-year time intervals respectively (Table 9).

Table 9: Discounts assumed for 20- and 40-year time horizons

Extended Time Horizon	**Treatment**	**Additional Discounted QALY**	***Additional Discounted Monitoring Costs £***
20-years	MEPACT	7.7	*1706*
20-years	NO MEPACT	6.9	*1706*
40-years	MEPACT	11.5	*2564*
40-years	NO MEPACT	10.4	2564

Details of all assumptions are presented in Section 10.5.

7.2.8 Measurement and valuation of health effects

7.2.8.1 If health effects were not expressed using QALYs, what health outcome measure was used and what was the justification for this approach?

QALYs are presented.

7.2.8.2 Which health effects were measured and valued? Health effects include both those that have a positive impact and those with a negative impact, such as adverse events.

Two sets of health effects were measured and valued:

a) Utilities were estimated for the following osteosarcoma health states corresponding to those used in the economic model: with the initial state corresponding to patients receiving post-operative maintenance chemotherapy and in disease-free state, disease-progression (to death) state, recurrence, recurrence/disease-free state, recurrence / disease-progression state or death.

b) The disutility associated with hearing loss, which was identified as having a higher incidence in the MEPACT arm of trial INT-0133

compared with the post-operative 3-agent multi-agent chemotherapy alone arm. However, as this adverse event was considered by expert opinion unlikely to be related to MEPACT the disutility was applied only in sensitivity analysis.

7.2.8.3 How were health effects measured and valued? Consideration should be given to all of the following:

Background

The issue of quality of life outcome in patients with osteosarcoma is complex, multifactorial and closely linked to the type of surgery that patients receive. There has been little direct attention given to quality of life issues related to chemotherapy and its side effects, and research covering this area has focussed on long-term post-treatment outcomes associated with surgery and chemotherapy.

From the evidence available it can be assumed that good long-term quality of life and physical/social functioning can be achieved in survivors of osteosarcoma and other bone tumours. In addition, long-term quality of life is not necessarily worse for amputees compared with those receiving limb-salvage surgery. The overall picture is likely to be more complex than identified in studies using generic quality of life instruments (Section 7.1.2). These studies were generally too small to be conclusive and use generic quality of life scores not suited to assessing children[52,21]. They often do not consider aspects such as the psychological impact of failed limb-salvage surgery, issues over body image related to surgery, or the impact of phantom limb pain on quality of life for amputees [52,101]. One study in Israel in 18 bone sarcoma patients, concluded that amputation was a worthwhile procedure as quality of life was significantly improved in two thirds of patients and no cases of severe phantom pain were reported[102]. In general psychological factors have been under-investigated, and it seems that the greatest long-term coping challenges faced by survivors are associated with emotional adjustment, especially for those who have undergone amputation.

Despite limitations, the evidence shows that patients surviving osteosarcoma can have a good long-term quality of life and do not suffer excess

socioeconomic disadvantage in adult life, despite having had major limb surgery.

In terms of utility-based measures The INT 0133 trial did not include a generic utility measure such as the EQ 5D, nor did it contain a disease specific HRQoL instrument to enable mapping to EQ 5D domains.

In addition, a literature search did not identify any utility estimates specifically for osteosarcoma related health states (Section 7.1.1 and 7.1.2).

In the absence of trial-based or published estimates, two main sources were used to provide utility estimates for the economic model health states:

1) The primary source was a survey using the EQ 5D conducted in survivors of osteosarcoma from a single UK treatment centre.

2) A review of utilities used in independent economic models developed by the NICE Assessment Group for published or ongoing cancer technology appraisals.

The EQ 5D survey

A questionnaire based survey of osteosarcoma patients treated in a single UK treatment centre (St James Hospital, Leeds) was conducted. Patients were all current survivors of osteosarcoma and were off treatment, although some had recently finished a course of chemotherapy. Questionnaires were completed for 22 patients, as co-ordinated by a research nurse at the treatment centre. The questionnaire consisted of two parts:

Part 1 contained a set of six background questions relating to patient gender, age now, age at diagnosis, whether currently receiving treatment for osteosarcoma, whether the patient had experienced relapse or recurrence, and the type of surgery received (amputation, limb-salvage or other related surgery). The information for this part of the questionnaire was abstracted from patient records.

Part 2 contained the five questions from the EQ 5D instrument and was administered by telephone interview by the research nurse (after training by

an experienced health economist) to patients (n=18) or their parents/caregivers (n=4). Three situations were presented to the patient relating to:

- How the patient feels now (i.e. off treatment, in a disease-free state).
- How the patient recalls feeling in the first 6 months after diagnosis (when they received surgery and adjuvant chemotherapy).
- How the patient recalls feeling at the time the cancer recurred, and a second course of chemotherapy was required.

The average age of patients was 21 (range 9-37 years), with an average age at diagnosis of 12 years (range 6-26 years) and all but two patients aged ≤18 at diagnosis. All patients had received surgery, with the majority undergoing only limb-salvage (typically endoprosthetic replacement), 4 patients had also undergone leg amputation (post-limb-salvage surgery) and 1 had undergone amputation alone. The full details of patient characteristics are provided in Section10.5.10.1, Table 30.

The population-based time trade-off tariff for the EQ 5D was applied to the patient responses to part 2 of the questionnaire. This resulted in a mean utility for the current disease-free health state of 0.753 (SD: 0.178) and of -0.016 (SD: 0.336) for the 6 months post-diagnosis (starting disease state). Both of these estimates were based on the full sample of 22 patients. The mean utility for the disease recurrence scenario was 0.217 (SD: 0.544), but was only completed by the 4 patients who had experienced this disease state and so has low reliability. The mean utility values did not change significantly when the 4 parent/caregiver respondents were excluded: 0.748 for disease-free, 0.035 for the 6 months post-diagnosis).

NICE HTA review

To support the EQ 5D survey a review was conducted of utilities for relevant health states that were applied by the NICE Assessment Groups in independent economic models developed as part of published or ongoing cancer technology appraisals. To be included the utilities had to be clearly reported in the Assessment Group report for the appraisal (each report was

available from the NICE website). Only utilities from independent models were included as these were considered most likely to be robust, and to meet NICE reference case standards. Hence, utilities from cancer single technology appraisals (STAs) were not included.

In total of six NICE technology appraisals met the inclusion criteria, covering the following:

- TA70**-** Imatinib for first-line treatment of chronic myeloid leukaemia in chronic phase. Guidance published October 2003.
- TA100 - Oxaliplatin and capecitabine for adjuvant treatment of colon cancer. Guidance published April 2006.
- TA 101 - Docetaxel in combination with prednisone or prednisolone for the treatment of hormone-refractory metastatic prostate cancer. Guidance published June 2006.
- TA118 - Bevacizumab and cetuximab for the treatment of metastatic colorectal cancer. Guidance published January 2007.
- TA121 - Carmustine implants and temozolomide for the treatment of newly diagnosed high-grade glioma. Guidance published June 2007.
- Ongoing technology appraisal: Bevacizumab, sorafenib, sunitinib and temsirolimus for renal cell carcinoma.

Details of the Assessment Group reports for each of these appraisals are provided in Section 10.5.10.2. None of the appraisals identified considered paediatric cancer and this is, therefore, a limitation when generalising the utilities reported to osteosarcoma. However, utilities were reported for a number of health states that correspond reasonably with those included in the osteosarcoma economic model for this submission. The average utilities from the appraisals for grouped health state categories were: 0.85 for disease-free, 0.69 for disease-progression or recurrence and 0.44 for disease-progression/late phase cancer (to death). Further details on methods used are provided in Section 10.5.10.2 (Tables 31 and 32).

Utilities used in the model

The utilities in Table 10 were selected for the economic model base-case analysis, corresponding to health states in Figure 6 and Table 7. The primary source was intended to be the EQ 5D survey as the data is from patients who have experienced a number of the model disease states and meets the NICE reference case. Gaps were then filled using data from the NICE HTA review, based on a number of approaches used by the Assessment Groups and including use of EQ 5D estimates where available (Section 10.5.10.2, Tables 31 and 32).

The specific base case utilities and rationale for the choice of utility for each health state is also provided in Table 10, with alternative scenarios that were investigated in sensitivity analysis for impact on cost-effectiveness.

Table 10: Utilities for modelling

Disease state	Base case utility	Alternative value	Source/rationale
Initial maintenance phase (cycle 1 only for starting states)	0.0	0.20	EQ 5D survey, with value rounded to zero. Alternative value based on adjustment for the survey covering the first 6 months pre- and post-surgery (covering an induction treatment phase) whereas the model health state starts post operative covering only the maintenance phase
Disease-free	0.75	-	EQ 5D survey. This value is supported by a study in 31 survivors of childhood bone tumours which also reported a value of 0.75 using the HUI3 instrument[103]
Recurrence	0.61	0.22	NICE HTA review. The HTA review provided an estimate of 0.69 for disease-progression/recurrence category. A correction factor of -12% was applied based on the ratio for the average utility for disease-free state in the EQ 5D survey and[103] (0.75) and the disease-free category in the NICE HTA review (0.85). The alternative value is based on four responses from the EQ 5D survey
Disease-progression (to death)	0.39	0.22	NICE HTA review. The HTA review provided an estimate of 0.44 for the disease progression to death category, which was adjusted by the -12% correction factor as above.
Recurrence/ disease-free	0.75	-	Assumed to be the same as disease-free value
Recurrence/ disease-progression	0.39	0.22	Assumed to be the same as disease-progression value
Death	0	-	

The most robust utility value is that for the disease-free state as it is based on the current situation for the 22 patients completing the EQ 5D. This value is supported by the findings of a study reporting HUI3 derived utilities for childhood bone tumours[103]. This study followed up 1005 patients from the childhood cancer registry of Piedmont, Italy who had been diagnosed with cancer >5 years previously, of whom 31 had bone tumours. A mean utility of 0.75 was found for these patients, which compared with utilities for other childhood cancers ranging from 0.73 for CNS tumours to 0.88 for non-Hodgkin lymphoma[103]. The average utility of 0.85 for disease-free states in the NICE HTA review is based on appraisals in adult cancer patients, as none were available for children. A relatively low quality of life for osteosarcoma survivors

could be associated with the additional physical/emotional restrictions that major surgery places on these patients at a young age. The review of quality of life outcomes presented in Section 4.1.4 found evidence that young patients adjust well to these limitations and can have quite good long-term quality of life outcomes[53,69]. However, studies in osteosarcoma and childhood cancer survivors, generally using the SF 36 and HUI instruments found long-term quality of life was lower than the age-based population norms[54,104,105,106].

The utilities include allowance for patients having experienced amputation or limb-salvage surgery. The proportion of patients in the EQ 5D survey with amputation was 18%, which is similar to that expected in the UK for osteosarcoma, and so can be considered representative. The quality of life evidence reported in Section 4.1.4 is generally supportive of an assumption that in the long-term there are limited differences in osteosarcoma patient quality of life, related to whether they had amputation or limb-salvage. It is possible that there may be some differences that impact on quality of life in the short-term. However as the utility associated with the initial disease phase is estimated to be zero, it is assumed no further disutility is experienced by patients having amputation rather than limb-salvage surgery.

AE disutility

From the INT-0133 trial hearing-loss was identified as the main adverse event for MEPACT. The disutility for this is not captured by the health state utilities in Table 10, and hence has been included as an additional disutility factor across the health states for patients experiencing this event. From a Medline search one study was identified that contained a disutility factor of -18% for hearing-loss in cancer patients[107]. This value was assessed in a sensitivity analysis, but not in the reference case as such events were considered to be an anomaly of the data as hearing loss is associated with cisplatin

7.2.8.4 Were any other generic or condition-specific preference based measures used in the clinical trials? Provide a description of the data below. The results should be considered in a sensitivity analysis (see Section 6.2.11).

There were no generic or condition specific preference based measures included in the INT -0133 trial.

7.2.8.5 Were any health effects excluded from the analysis? If so, why were they excluded?

Yes, health effects, such as hypotension and creatinine clearance with a higher incidence in the no MEPACT arm were excluded to take a conservative approach to the evaluation.

7.2.9 Resource identification, measurement and valuation

7.2.9.1 What resources were included in the evaluation? (The list should be comprehensive and as disaggregated as possible.)

A list and details of resources are outlined in Section 10.5 and include those outlined in Table 11.

Table 11: Resources use

Description
Adjuvant chemotherapy, cisplatin, doxorubicin, ifosfamide, methotrexate
Mepact dose Extra pharmacy time to prepare dose Outpatient visit for MEPACT dosing, if required
Paracetamol for treatment of infusion reaction adverse events
Second line chemotherapy with ifosfamide and etoposide, post recurrence
Audiology assessments, hearing aid fittings
X-rays
Central line insertion, after recurrence
At recurrence: Cost of CT scan, bone isotope scanm MRI scan Recurrence: Surgery and inpatient hospitalization
Palliative care
Cost of outpatient visit follow up visits

7.2.9.2 How were the resources measured?

Resource use was assessed within each state in the model and quantified based on both clinical expert opinion and literature estimates.

7.2.9.3 Were the resources measured using the same source(s) of evidence as the baseline and relative risks of disease progression?

Yes, these were measured based on the transition probabilities obtained from study INT-0133, computed separately for MEPACT and no MEPACT arms.

7.2.9.4 Were resources used to treat the disease/condition included for all relevant years (including those following the initial treatment period)? Provide details and a justification for any assumptions that were made (for example, assumptions regarding types of subsequent treatment).

Resource use was specified for all health states and relevant years and cycles. Resource utilisation for certain cycles e.g. Disease-Free was cycle dependent as follow-up visits vary over a time horizon. Resource use assumptions are detailed in Section 10.5.

7.2.9.5 What sources of information were used to value the resources? Were alternative sources of information available? Provide a justification for the preferred source and explain any discrepancies between the alternatives.

NHS References costs 2006-07 and the British National Formulary 56, September 2006 were mostly used to value resources. To evaluate palliative care, resource and costing estimates were taken from the literature as they could not be quantified for this rare disease. Assumptions for palliative care are outlined in Section 10.5.4.2.

7.2.9.6 What is the unit cost (excluding VAT) of the intervention(s) included in the analysis? Does this differ from the (anticipated) acquisition cost reported in section 1? If price discounts are presented in sensitivity analyses provide details of formal agreements regarding the discount including the period over which the discount is agreed and confirmation of national organisations with which the discount has been agreed for the whole of the NHS in England and Wales.

The unit cost for one MEPACT dose is £2,375 with a total cost of £114,000 for a full treatment course of 48 doses. No price discounts are presented.

7.2.9.7 Does the technology require additional infrastructure to be put in place? Provide details of data sources used to inform resource estimates and values.

It is expected that the infrastructure is already in place for the preparation and administration of MEPACT, as MEPACT is usually administered alongside other adjuvant chemotherapy agents in specialised centres with existing infrastructure. Resources are factored in for extra outpatient visits for MEPACT administration when no other adjuvant chemotherapy agents are scheduled. Estimates for these additional outpatient visits are based on study INT-0133 data and UK expert opinion. An additional 30 minutes of pharmacy time has also been factored in for MEPACT preparation.

7.2.9.8 Were the resources measured and valued in a manner consistent with the reference case? If not, how and why do the approaches differ?

Yes

7.2.9.9 Were resource values indexed to the current price year?

All resources have been indexed to 2006-07 prices in line with the NHS Reference costs.

7.2.9.10 Provide details of and a justification for any assumptions that were made in the estimation of resource measurement and valuation.

Detailed assumptions are outlined in the Section 10.5 (Economic Appendix) for all assumptions and justifications used in the estimation of resource measurement and valuation.

7.2.10 Time preferences

Were costs and health benefits discounted at the rates specified in NICE's reference case?

Yes, both were discounted using a rate of 3.5%.

7.2.11 Sensitivity analysis

7.2.11.1 Has the uncertainty around structural assumptions been investigated? Provide details of how this was investigated including a description of alternative scenarios included in the analysis.

The uncertainty surrounding structural assumptions has been assessed by investigating the limitations of the time horizon, within the reference case framework by extending the follow-up period to beyond this horizon.

The scenario analysis considered the cost-effectiveness of MEPACT when extending patient follow by an additional 20 and 40 years, by extrapolating beyond the clinical trial horizon. Patients in the Disease-Free state at the end of the trial period were assumed to remain disease-free for the extended follow up period, based on expert opinion. By extending the horizon to beyond the clinical trial follow-up period, the long-term survival and patient utility benefits are more fully captured. The analysis demonstrated the model to be very sensitive to duration of follow up. When considering the ultra-orphan threshold range of £200,000-£300,000 proposed by NICE, MEPACT is demonstrated to be a highly cost-effective ultra-orphan drug at its proposed acquisition cost. Incremental cost-effective ratios of £92,259 and £68,463 resulted from 20- and 40-year extended follow up, respectively. These ICERs assume that at all patients receive 48 doses at the proposed UK acquisition cost.

7.2.11.2 Which variables were subject to sensitivity analysis? How were they varied and what was the rationale for this?

Table 12 summarises the list of variables that were assessed in a one-way sensitivity analysis, with their ranges:

Table 12: Costing of resources used in the model

Variable Name	Description	Value	Sensitivity Range
C_mepact_dose	Cost of a MEPACT dose ± 25%	£2375	£1781-2969
no_2nd_chemo_cycles	Number of second-line chemotherapy cycles	5	4-10
no_mepact_doses	Number of MEPACT doses	48	36-48*
P_AE_hearing_MEPACT	Probability of hearing loss AE MEPACT	0.15	Not included in reference case
P_AE_hearing_NOMEPACT	Probability of hearing AE NOMEPACT	0.08	Not included in reference case
p_mepact_outvisit	Proportion of outpatient visits required for MEPACT	0.3	0-0.3^
p_recur_lungmets	Probability of recurrence with lung metastases MEPACT	0.5	0.75**
u_disease	Utility for disease progression	0.39	0.22**
u_maintain	Utility for maintenance phase (cycle 1)	0	0.20**
u_postrecurr_disease	Utility post-recurrence disease progression	0.39	0.22**
u_recurrence	Utility for recurrence	0.61	0.22**
Model horizon	Length of follow up	12.25	20, 40 years

*INT-0133
**Literature and utility study (Section 7,2,8)
^INT-0133 and expert opinion

7.2.11.3 Was probabilistic sensitivity analysis (PSA) undertaken? If not, why not? If it was, the distributions and their sources should be clearly stated; including the derivation and value of 'priors'.

No PSA was undertaken for the reference case as the clinical data was not extrapolated beyond the trial horizon, thus minimising the uncertainty around the estimates.

7.2.12 Statistical analysis

7.2.12.1 How were rates or probabilities based on intervals transformed into (transition) probabilities?

To compute transition probabilities from state X to states Y and Z at cycle t, the total number of patients in state X at the beginning of the cycle was considered as the denominator. The transition probabilities were then computed, from the proportion of patients transitioning to state Y and Z, for cycle t+1, from the overall number in state X. Transition states were mutually exclusive.

7.2.12.2 Is there evidence that (transition) probabilities should vary over time for the condition or disease? If so, has this been included in the evaluation? If there is evidence that this is the case, but it has not been included, provide an explanation of why it has been excluded.

The evidence suggests that transition probabilities may vary over time and, because of this, trial data were used to compute the transition probabilities for each 6-month period.

7.2.13 Validity

Model transition cost and effect rewards were checked using Excel for different Markov termination state assumptions. Individual states were assessed by setting the probabilities of entering other states=0 and the resulting total incremental rewards and discounting validated in Excel.

7.3 Results

7.3.1 Base-case analysis

7.3.1.1 What were the results of the base-case analysis?

The reference case results, based on a time horizon of 12.25 years, indicate a cost/QALY of £457,624 based on an incremental effect of 0.26QALYs and an incremental cost of £119,000 as shown in Table 13. Base case results are not based on probabilistic sensitivity analysis.

Table 13: Base-case cost-effectiveness for MEPACT

Strategy	Cost	Incremental Cost	QALY gain	Incremental effect	Cost/QALY	Incremental C/E (ICER)
No MEPACT	£34K		6.419 years		5,237 Cost/QALY	
MEPACT	£153K	£119K	6.679 years	0.260 years	22,855 Cost/QALY	457,624 Cost/QALY

7.3.2 Subgroup analysis

7.3.2.1 What were the results of the subgroup analysis/analyses if conducted?

Subgroup analyses were not conducted.

7.3.3 Sensitivity analyses

7.3.3.1 What were the main findings of the sensitivity analyses?

Sensitivity analysis demonstrated that cost-effectiveness results were most sensitive to the number of MEPACT doses received and the MEPACT acquisition cost, when considering the short-term horizon of 12.25 years.

Hearing loss also impacted on cost-effectiveness, due to the associated disutility. Clinical expert opinion considers hearing loss to be an anomaly of the trial data, as such events are recognised as being associated with cisplatin treatment. No other variable evaluated by sensitivity analysis had an impact on the cost-effectiveness of MEPACT. Table 14 presents the results of the sensitivity analyses.

Table 14: Summary of sensitivity analysis for all variables

Description	Value	Sensitivity Range	Results: Incremental Cost Effectiveness Ratios (ICERs)
Number of MEPACT doses	48	36-48*	Incremental effect: 0.26 to 0.26 ICER: £343,126 to £457,624
Cost of a MEPACT dose	2375	1900-2400	Incremental effect: 0.26 to 0.26 ICER: £348,003 to £567,245
Number of second-line chemo cycles	5	4-10	Incremental effect: 0.26 to 0.26 ICER: £457,571 to £457,890
Palliative care including voluntary/charity hospice costs	3403	5105	Incremental effect: 0.26 ICER: £457,561
Probability of hearing loss MEPACT NO MEPACT	 0.15 0.08	Not included in reference case	Incremental effect: 0.142 ICER: £837214
Proportion of outpatient visits required for MEPACT	0.3	0 to 0.3^	Incremental effect: 0.26 to 0.26 ICER: £447,160 to £457,624
Probability of recurrence with lung metastases MEPACT	0.5	0.75**	Incremental effect: 0.26 ICER: £456,889
Utility for disease progression	0.39	0.22**	Incremental effect: 0.26 ICER: £464,027
Utility for maintenance phase (cycle 1)	0	0.20**	Incremental effect: 0.26 ICER: £457,624
Utility post-recurrence disease progression	0.39	0.22**	Incremental effect: 0.26 ICER: £458,018
Utility for recurrence	0.61	0.22**	Incremental effect: 0.27 ICER: £435,535

7.3.3.2 What are the key drivers of the cost effectiveness results?

The key drivers of cost-effectiveness are the model time horizon, the number of MEPACT doses that a patient receives and the cost of a MEPACT dose. Tables 15-18 present the results of the scenario analysis and the sensitivity analysis results for the latter two drivers:

Table 15: Extrapolation to 20-years beyond the reference case horizon

Strategy	Cost	Incremental cost	QALY gain	Incremental effect	Cost/QALY (£)	Incremental C/E (ICER, £)
No MEPACT	£35K		10.73 years		3,232 Cost/QALY	
MEPACT	£154K	£119K	12.02 years	1.29 years	12,796 Cost/QALY	92,259 Cost/QALY

Table 16: Extrapolation to 40-years beyond the reference case horizon

Strategy	Cost	Incremental cost	QALY gain	Incremental effect	Cost/QALY (£)	Incremental C/E (ICER, £)
No MEPACT	£35K		12.92 years		2,726 Cost/QALY	
MEPACT	£154K	£119K	14.66 years	1.74 years	10,535 Cost/QALY	68,463 Cost/QALY

Table 17: Sensitivity analysis: number of MEPACT doses

Doses	Strategy	Cost	Incremental cost (£)	QALY gain	Incremental effect	Cost/ QALY(£)	ICER £
36	No MEPACT	£33,612		6.42 years		5,237	
	MEPACT	£122,858	£89,246	6.68 years	0.26 years	18,396	343,126
37	No MEPACT	£33,612		6.42 years		5,237	
	MEPACT	£125,340	£91,727	6.68 years	0.26 years	18,767	352,668
38	No MEPACT	£33,612		6.42 years		5,237	
	MEPACT	£127,822	£94,209	6.68 years	0.26 years	19,139	362,209
39	No MEPACT	£33,612		6.42 years		5,237	
	MEPACT	£130,303	£96,691	6.68 years	0.26 years	19,510	371,751
40	No MEPACT	£33,612		6.42 years		5,237	
	MEPACT	£132,785	£99,172	6.68 years	0.26 years	19,882	381,292
41	No MEPACT	£33,612		6.42 years		5,237	
	MEPACT	£135,267	£101,654	6.68 years	0.26 years	20,253	390,834
42	No MEPACT	£33,612		6.42 years		5,237	
	MEPACT	£137,748	£104,136	6.68 years	0.26 years	20,625	400,375
43	No MEPACT	£33,612		6.42 years		5,237	
	MEPACT	£140,230	£106,618	6.68 years	0.26 years	20,997	409,917
44	No MEPACT	£33,612		6.42 years		5,237	
	MEPACT	£142,712	£109,099	6.68 years	0.26 years	21,368	419,458
45	No MEPACT	£33,612		6.42 years		5,237	
	MEPACT	£145,193	£111,581	6.68 years	0.26 years	21,740	429,000
46	No MEPACT	£33,612		6.42 years		5,237	
	MEPACT	£147,675	£114,063	6.68 years	0.26 years	22,111	438,541
47	No MEPACT	£33,612		6.42 years		5,237	
	MEPACT	£150,157	£116,544	6.68 years	0.26 years	22,483	448,083
48	No MEPACT	£33,612		6.42 years		5,237	
	MEPACT	£152,639	£119,026	6.68 years	0.26 years	22,855	457,624

Table 18: Sensitivity analysis: cost of MEPACT dose

Cost of MEPACT	Strategy	Cost	Incremental cost (£)	QALY gain	Incremental effect	Cost/QALY (£)	ICER £
1781	No MEPACT	£33,612		6.42 years		5,237 Cost/QALY	
	MEPACT	£124,127	£90,514	6.68 years	0.26 years	18,585 Cost/QALY	348,003 Cost/QALY
1880	No MEPACT	£33,612		6.42 years		5,237 Cost/QALY	
	MEPACT	£128,879	£95,266	6.68 years	0.26 years	19,297 Cost/QALY	366,273 Cost/QALY
1979	No MEPACT	£33,612		6.42 years		5,237 Cost/QALY	
	MEPACT	£133,631	£100,018	6.68 years	0.26 years	20,008 Cost/QALY	384,543 Cost/QALY
2078	No MEPACT	£33,612		6.42 years		5,237 Cost/QALY	
	MEPACT	£138,383	£104,770	6.68 years	0.26 years	20,720 Cost/QALY	402,814 Cost/QALY
2177	No MEPACT	£33,612		6.42 years		5,237 Cost/QALY	
	MEPACT	£143,135	£109,522	6.68 years	0.26 years	21,431 Cost/QALY	421,084 Cost/QALY
2276	No MEPACT	£33,612		6.42 years		5,237 Cost/QALY	
	MEPACT	£147,887	£114,274	6.68 years	0.26 years	22,143 Cost/QALY	439,354 Cost/QALY
2375	No MEPACT	£33,612		6.42 years		5,237 Cost/QALY	
	MEPACT	£152,639	£119,026	6.68 years	0.26 years	22,855 Cost/QALY	457,624 Cost/QALY
2474	No MEPACT	£33,612		6.42 years		5,237 Cost/QALY	
	MEPACT	£157,391	£123,778	6.68 years	0.26 years	23,566 Cost/QALY	475,894 Cost/QALY
2573	No MEPACT	£33,612		6.42 years		5,237 Cost/QALY	
	MEPACT	£162,143	£128,530	6.68 years	0.26 years	24,278 Cost/QALY	494,165 Cost/QALY

Cost of MEPACT	Strategy	Cost	Incremental cost (£)	QALY gain	Incremental effect	Cost/QALY (£)	ICER £
2672	No MEPACT	£33,612		6.42 years		5,237 Cost/QALY	
	MEPACT	£166,895	£133,282	6.68 years	0.26 years	24,989 Cost/QALY	512,435 Cost/QALY
2771	No MEPACT	£33,612		6.42 years		5,237 Cost/QALY	
	MEPACT	£171,647	£138,034	6.68 years	0.26 years	25,701 Cost/QALY	530,705 Cost/QALY
2870	No MEPACT	£33,612		6.42 years		5,237 Cost/QALY	
	MEPACT	£176,399	£142,786	6.68 years	0.26 years	26,412 Cost/QALY	548,975 Cost/QALY
2969	No MEPACT	£33,612		6.42 years		5,237 Cost/QALY	
	MEPACT	£181,151	£147,538	6.68 years	0.26 years	27,124 Cost/QALY	567,245 Cost/QALY

7.3.4 Interpretation of economic evidence

7.3.4.1 Are the results from this economic evaluation consistent with the published economic literature? If not, why do the results from this evaluation differ, and why should the results in the submission be given more credence than those in the published literature?

There are no economic evaluations published for osteosarcoma so no consistency check can be made.

7.3.4.2 Is the economic evaluation relevant to all groups of patients who could potentially use the technology?

Yes, the population reflects the expected labelled indication.

7.3.4.3 What are the main strengths and weaknesses of the evaluation? How might these affect the interpretation of the results?

A strength of this evaluation is that the reference cased is modelled on the clinical estimates from a long-term clinical trial (follow up 12.25 years post maintenance). As a result no assumptions regarding extrapolation need to be made over this time horizon reducing uncertainty. However this strength can also be a weakness as choosing this horizon is highly conservative, as a differential survival effect between the MEPACT and comparator arm persists at the end of 12.25 years. However the additional analyses assessing 20-year and 40-year time horizons are based on final state probabilities of the 12.25-year model, and indicate the long-term cost-effectiveness benefits to be gained with MEPACT when long-term survival and utility benefits are considered. This approach is supported by expert opinion, whereby most patients surviving after 6 years are considered go on to live a full and normal lives.

Another strength of the model is the comprehensive approach to ascertaining utilities in this ultra-orphan disease, where there is minimal information.

7.3.4.4 What further analyses could be undertaken to enhance the robustness/completeness of the results?

Potential modelling and extrapolation of the survival curves, however this was not performed as clinical opinion reported that most if not all of the patients will survive if disease-free at 12.25 years and this assumption was applied in 20- and 40-year time horizon analyses.

8 Assessment of factors relevant to the NHS and other parties

8.1 What is the estimated annual budget impact for the NHS in England and Wales?

The estimated annual budget impact for the NHS in England and Wales will be £4.7 million in 2009 rising to £5.8 million in 2013. The budget estimates associated with MEPACT use are presented in Table 19.

Table 19: Budget Impact Estimates

POPULATION DATA		**2009**	**2010**	**2011**	**2012**	**2013**
Total UK population (millions)		61	61.5	62	62.5	63
England and Wales population	0.89	54.3	54.7	55.2	55.6	56.1
Incidence in children (0-14 years)*	0.7	38	38	39	39	39
Incidence in adolescents (15-19 years)*	0.7	35	36	36	36	36
Incidence in young adults (>20 years)*	0.3	14	14	14	14	14
Total metastatic and non-metastatic		87	88	88	89	90
% of patients with non-metastatic	80%					
POTENTIAL PATIENT POPULATION		**69**	**70**	**71**	**71**	**72**
Uptake rate		50%	50%	60%	60%	60%
TREATED PATIENTS		**35**	**35**	**42**	**43**	**43**
MEPACT	**/dose**	**Cost/cycle of 48 doses**				
	£2375	£114,000				
BUDGET IMPACT (including VAT @17.5%) (All patients have 48 doses)		**£4,657,371**	**£4,695,520**	**£5,679,763**	**£5,725,542**	**£5,771,321**

8.2 What number of patients were assumed to be eligible? How was this figure derived?

Table 19 shows the number of patients assumed to use MEPACT based on reported UK incidence rates for osteosarcoma in children, adolescents, and young adults of approximately 0.7/million, 0.7/million and 0.3/million of the population, respectively (Section 4.1.1). These figures are based on adjusted incidence rates per million of the population rather than unadjusted rates which sometimes report rates per million of a sub-group (e.g. children). It was assumed that:

- 80% of all osteosarcomas would be newly diagnosed, non-metastatic and resectable.
- All patients would receive a full course of MEPACT i.e. 48 doses. This is a conservative approach as the trial data demonstrates that not all patients received the full course.
- 89% of the total UK population is located in England and Wales.

8.3 What assumption was made about current treatment options and uptake of technologies?

It was assumed that MEPACT would not displace existing treatments but would be added-on to existing 3- or 4-arm adjuvant chemotherapy treatment.

8.4 What assumption was made about market share?

It was assumed that in 2009 and 2010 there will be 50% uptake, increasing to 60% over a further 3 years until 2013. As the standard of care is to enter patients into the EURAMOS I study, which does not include MEPACT, these estimates are expected to be conservative.

8.5 What unit costs were assumed? How were these calculated?

A unit cost of £2375/dose was assumed. This is based on a total cost of £114,000 per 48-dose course, administered over a 9-month period. Patients receive one course of MEPACT only.

8.6 In addition to drug costs, consider other significant costs associated with treatment. What is the recommended treatment regimen – for example, what is the typical number of visits, and does treatment involve daycase or outpatient attendance? Is there a difference between recommended and observed doses? Are there likely to be any adverse events or a need for other treatments in combination with the technology?

MEPACT treatment can be administered on an outpatient basis. MEPACT is administered in combination with 3- or 4-agent adjuvant chemotherapy regimens comprising: methotrexate, cisplatin, doxorubin with or without ifosfamide. The proposed dose of MEPACT for all patients is 2mg/m^2 body surface area. MEPACT is to be administered for 36 weeks as adjuvant

therapy following tumour resection as a total of 48 infusions: to be given twice weekly for 12 weeks, with dosing at least 3 days apart; followed by once weekly treatment for an additional 24 weeks. MEPACT is to be infused intravenously over 1 hour.

The administration of the 48 doses of MEPACT can be scheduled to coincide with hospital visits for methotrexate, cisplatin, doxorubin and ifosfamide administration for 70% of doses. It is estimated that approximately 30% of MEPACT doses will incur an outpatient visit cost, at a cost of £189/visit. These estimates have been factored into the budget impact analysis.

Grade I and 2 infusion related reactions may be observed following MEPACT administration (chills and influenza like symptoms), which can be treated with paracetamol or ibuprofen. These costs have not been factored into the budget impact analysis.

8.7 Were there any estimates of resource savings? If so, what were they?

No

8.8 Are there any other opportunities for resource savings or redirection of resources that it has not been possible to quantify?

Yes. Participation in the international EURAMOS I clinical trial is currently the standard of clinical care in the UK for newly diagnosed patients with osteosarcoma. There is uncertainty regarding the proportions of patients who would continue to be randomised to this trial and those who would be given the option of MEPACT treatment outside of the trial setting.

There is also uncertainty regarding plans for further EURAMOS clinical trials, when EURAMOS I completes. As such it is unknown if MEPACT could be used as part of a treatment regimen in future trials.

Both uncertainties above have implications for MEPACT with respect to patient numbers and budget impact.

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10 Appendices

10.1 Appendix 1: Summary of Product Characteristics

1. NAME OF THE MEDICINAL PRODUCT

MEPACT 0.08 mg/ml powder for suspension for infusion.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One 50 ml vial contains 4 mg mifamurtide*.
After reconstitution with 50 ml sodium chloride 9 mg/ml (0.9%) solution for injection, each ml contains 0.08 mg mifamurtide. (MEPACT must be further diluted for use.)

*fully synthetic analogue of a component of *Mycobacterium sp.* cell wall.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for suspension for infusion.

White to off-white homogeneous lyophilised powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

MEPACT is indicated in children from the age of 2-12 years, adolescents from the age of 12-18 years and adults for the treatment of high-grade resectable non-metastatic osteosarcoma after macroscopically complete surgical resection. It is used in combination with post-operative multi-agent chemotherapy.

4.2 Posology and method of administration

MEPACT treatment should be initiated and supervised by specialist physicians experienced in the diagnosis and treatment of osteosarcoma.

<u>Posology</u>
The recommended dose of mifamurtide for all patients is 2 mg/m^2 body surface area. It should be administered for 36 weeks as adjuvant therapy following resection: twice weekly at least 3 days apart for 12 weeks, followed by once-weekly treatments for an additional 24 weeks for a total of 48 infusions.

Paediatric patients

The safety and efficacy of MEPACT have been established in children 2 to 12 years, adolescents 12 to 18 years, and adults 18 to 30 years. It is not recommended for use in children below the age of 2 due to a lack of data on efficacy and safety in this age group.

Elderly patients
None of the patients treated in the osteosarcoma studies were 65 or older. Therefore, there are no data to recommend the use of MEPACT in patients ≥ 65 years of age. Of the 248 subjects in the uncontrolled clinical studies of MEPACT, 37 (15%) were ≥ 65 years old. No overall differences in safety were observed.

Patients with impaired renal or hepatic function
The pharmacokinetics of mifamurtide in patients with renal or hepatic impairment have not been formally studied.

Continued monitoring of the kidney and liver function is recommended if MEPACT is used beyond completion of chemotherapy until all therapy is completed.

Administration
MEPACT must be reconstituted and further diluted prior to administration. The reconstituted, filtered suspension for infusion is a homogenous, white to off-white, opaque liposomal suspension, free of visible particles and free of foam and lipid lumps.
After reconstitution, MEPACT is administered by intravenous infusion over a period of 1 hour.
MEPACT **must not** be administered as a bolus injection.
For further instructions on reconstitution and dilution prior to administration, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.

Concurrent use with ciclosporin or other calcineurin inhibitors (see section 4.5).

Concurrent use with high-dose non-steroidal anti-inflammatory drugs (NSAIDs, cyclooxygenase inhibitors) (see section 4.5).

4.4 Special warnings and precautions for use

Respiratory distress
In patients with a history of asthma or other chronic obstructive pulmonary disease, consideration should be given to administration of bronchodilators on a prophylactic basis. Two patients with pre-existing asthma developed mild to moderate respiratory distress associated with the treatment. If a severe respiratory reaction occurs, administration of MEPACT should be discontinued and appropriate treatment initiated.

Neutropenia
Administration of MEPACT was commonly associated with transient neutropenia, usually when used in conjunction with chemotherapy. Episodes of neutropenic fever should be monitored and managed appropriately. MEPACT may be given during periods of neutropenia, but subsequent fever attributed to the treatment should be monitored closely. Fever or chills persisting for more than 8 hours after administration of MEPACT should be evaluated for possible sepsis.

Inflammatory response
MEPACT has been occasionally associated with signs of pronounced inflammatory response, including pericarditis and pleuritis. It should be used with caution in patients with a history of autoimmune, inflammatory or other collagen diseases. During MEPACT administration, patients should be monitored for unusual signs or symptoms, such as arthritis or synovitis, suggestive of uncontrolled inflammatory reactions.

Cardiovascular disorders
Patients with a history of venous thrombosis, vasculitis or unstable cardiovascular disorders should be closely monitored during MEPACT administration. If symptoms are persistent and worsening, administration should be delayed or discontinued. Haemorrhage was observed in animals at very high doses. These are not expected at the recommended dose, however monitoring of clotting parameters after the first dose and once again after several doses is recommended.

Allergic reactions
Occasional allergic reactions have been associated with MEPACT treatment, including rash, shortness of breath and Grade 4 hypertension. It may be difficult to distinguish allergic reactions from exaggerated inflammatory responses, but patients should be monitored for signs of allergic reactions.

Gastrointestinal toxicity
Nausea, vomiting and loss of appetite are very common adverse reactions to MEPACT. Gastrointestinal toxicity may be exacerbated when MEPACT is used in combination with high dose, multi-agent chemotherapy and was associated with an increased use of parenteral nutrition.

4.5 Interaction with other medicinal products and other forms of interaction

Limited studies of the interaction of MEPACT with chemotherapy have been conducted. Although these studies are not conclusive, there is no evidence of interference of MEPACT with the anti-tumour effects of chemotherapy and vice versa.

It is recommended to separate the administration times of MEPACT and doxorubicin or other lipophilic medicinal products if used in the same chemotherapy regimen.

The use of MEPACT concurrently with ciclosporin or other calcineurin inhibitors is contraindicated due to their hypothesised effect on splenic macrophages and mononuclear phagocytic function (see section 4.3).

Also, it has been demonstrated *in vitro* that high-dose NSAIDs (cyclooxygenase inhibitors) can block the macrophage activating effect of liposomal mifamurtide. Therefore the use of high-dose NSAIDs is contraindicated (see section 4.3).

Because mifamurtide acts through stimulation of the immune system, the chronic or routine use of corticosteroids should be avoided during treatment with MEPACT.

In vitro interaction studies showed that liposomal and non-liposomal mifamurtide do not inhibit the metabolic activity of cytochrome P450 in pooled human liver microsomes. Liposomal and non-liposomal mifamurtide do not induce the metabolic activity or the transcription of cytochrome P450 in primary cultures of freshly isolated human hepatocytes. Mifamurtide is therefore not expected to interact with the metabolism of substances that are hepatic cytochrome P450 substrates.

In a large controlled randomised study, MEPACT used at the recommended dose and schedule with other medicinal products that have known renal (cisplatin, ifosfamide) or hepatic (high dose methotrexate, ifosfamide) toxicities did not exacerbate those toxicities and there was no need to adjust mifamurtide dose.

4.6 Pregnancy and lactation

Pregnancy

There are no data from the use of mifamurtide in pregnant patients. Animal studies are insufficient with respect to reproductive toxicity (see section 5.3). MEPACT should not be used during pregnancy and in women not using effective contraception.

Lactation

It is unknown whether mifamurtide is excreted in human milk. The excretion of mifamurtide in milk has not been studied in animals. A decision on whether to continue/discontinue breast-feeding or to continue/discontinue therapy should be made taking into account the benefit of breast-feeding to the child and the benefit of MEPACT therapy to the woman.

4.7 Effects on ability to drive and use machines

No studies of the effects on the ability to drive and use machines have been performed. Some very common or common undesirable effects of MEPACT treatment (such as dizziness, vertigo, fatigue and blurred vision) may have an effect on the ability to drive and use machines.

4.8 Undesirable effects

Each of the 248 patients treated with MEPACT during the early phase single arm studies in patients with mostly advanced malignancies experienced at least one undesirable effect. Many of the most frequently reported undesirable effects as shown in the following summary table are thought to be related to the mechanism of action of mifamurtide. The majority of these events were reported as either mild or moderate. This profile is consistent whether summarising all early studies (n=248) or only those studies in osteosarcoma (n=51). It is likely that undesirable effects also occurred in the large randomised study, but they were not recorded because only serious and life-threatening adverse reactions were collected in that study.

Adverse reactions are classified according to system organ class and frequency. Frequency groupings are defined according to the following convention: Very common (≥1/10), common (≥1/100 to <1/10). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Adverse reactions associated with MEPACT in ≥ 1/100 patients

Infections and infestations

Common: Sepsis, cellulitis, nasopharyngitis, catheter site infection, upper respiratory tract infection, urinary tract infection, pharyngitis, *Herpes simplex* infection

Neoplasms benign and malignant (including cysts and polyps)

Common: Cancer pain

Blood and the lymphatic system disorders

Very common: Anaemia

Common: Leukopenia, thrombocytopenia, granulocytopenia

Metabolism and nutrition disorders

Very common: Anorexia

Common: Dehydration, hypokalaemia, decreased appetite

Psychiatric disorders

Common: Confusional state, depression, insomnia, anxiety

Nervous system disorders

Very common: Headache, dizziness

Common: Paraesthesia, hypoaesthesia, tremor, somnolence, lethargy

Eye disorders

Common: Blurred vision

Ear and labyrinth disorders

Common: Vertigo, tinnitus

Cardiac disorders

Very common: Tachycardia

Common: Cyanosis, palpitations

Vascular disorders

Very common: Hypertension, hypotension

Common: Phlebitis, flushing, pallor

Respiratory, thoracic and mediastinal disorders

Very common: Dyspnoea, tachypnoea, cough

Common: Pleural effusion, exacerbated dyspnoea, productive cough, haemoptysis, wheezing, epistaxis, exertional dyspnoea, sinus congestion, nasal congestion, pharyngolaryngeal pain

Gastrointestinal disorders

Very common: Vomiting, diarrhoea, constipation, abdominal pain, nausea

Common: Upper abdominal pain, dyspepsia, abdominal distension, lower abdominal pain

Hepatobiliary disorders

Common: Hepatic pain

Skin and subcutaneous tissue disorders

Very common: Hyperhidrosis

Common: Rash, pruritis, erythema, alopecia, dry skin

Musculoskeletal, connective tissue and bone disorders

Very common: Myalgia, arthralgia, back pain, pain in extremity

Common: Muscle spasms, neck pain, groin pain, bone pain, shoulder pain, chest wall pain, musculoskeletal stiffness

Renal and urinary disorders

Common: Haematuria, dysuria, pollakiuria

Reproductive system and breast disorders

Common: Dysmenorrhoea

General disorders and administration site conditions

Very common: Fever, chills, fatigue, hypothermia, pain, malaise, asthenia, chest pain

Common: Peripheral oedema, oedema, mucosal inflammation, infusion site erythema, infusion site reaction, catheter site pain, chest discomfort, feeling cold

Investigations

Common: Weight decreased

Surgical and medical procedures

Common: Post-procedural pain

Blood and lymphatic system disorders

Anaemia has most commonly been reported when MEPACT is used in conjunction with chemotherapeutic agents. In a randomised controlled trial, the incidence of myeloid malignancy (acute myeloid leukaemia/myelodysplastic syndrome) was the same in patients receiving

MEPACT plus chemotherapy as in patients receiving only chemotherapy (approximately 2.5%).

Metabolism and nutritional disorders
Anorexia (21%) was very commonly reported in trials of MEPACT in late stage cancer patients.

Nervous system disorders
Consistent with other generalised symptoms, the most common nervous system disorders were headache (50%) and dizziness (17%).

Ear and labyrinth disorders
Although hearing loss may be attributable to ototoxic chemotherapy, like cisplatin, it is unclear whether MEPACT in conjunction with multi-agent chemotherapy may increase hearing loss.

Cardiac and vascular disorders
Mild-moderate tachycardia (50%), hypertension (26%) and hypotension (29%) were commonly reported in uncontrolled trials of MEPACT. One serious incident of subacute thrombosis was reported in early studies, but no serious cardiac events were associated with MEPACT in a large randomised controlled trial.

Respiratory disorders
Respiratory disorders, including dyspnoea (21%), cough (18%) and tachypnoea (13%) were very commonly reported, and two patients with pre-existing asthma developed mild to moderate respiratory distress associated with MEPACT treatment in a phase II study.

Gastrointestinal disorders
Gastrointestinal disorders were frequently associated with MEPACT administration, including nausea (57%) and vomiting (44%) in about half of patients, constipation (17%), diarrhoea (13%) and abdominal pain.

Skin and subcutaneous disorders
Hyperhidrosis (11%) was very common in patients receiving MEPACT in uncontrolled studies.

Musculoskeletal and connective tissue disorders
Low grade pain was common in patients receiving MEPACT, including myalgia (31%), back pain (15%), extremity pain (12%) and arthralgia (10%).

General disorders and administration site conditions
The majority of patients experience chills (89%), fever (85%) and fatigue (53%). These are typically mild to moderate, transient in nature and generally respond to palliative treatment (e.g., paracetamol for fever). Other generalised symptoms that were typically mild to moderate and very common included hypothermia (23%), malaise (13%), pain (15%), asthenia (13%) and chest pain (11%). Oedema, chest discomfort, local infusion or catheter site reactions and 'feeling cold' were less frequently reported in these patients, mostly with late stage malignant disease.

Investigations
Increase in blood urea and blood creatinine was associated with MEPACT use in one patient with osteosarcoma.

4.9 Overdose

No case of overdose has been reported. The maximum tolerated dose in phase I studies was 4-6 mg/m^2 with a high variability of adverse reactions. Signs and symptoms that were associated with higher doses and/or were dose limiting were not life-threatening, and included fever, chills, fatigue, nausea, vomiting, headache and hypo- or hypertension.

In the event of an overdose, it is recommended that appropriate supportive treatment be initiated.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other cytokines and immunomodulators, ATC code: L03AX15

Mechanism of action
Mifamurtide (muramyl tripeptide phosphatidyl ethanolamine, MTP-PE) is a fully synthetic derivative of muramyl dipeptide (MDP), the smallest naturally-occurring immune stimulatory component of cell walls from *Mycobacterium sp*. It has similar immunostimulatory effects as natural MDP with the additional advantage of a longer half-life in plasma. MEPACT is a liposomal formulation specifically designed for *in vivo* targeting to macrophages by intravenous infusion.

MTP-PE is a specific ligand of NOD2, a receptor found primarily on monocytes, dendritic cells and macrophages. MTP-PE is a potent activator of monocytes and macrophages. *In vitro* activation of human macrophages by MEPACT is associated with production of cytokines, including tumour necrosis factor (TNF-α), interleukin-1 (IL-1β), interleukin-6 (IL-6), interleukin-8 (IL-8), and interleukin-12 (IL-12) and adhesion molecules, including lymphocyte function-associated antigen-1 (LFA-1) and intercellular adhesion molecule-1 (ICAM-1). *In vitro*-treated human monocytes killed allogeneic and autologous tumor cells (including

melanoma, ovarian, colon, and renal carcinoma[1,2,3,4]), but had no toxicity towards normal cells[5,6].
In vivo administration of MEPACT resulted in the inhibition of tumour growth in mouse and rat models of lung metastasis, skin and liver cancer, and fibrosarcoma[7,8,9,10,11]. Significant enhancement of disease-free survival was also demonstrated in the treatment of dog osteosarcoma and hemangiosarcoma with MEPACT as adjuvant therapy[12,13,14,15]. The exact mechanism by which MEPACT activation of monocytes and macrophages leads to antitumour activity in animals and humans is not yet known.

Clinical safety and efficacy
The safety of liposomal mifamurtide has been assessed in more than 700 patients with various kinds and stages of cancer and in 21 healthy adult subjects (see section 4.8).

MEPACT significantly increased the overall survival of patients with newly-diagnosed resectable high-grade osteosarcoma when used in conjunction with combination chemotherapy when compared to chemotherapy alone. In a randomised phase III study of 678 patients with newly-diagnosed resectable high-grade osetosarcoma, the addition of adjuvant MEPACT to chemotherapy resulted in a relative reduction in the risk of death of 28% (p = 0.0313, hazard ratio (HR) = 0.72 [95% confidence interval (CI): 0.53, 0.97]).

[1] Bucana CD, Hoyer IC, Schroit AJ et al. Ultrastructural studies of the interaction between liposome-activated human blood monocytes and allogeneic tumor cells in vitro. *Am J Pathol* 1983, 112: 101-111.
[2] Galligioni E, Quaia M, Spada A et al. Activation of cytolytic activity in peripheral blood monocytes of renal cancer patients against non-cultured autologous tumor cells. *Int J Cancer* 1993, 55: 380-385.
[3] Sone S, Utsugi T, Tandon P et al. Tumor cytotoxicity and interleukin 1 production of blood monocytes of lung cancer patients. *Cancer Immunol Immunother* 1990, 30: 357-362.
[4] Galligioni E, Santarosa M, Favaro D et al. In vitro synergic effect of interferon gamma combined with liposomes containing muramyl tripeptide on human monocyte cytotoxicity against fresh allogeneic and autologous tumor cells. *Tumori* 1994, 80: 385-391.
[5] Kleinerman ES, Erickson KL, Schroit AJ et al. Activation of tumoricidal properties in human blood monocytes by liposomes containing lipophilic muramyl tripeptide. *Cancer Res* 1983, 43: 2010-2014.
[6] Fidler IJ, Jessup JM, Fogler WE et al. Activation of tumoricidal properties in peripheral blood monocytes of patients with colorectal carcinoma. *Cancer Res* 1986, 46:994-998.
[7] Key ME, Talmadge JE, Fogler WE et al. Isolation of tumoricidal macrophages from lung melanoma metastases of mice treated systemically with liposomes containing a lipophilic derivative of muramyl dipeptide. *J Natl Cancer Inst* 1982, 69: 1198-1198.
[8] Talmadge E, Lenz BF, Collins MS et al. Tumor models to investigate the therapeutic efficiency of immunomodulators. *Behring Inst. Mitt* 1984, 219-229.
[9] Talmadge JE, Lenz BF, Klabansky R, et al. Therapy of autochthonous skin cancers in mice with intravenously injected liposomes containing muramyltripeptide. *Cancer Res* 1986, 46: 1160-1163.
[10] Karpoff HM, Jarnagin W, Delman K, Fong Y. Regional muramyl tripeptide phosphatidylethanomamine administration enhances hepatic immune function and tumor surveillance. *Surgery* 2000, 128: 213-218.
[11] Thomas K, Nijenhuis AM, Dontje BH et al. Antitumor reactivity induced by liposomal MTP-PE in a liver metastasis model of colon cancer in the rat. *Clin Exp Metastas* 1995, 13:328-336.

[12] MacEwen EG, Kurzman ID, Rosenthal RC et al. Therapy for osteosarcoma in dogs with intravenous injection liposome-encapsulated muramyl tripeptide. *J Nat'l Cancer Inst* 1989, 81: 935-938.
[13] Kurzman ID, MacEwen EG, Rosentahl RC et al. Adjuvant therapy for osteosarcoma in dogs: results of randomized clinical trials using combined liposome-encapsulated muramyl tripeptide and cisplatin. *Clin Cancer Res* 1995, 1: 1595-1601.
[14] Vail DM, MacEwen EG, Kurzman ID et al. Liposome-encapsulated muramyl tripeptide phosphatidylethanolamine adjuvant immunotherapy for splenic hemangiosarcoma in the dog: a randomized multi-institutional clinical trial. *Clin Cancer Res* 1995, 1: 1165-1170.
[15] MacEwen EG, Kurzman ID, Helfand S et al. Current studies of liosome muramyl tripeptide (CGP 19825A lipid) therapy for metastasis in spontaneous tumors: a progress review. *J Drug Target* 1994, 2: 391-396.

5.2 Pharmacokinetic properties

After intravenous administration in 14 patientsmifamurtide was cleared rapidly from plasma (minutes), resulting in very low plasma concentrations of free (non-liposomal) mifamurtide and total (liposomal and free) mifamurtide. Mean serum concentration-time curves of total and free mifamurtide that were assessed after the first infusion of MEPACT and after a last infusion 11 or 12 weeks later, were almost superimposable and the mean AUC values of the free mifamurtide after the first and last infusion were similar. These data indicate that neither total nor free mifamurtide accumulated during the treatment period.

At 6 hours after injection of radiolabelled liposomes containing 6 mg mifamurtide, radioactivity was found in liver, spleen, nasopharynx, thyroid, and, to a lesser extent, in lung. The liposomes were phagocytosed by cells of the reticuloendothelial system. In 2 of 4 patients with lung metastases, radioactivity was associated with lung metastases. Mean half-life of radiolabelled material was biphasic with an α phase of about 15 minutes and a terminal half-life of approximately 18 hours.

5.3 Preclinical safety data

In sensitive species (rabbit and dog) the highest daily dose of liposomal mifamurtide that did not cause adverse effects was 0.1 mg/kg, corresponding to 1.2 and 2 mg/m^2, respectively. The no-adverse-effect level for MEPACT in animals corresponds roughly to the 2 mg/m^2 recommend dose for humans.

Data from a six month dog study of daily intravenous injections of up to 0.5 mg/kg (10 mg/m^2) MEPACT provide an 8- to 19-fold cumulative exposure safety margin for overt toxicity for the intended clinical dose in humans. Major toxic effects associated with these high daily and cumulative doses of MEPACT were mainly exaggerated pharmacological effects: pyrexia, signs of pronounced inflammatory response manifested as synovitis, bronchopneumonia, pericarditis and inflammatory necrosis of the liver and bone marrow. The following events were also observed: haemorrhage and prolongation of coagulation times, infarcts, morphological changes in the wall of small arteries, oedema and congestion of the central nervous system, minor cardiac effects, and slight hyponatraemia. MEPACT was not

mutagenic and did not cause teratogenic effects in rats and rabbits. Embryotoxic effects were observed only at maternal toxic levels.

There were no results from general toxicity studies that suggested harmful effects on male or female reproductive organs. Specific studies addressing reproductive function, perinatal toxicity and carcinogenic potential have not been performed.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

1-Palmitoyl-2-oleoyl-sn-glycero-3-phosphocholine (POPC)
1,2-Dioleoyl-sn-glycero-3-phospho-L-serine monosodium salt (OOPS)

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

Unopened vial of Powder*:*
2 years

Reconstituted suspension*:*
Chemical and physical stability has been demonstrated for 6 hours up to 25ºC.

From a microbiological point of view, immediate use is recommended. If not used immediately, the constituted and diluted solution in-use storage times and conditions prior to use of the reconstituted product are the responsibility of the user and must not be longer than 6 hours at 25ºC. Do not store in a refrigerator and do not freeze the solution.

6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C). Do not freeze.
Keep the vial in the outer carton in order to protect from light.

For storage conditions of the reconstituted medicinal product, see section 6.3.

6.5 Nature and contents of container

50 ml type I glass vial with a grey butyl rubber stopper, aluminium seal and plastic flip-off cap, containing 4 mg of mifamurtide.

Each carton contains one vial and one single-use, non-pyrogenic, latex-free sterile Filter for MEPACT supplied in a PVC-grade blister.

6.6 Special precautions for disposal and other handling

MEPACT must be reconstituted and further diluted using aseptic technique.

Each vial should be reconstituted with 50 ml of sodium chloride 9 mg/ml (0.9 %) solution for injection. After reconstitution, each ml suspension contains 0.08 mg mifamurtide. The volume of reconstituted suspension corresponding to the calculated dose is extracted and further diluted with additional 50 ml sodium chloride 9 mg/ml (0.9 %) solution for injection according to the detailed instructions shown below.

Instructions for Preparation of Mepact 0.08 mg/ml **for Intravenous Infusion**

Materials Provided in Each Package -

- MEPACT powder for suspension for infusion (vial)
- Filter for MEPACT

Materials Required But Not Provided -

- Sodium chloride 9 mg/ml (0.9%) solution for injection, EP/USP 100 ml bag
- One single use 60or 100 ml sterile syringe with luer lock
- Two medium (18) gauge sterile injection needles

Procedure for Constitution of Liposomal Suspension

It is recommended that the constitution of the liposomal suspension should be performed in a laminar flow cabinet utilising sterile gloves using aseptic technique.

The lyophilised powder should be allowed to reach a temperature between approximately 20°C – 25°C prior to reconstitution and dilution. This should take approximately 30 minutes.

1. The cap of the vial should be removed and the stopper cleaned using an alcohol pad.
2. The filter should be removed from the blister pack, and the cap removed from the filter spike. The spike should then be inserted into the vial septum firmly until seated. The filter luer connector cap should not be removed at this time.
3. The 100 ml sodium chloride 9 mg/ml (0.9%) solution for injection bag, needle and syringe should be unpacked (not provided in the pack).
4. The site of the sodium chloride 9 mg/ml (0.9%) solution for injection bag where the needle is going to be inserted should be swabbed with an alcohol pad.
5. Using the needle and syringe, 50 ml of sodium chloride 9 mg/ml (0.9%) solution for injection should be withdrawn from the bag.

6. After removing the needle from the syringe, the syringe should be attached to the filter by opening the filter luer connector cap (Figure 1).

Figure 1

7. The sodium chloride 9 mg/ml (0.9%) solution for injection is added to the vial by slow, firm depression of the syringe plunger. **The filter and syringe must not be removed from the vial.**
8. The vial should be allowed to stand undisturbed for one minute to ensure thorough hydration of the dry substance.
9. **The vial should then be shaken vigorously for one minute while keeping the filter and syringe attached**. During this time the liposomes are formed spontaneously (Figure 2).

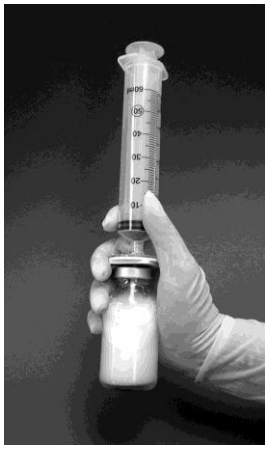

Figure 2

10. The desired dose may be withdrawn from the vial by inverting the vial and slowly pulling back on the syringe plunger (Figure 3). Each ml reconstituted suspension contains 0.08 mg mifamurtide. The volume of suspension to be withdrawn for dose quantities is calculated as follows:

    Volume to withdraw = [12.5 x calculated dose (mg)] ml

For convenience, the following table of concordance is provided:

Dose	Volume
1.0 mg	12.5 ml
2.0 mg	25 ml
3.0 mg	37.5 ml
4.0 mg	50 ml

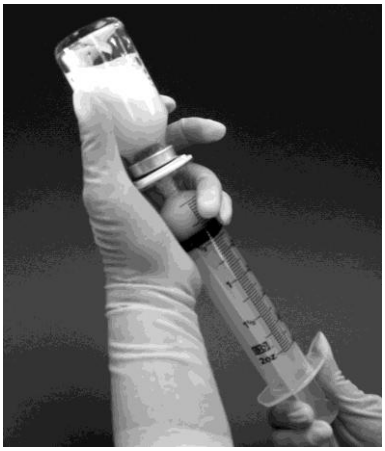

Figure 3

11. The syringe should then be removed from the filter and a new needle placed on the suspension-filled syringe. The bag injection site should be wiped with an alcohol pad and the suspension in the syringe should be injected into the original bag containing the remaining 50 ml of sodium chloride 9 mg/ml (0.9%) solution for injection (Figure 4).

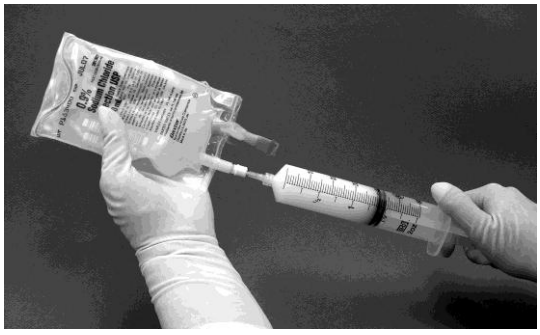

Figure 4

12. The bag should be gently swirled to mix the solution.
13. Patient identification, time and date should be added to the label on the bag containing the reconstituted and diluted liposomal suspension.
14. Chemical and physical in-use stability has been demonstrated for 6 hours at room temperature (between approximately 20°C – 25°C).
15. From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 6 hours at room temperature.
16. The liposomal suspension is infused intravenously over about one hour.

7. MARKETING AUTHORISATION HOLDER

IDM Pharma, S.A.
47 rue de Chaillot
75116 Paris
France
Tel: +33 467 55 84 62
Fax: +33 174 90 00 17

8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

Detailed information on this product is available on the website of the European Medicines Agency (EMEA) http://www.emea.europa.eu/

10.2 Appendix 2: Search strategy for Section 6

10.2.1 The following databases were searched:

- Medline (via OVID)
- Medline in Process (via OVID)
- Embase (via OVID)
- Cochrane Library (via Wiley InterScience)

10.2.2 The date on which the search was conducted

The search was conducted on 10th September 2008

10.2.3 The date span of the search

The search covered the period from 1990 to September, Week 1 2008.

10.2.4 The complete search strategies used

The strategy used to search Medline for RCTs was as specified below, and was adapted to search the other databases and for other study designs.

1. Osteosarcoma/
2 . osteosarcom$.tw.
3 . ((osteogenic or bone or osteoid or osteolytic) adj sarcom$).tw.
4 . or/1-3
5 . Antineoplastic Combined Chemotherapy Protocols/ (75645)
6 . (Mepact or Mifamurtide or CGP 19835? or L-MTP-PE or MTP-PE or MLV 19835A or muramyl?tripeptide phosphatid?lethanolamine or Junovan or muramyl tripeptide).tw.
7. 4 and 5
8. 4 and 6
9. 7 or 8
10. limit 9 to (english language and humans and ("all infant (birth to 23 months)" or "all child (0 to 18 years)" or "all adult (19 plus years)" or "newborn infant (birth to 1 month)" or "infant (1 to 23 months)" or "preschool child (2 to 5 years)" or "child (6 to 12 years)" or "adolescent (13 to 18 years)" or "adult (19 to 44 years)"))
11. exp clinical trial/
12. randomized.ab.
13. placebo.ab.
14. exp Clinical Trials as Topic/
15. randomly.ab.
16. trial.ti.
17. or/11-16

18. Animals/
19. Humans/
20. 18 not (18 and 19)
21. 17 not 20
22. 10 and 21
23. Meta-analysis.pt.
24. Review.pt.
25. exp Review Literature/
26. Meta-Analysis/
27. (metaanaly$ or metanaly$ or (meta adj2 analy$)).tw.
28. (review$ or overview$).ti.
29. (systematic$ adj4 (review$ or overview$)).tw.
30. ((quantitative$ or qualitative$) adj4 (review$ or overview$)).tw.
31. ((studies or trial$) adj1 (review$ or overview$)).tw.
32. (integrat$ adj2 (research or review$ or literature)).tw.
33. (pool$ adj1 (analy$ or data)).tw.
34. MEDLINE/
35. (medline or medlars or embase or cochrane or cinahl or psycinfo or psychinfo or psyclit or psychlit or science citation index or scisearch or web of science or pubmed).tw.
36. (handsearch$ or (hand adj2 search$)).tw.
37. (manual$ adj2 search$).tw.
38. or/23-37
39. Letter.pt.
40. Editorial.pt.
41. Comment.pt.
42. Case Reports.pt.
43. or/39-42
44. 38 not 43
45. 10 and 43
46. 22 or 45
47. limit 46 to yr="1990 - 2008"
48. from 47 keep 1-186

10.2.5 Details of any additional searches

The following specific websites were also searched:

NICE (www.nice.org.uk)
National Coordinating Centre for Health Technology Assessment (www.ncchta.org)
Health Services/Technology Assessment Text (www.ncbi.nlm.nih.gov/books/bv.fcgi?rid=hstat)
Scottish Intercollegiate Guidelines Network (www.sign.ac.uk)
Health Evidence Network (www.euro.who.int/HEN)
National Horizon Scanning Centre (www.pcpoh.bham.ac.uk/publichealth/horizon/)
Aggressive Research Intelligence Facility (www.arif.bham.ac.uk/)
Clinical Evidence (www.clinicalevidence.bmj.com/ceweb/index.jsp)
Clinical Knowledge Summaries (www.cks.library.nhs.uk/home)
Turning Research into Practice (www.tripdatabase.com/index.html)

Bandolier (www.medicine.ox.ac.uk/bandolier/)
Scottish Medicines Consortium (www.scottishmedicines.org.uk/)
Chief Scientists Office (www.sehd.scot.nhs.uk/cso/)
National Research Register (www.nrr.nhs.uk/)
UK Clinical Research Network (www.ukcrn.org.uk/index.html)
Database of Uncertainties about the Effects of Treatments (www.duets.nhs.uk/Default.asp)
British National Formulary (www.bnf.org/bnf/)
DailyMed (dailymed.nlm.nih.gov/dailymed/about.cfm)
Medicines Complete (www.medicinescomplete.com/mc/)
National Prescribing Centre (www.npc.co.uk/)
UK Medicines Information (www.ukmi.nhs.uk/)
National Electronic Library for Medicines (www.nelm.nhs.uk/)
National Electronic Library for Health Guidelines Finder (www.library.nhs.uk/guidelinesFinder/)
ClinicalTrials.gov (clinicaltrials.gov/)
Current Controlled Trials (controlled-trials.com/mrct)
Centerwatch (www.centerwatch.com/)
Computer Retrieval of Information on Scientific Products (www.centerwatch.com/)
ABPI Clinical Trials database (www.cmrinteract.com/clintrial/)
International Clinical Trials Registry Platform (www.who.int/ictrp/search/en/index.html)
National Library of Medicine Gateway (gateway.nlm.nih.gov/gw/Cmd)
National Cancer Institute (gateway.nlm.nih.gov/gw/Cmd)
International Cancer Research Portfolio (www.cancerportfolio.org/index.jsp)
Community Research and Development Information Service (cordis.europa.eu/home_en.html)
General google search (www.google.com)

10.2.6 Inclusion and exclusion criteria

Literature was included if it was published in English, or was in a foreign language, but had an English abstract. Animal studies were excluded.

10.2.7 The data abstraction strategy

The data abstraction strategy is described in Section 6.2. Studies were selected according to the PICO (Population, Intervention, Comparison, Outcome) stratagem: The study population comprised children, adolescents and young adults diagnosed with high-grade, non-metastatic osteosarcoma. The intervention comprised neoadjuvant chemotherapy with high-dose methotrexate, doxorubicin and cisplatin with/without ifosfamide followed by adjuvant therapy with the same regimen plus MEPACT. The comparator comprised neoadjuvant and adjuvant chemotherapy with high-dose methotrexate, doxorubicin and cisplatin with/without ifosfamide. Outcome measures comprised disease-free survival, overall survival, quality of life and safety.

10.3 Appendix 3: Search strategy for Section 7

10.3.1 The following databases were searched:

- Medline (via OVID)
- Medline in Process (via OVID)
- Embase (via OVID)
- NHS Economic Evaluation Database (NHS EED) (via Cochrane Library)
- Health Economic Evaluation Database (via Wiley InterScience)

10.3.2 The date on which the search was conducted

The search was conducted on 10th September 2008.

10.3.3 The date span of the search

The search covered the period from 1990 to September, Week 1 2008.

10.3.4 The complete search strategies used

The following strategy was used to search Medline and was adapted as appropriate to search the other sources.

1. OSTEOSARCOMA/
2. osteosarcom$.tw.
3. ((osteogenic or bone or osteoid or osteolytic) adj sarcom$).tw.
4. or/1-3
5. Antineoplastic Combined Chemotherapy Protocols/
6. (Mepact or Mifamurtide or CGP 19835? or L-MTP-PE or MTP-PE or MLV 19835A or muramyl?tripeptide phosphatid?lethanolamine or Junovan or muramyl tripeptide).tw.
7. 4 and 5
8. 4 and 6
9. 7 or 8
10. exp Economics/
11. quality of life/
12. value of life/
13. Quality-adjusted life years/
14. models, economic/
15. markov chains/
16. monte carlo method/
17. decision tree/
18. ec.fs.
19. economic$.tw.
20. (cost? or costing? or costly or costed).tw.
21. (price? or pricing?).tw.
22. (pharmacoeconomic? or (pharmaco adj economic?)).tw.
23. budget$.tw.

24. expenditure$.tw.
25. (value adj1 (money or monetary)).tw.
26 (fee or fees).tw.
27 "quality of life".tw.
28 qol$.tw.
29 hrqol$.tw.
30 "Quality adjusted life year$".tw.
31 qaly$.tw.
32 cba.tw.
33 cea.tw.
34 cua.tw.
35 utilit$.tw
36 markov$.tw.
37 monte carlo.tw.
38 (decision adj2 (tree$ or analys$ or model$)).tw.
39 ((clinical or critical or patient) adj (path? or pathway?)).tw.
40 (managed adj2 (care or network?)).tw.
41 or/10-40
42 9 and 41

10.3.5 Details of additional searches

The following specific websites were also searched:

Cost Effectiveness Analysis Registry (research.tufts-nemc.org/cear/default.aspx)
Centre for Health Economics, University of York (www.york.ac.uk/inst/che/)
Health Economics Research Group, Brunel University (www.brunel.ac.uk/about/acad/herg)
Health Economics and Decision Science, University of Sheffield (www.shef.ac.uk/scharr/sections/heds)
Health Economics Research Unit, University of Aberdeen (www.abdn.ac.uk/heru/)
Health Economics Research Centre, University of Oxford (www.herc.ox.ac.uk/)
Health Economics Group, University of East Anglia (www.med.uea.ac.uk/research/research_econ/welcome.htm)
Centre for Health Economics Research and Evaluation, University of Sydney (www.chere.uts.edu.au/)
Centre for Health Economics and Policy Analysis, McMaster University (www.chepa.org/)
Health Economics.com (www.healtheconomics.com/)
NetEc (netec.mcc.ac.uk/NetEc.html)

The sources listed in Section 10.2.5 were also interrogated for economics information.

10.3.6 Additional search for quality of life and utility

A further search of Medline/PubMed was performed to identify additional studies relating to health related quality of life and utility outcomes associated with osteosarcoma. This was to provide evidence for Sections 4.1.4 and Section 7.2.8. The search used the key words:

Osteosarcoma OR lower extremity sarcoma in the title and abstract (limit 1990-2008) AND:

quality of life; functional outcome; short form 36; SF36; EQ 5D; EuroQoL; health utilities index; HUI; quality of well being; QWB; visual analogue scale; VAS; Utility; quality adjusted life; QALY; Time trade-off; standard gamble; TESS; MSTS; health status indicator; health status; cost-utility.

A further search was performed on cancer AND hearing loss in the title and abstract (limit 1990-2008).

The following specific websites were also searched:

Cost Effectiveness Analysis Registry (research.tufts-nemc.org/cear/default.aspx)
Centres for Review and Dissemination EED and HTA databases (http://www.crd.york.ac.uk/crdweb/Home.aspx)
Technology appraisals on the NICE website (http://www.nice.org.uk/Guidance/TA)

Citations in articles reviewed were also explored. A general search of the internet was conducted using the terms osteosarcoma, cost-utility, and quality of life.

10.4 Appendix 4: Clinical Evidence Appendices

Table 20: Clinical studies informing on MEPACT use in osteosarcoma

Study ID	Centres	Study dates	Study design	Treatment	Objective	Patients entered/ completed	Gender, age	Diagnosis inclusion criteria	Primary endpoint
INT-0133 (Phase III)	178 Children's Oncology Group institutions (previously Children's Cancer Group and Pediatric Oncology Group)	Enrolment Nov 1993–Nov 1997 Completed Enrolment 678: goal 585	Prospective, randomised, controlled	MEPACT 2mg/m^2 twice weekly for 12 weeks then once weekly for 24 weeks – dose could be escalated to 2mg/m^2 + 1mg or 2mg/m^2 + 2mg Administered with doxorubicin, cisplatin, high dose methotrexate with/ without ifosfamide	To determine if addition of ifosfamide or MEPACT would increase overall survival, and determine impact on disease-free survival and, histologic response	Reg A: 174/130 Reg A + MEPACT: 167/108 Reg B: 166/120 Reg B + MEPACT: 171/106	372 M, 306 F Median age 14 (1.4–30.6 years)	≤30 years of age with newly diagnosed (≤ 1 month from diagnostic biopsy) malignant, high-grade non-metastatic resectable osteosarcoma	Overall survival with disease-free survival as an intermediate endpoint
INT-0133 (Phase III)	103 Children's Cancer Group institutions	Enrolment Nov 1993–Nov 1997 Completed Enrolment 115: no goal	Prospective, randomised, controlled	As above	As above	Reg A: 29/11 Reg A + MEPACT: 28/12 Reg B: 29/7 Reg B + MEPACT: 29/10	71 M, 44 F Median age 14 (3.7–30.2 years)	≤30 years of age with newly diagnosed (≤1 month from diagnostic biopsy) malignant, high-grade metastatic or unresectable osteosarcoma	Overall survival with disease-free/ progression-free survival as an intermediate endpoint

Study ID	Centres	Study dates	Study design	Treatment	Objective	Patients entered/ completed	Gender, age	Diagnosis inclusion criteria	Primary endpoint
Protocol 08 (Phase II)	1 (MD Anderson)	Nov 1988-Jan 1992 Completed 33/30	Open-label, historical control Re-enrolment allowed	3-month: MEPACT 2mg/m^2 twice weekly for 12 weeks 6-month: MEPACT 2mg/m^2 twice weekly for 12 weeks then once weekly for 12 weeks	Efficacy, safety, immunomodulatory activity, 1 progression-free survival, overall survival	3-month: 15/8 6-month: 18/10 (6 patients re-enrolled)	3-month: 9M/6F 6-month: 8M/10F	8-70 years of age with histologically proven osteosarcoma and pulmonary metastases that either developed during chemotherapy or were present at diagnosis and persisted despite chemotherapy, and that had recurred after surgical excision	Progression-free survival
Protocol 10 (Phase IIb)	3 (MD Anderson, Memorial Sloan-Kettering, Mayo Clinic)	Dec 1991 – Oct 1992 Completed 12/15	Open-label, non-randomised	MEPACT 2mg/m^2 twice weekly for 12 weeks then once weekly for 12 weeks (could be titrated > 1st week) with ifosfamide 1.8g/m^2 for 5 days every 21 days for 8 courses or cisplatin 120mg/m^2 every 28 days for 6 courses	Safety, tolerability, histologic evaluation, immunomodulatory activity, efficacy	MEPACT + ifosfamide: 9/2 MEPACT + cisplatin: 2/0 MEPACT + both: 1/0	MEPACT + ifosfamide: 5M/4F MEPACT + cisplatin: 2M/0F MEPACT + both: 1M/0F Mean age: 16 years Range: 9-21 years	8-70 years of age with histologically proven osteosarcoma with primary tumour resected and developed resectable metastases during or after adjuvant chemotherapy, or who initially presented with resectable metastases that persisted despite chemotherapy	Immune response and histologic examination

Study ID	Centres	Study dates	Study design	Treatment	Objective	Patients entered/ completed	Gender, age	Diagnosis inclusion criteria	Primary endpoint
MTP-OS-403 (as of 24 July 2008)	4 (MD Anderson Houston, MD Anderson Orlando, Memorial Sloan Kettering NY, Children's Hospital Orange County)	Feb 2008-ongoing 31 /no specific enrolment goal	Single arm, open label; pharmaco-kinetics in patient subset	MEPACT 2mg/m^2 twice weekly for 12 weeks then once weekly for 24 weeks; can be administered in conjunction with other therapies	Provide access to high risk patients; pharmacokinetics in up to 20 patients ≤16 years	31/0	Gender data has not yet been reported. 18 (11-43)	Age ≤50 with high grade osteosarcoma with high-risk features	Safety and tolerability

A number of other studies have considered the use of MEPACT in other oncological indications dating from 1986-1996 (Protocols 1-9, BR/MA 1, 2, 4 and 6, BR/MB 1, BR/MC 1,BR/MS 1, DM89/031). In addition, the use of MEPACT in healthy subjects was considered in study MTP-OS-402.

10.5 Appendix 5: Economic Appendices

10.5.1 Introduction

The methods and assumptions used for the estimation of resource utilisation and associated costs are presented below. The information is presented for each of the model states and for the maintenance/adjuvant treatment phase. The maintenance phase corresponds to the time in study INT-0133 when MEPACT is administered as add-on treatment to adjuvant chemotherapy. In the economic model the maintenance phase is represented by cycle 1 in the two starting states, Disease-Progression and Disease-Free.

10.5.2 Maintenance phase (cycle 1) drug administration costs

10.5.2.1 MEPACT

MEPACT 2mg/m^2 is to be administered for 36 weeks as adjuvant therapy following tumour resection, as a total of 48 infusions: twice weekly for 12 weeks with dosing at least 3 days apart; followed by once weekly treatment for an additional 24 weeks. MEPACT is to be infused intravenously over 1 hour. Figure 2 (Section 6.3.1.2) indicates that a proportion of MEPACT doses will require an outpatient visit, with no other adjuvant agent being are scheduled for administration on these days. As UK dosing schedules can vary from that outlined in Figure 2, it is estimated that up to 30% of doses may require an outpatient visit. This uncertainty is explored in a sensitivity analysis.

10.5.2.2 Adjuvant chemotherapy (cisplatin, doxorubicin, methotrexate and ifosfamide)

Adjuvant chemotherapy is administered on an inpatient basis in the UK. From Figure 2 (Section 6.3.1.2) and expert opinion it was assumed that:

- 2 inpatient days are required for one dose of cisplatin administered alone.
- 4 inpatient days are required for one dose of cisplatin administered concomitantly with 3-days doxorubicin.
- 5 inpatient days are required for one dose of methotrexate.

- 6 inpatient days are required for 5-day dosing with ifosfamide.

The 5 inpatient days for methotrexate account for leucovorin rescue, which typically begins 20 hours after methotrexate dosing and continues until the blood methotrexate level has reduced to a specified level. The 6 inpatient days for ifosfamide also account for mensa administration and 24 hour rehydration post-dose.

From Figure 2 (Section 6.3.1.2) it is estimated that delivery of Regimen A and Regimen B (adjuvant chemotherapy) will require 56 and 68 in-patient days, respectively.

10.5.2.3 *Unit costs for adjuvant chemotherapy with/without MEPACT*

Table 21 summarises the unit costs for each of the agents in the adjuvant chemotherapy regimen together with the unit cost of a MEPACT dose. Table 22 summarises the unit costs associated with inpatient and outpatient visits for the delivery of adjuvant chemotherapy and MEPACT.

Table 21: Adjuvant chemotherapy and MEPACT medication costs during maintenance phase

Agent	Dose	Number of Doses in Regimen A	Number of Doses in Regimen B	Unit Cost/ Dose[1]	Assumptions
Doxorubicin	25mg/m^2/day	12	12	£102.00	2mg/mL, 25-mL vial = £102.00
Cisplatin	120mg/m^2	2*	4	£100.44	1 mg/mL, net price 10mL vial = £5.85, 50mL vial = £24.50, 100mL vial = £50.22
Methotrexate	12g/m^2	8	8	£1,369	methotrexate 100mg/mL (not for intrathecal use), net price 10mL vial = £78.33, 50mL vial = £380.07
Ifosfamide	1.8g/m^2/day		15	£72.52	Net price 1g vial = £27.03; 2g vial = £45.49
MEPACT	2mg/m^2	48	48	£2,375	

[1]British National Formulary (BNF) 56, September 2008
* 2 doses of cisplatin were administered during the induction phase for Regimen A

Table 22: Adjuvant chemotherapy and MEPACT administration costs

Description	Frequency	Unit cost
In-patient visit to deliver adjuvant chemotherapy treatment in Regimen A (first visit)	1	£4,301
In-patient visit to deliver adjuvant chemotherapy treatment in Regimen A	55	£2,552
In-patient visit to deliver adjuvant chemotherapy treatment in Regimen B (first visit)	1	£4,301
In-patient visit to deliver adjuvant chemotherapy treatment in Regimen B	67	£2,552
Outpatient visit for MEPACT administration	0.6 of total MEPACT doses	£1,893
Pharmacy time to prepare a MEPACT dose	1 hour/dose	£504

NHS Reference Costs 2006-07
[1]SB14Z: Inpatient chemotherapy: Deliver complex chemotherapy, including prolonged infusional treatment at first attendance
[2]SB15Z: Outpatient chemotherapy: Deliver subsequent elements of a chemotherapy cycle
[3]SB15Z: Outpatient chemotherapy: Deliver subsequent elements of a chemotherapy cycle
[4]Clinical estimate

10.5.2.4 Model assumptions for maintenance chemotherapy and MEPACT costs

The model reflects the treatment groups used in clinical trial INT-0133 and the following assumptions are made regarding treatment costs:

- MEPACT arm: as the MEPACT arm includes patients with MEPACT added on to a 3-agent adjuvant chemotherapy regimen (Regimen A) and 4-agent regimen (Regimen B), the model will assume an average cost for Regimen A and Regimen B, and the cost of a course of MEPACT for maintenance treatment in cycle 1.

- No MEPACT arm: as this arm includes patients with a 3-agent adjuvant chemotherapy regimen (Regimen A) and a 4-agent regimen (Regimen B), the model will assume an average cost for Regimen A and Regimen B for maintenance treatment in cycle 1.

10.5.2.5 Cost of adverse events during maintenance phase

Only clinically relevant treatment-differentiating adverse events are considered in the economic evaluation i.e. those adverse events with a potentially higher incidence rate in the MEPACT treatment arm compared with the no-MEPACT arm are included, which were of clinical relevance. These include:

- Grade 1 and 2 infusion reactions (chills and influenza): MEPACT 98%, no-MEPACT 0%. As Grade 1 and 2 adverse events were not collected in study INT-0133, this estimate was taken from the MEPACT Phase II study (Section 6.7.1), however no comparative estimates were available. Therefore the assumption of 0% for the no-MEPACT arm represents a conservative assumption.
- Hearing loss (objective or subjective): MEPACT 15%, No-MEPACT 8% (INT-0133). Expert opinion considered the higher incidence of hearing loss in the MEPACT group as a data anomaly as hearing loss is associated with cisplatin use. Hearing loss therefore has not been included in the reference case but is explored in a sensitivity analysis.

Table 23 details the adverse events occurring during the maintenance phase, with their associated unit costs.

Table 23: Costs of treatment-differentiating adverse events during maintenance

Adverse event	MEPACT incidence	No MEPACT	Treatment during maintenance phase	Unit cost
Infusion related influenza like symptoms (chills & fever)	98%	0%	Paracetamol 0.5–1g every 4-6 hours to a maximum of 4g daily	£1.91[1]
Hearing loss (objective or subjective)	15%	8%	One audiometry assessment	£50[2]

[1]BNF 56, September 2008, paracetamol 500 mg. Net price 16 = 17p, 32 = 46p, 100 = £1.91 (100 tablets per patient)
[2]NHS Reference Costs 2006-07. AS1A: Fitting of hearing aids and counselling assessment

10.5.3 Disease-Free (DF) State

The Disease-Free state is one of two starting states in the model. Patients are assumed to start in the DF state if they have no evidence of disease post-neoadjuvant chemotherapy and surgery, by post-surgical pathologic assessment i.e. free of gross or microscopic disease.

10.5.3.1 Routine Monitoring

The timing and frequency of routine monitoring of patients, post-maintenance phase has been informed by expert opinion and the EURAMOS I study protocol.

Routine monitoring of patients for weight assessment, clinical examination, thyroid function tests and blood chemistry is usually considered to continue up to and beyond 12 years i.e. the model horizon, if a patient is still alive.

Routine chest X-rays commence after the first 4-months post-maintenance phase and are performed at every visit up to the end of Year 5. Thereafter, no further routine chest X-rays are performed as the risk of disease recurrence is considered small. It is assumed that routine chest X-rays are performed on the same day as routine monitoring, physical examination and blood investigations.

Patients without an amputation are assumed to have a routine X-ray of their primary tumour site every 4-months, up to the end of Year 4 and every 6-months in Year 5. X-rays of primary tumour sites are performed on the same day as routine monitoring, physical examination and blood investigations.

Within 6-months of completion of the maintenance phase, patients experiencing hearing loss have a hearing aid fitted and a post-fitting assessment. Thereafter, patients are assumed to have annual follow-up visits with the audiology department, until the end of 4-years post-maintenance phase, when a replacement hearing aid is fitted. Annual assessments continue after the replacement fitting.

Table 24 and 25 present the estimates for frequency of routine monitoring and resource unit costs, respectively. The cost of routine monitoring is applied for each patient at the appropriate cycle in the model, provided that the patient has survived. Routine monitoring costs cease to be applied when patients move out of the DF state.

Table 24: Frequency of routine monitoring in Disease-Free state

Timing of visit post-maintenance phase	Frequency
Up to 4 months	Monthly
5 months to 1 year	Every 2 months
Year 2	Every 3 months
Years 3 and 4	Every 4 months
Year 5	Every 6 months
Year 6 onwards	Once a year (The EURAMOS 1 study is required twice yearly monitoring but UK expert opinion noted that this is not typical UK practice)

Table 25: Unit costs of routine monitoring

Resource	Description	Unit cost
Outpatient visit	Medical oncology	£116[1]
X-ray	Plain film	£28[2]
Hearing loss	Hearing aid	£105[3]
	Hearing aid fitting	£62[3]
	Follow up assessment	£42[3]

[1]NHS Reference Costs 2006-07. Outpatient specialty code 370 – medical oncology, attendance without treatment
[2]NHS Reference Costs 2006-07. RA28Z, plain film one area: £28
[3]NHS Reference Costs 2006-07. DHA1 Digital Hearing Aid, AS1FA Hearing Aid fitting, AS1FU: Hearing Aid follow up

10.5.4 Disease-Progression (DP) state

The Disease-Progression state is the second of the two model starting states. Patients are assumed to start in this state, if they are not disease-free after neoadjuvant chemotherapy and surgery i.e. there is evidence of disease via post-surgery pathologic assessment, which indicates that the patient is not free of gross or microscopic disease. Such patients are assumed to have never been disease-free. A minority of patients start in this state (Table 29).

10.5.4.1 Second-line chemotherapy for disease progression

Second-line chemotherapy is assumed to be initiated at the end of the maintenance phase, upon recognised disease progression as recorded during the maintenance phase. As there is no standard second-line treatment for

osteosarcoma, UK expert opinion and the EURAMOS trial indicate ifsofamide and etoposide, as appropriate agents. Expert opinion noted that second-line chemotherapy can be administered over a course of 4-10 cycles, with 4-6 cycles being the average number of cycles expected for most patients. Patients with DP are assumed to have no further surgery.

Ifsofamide and etoposide are to be administered on an inpatient basis for an average of 5 cycles, as follows:

- Both treatments are administered on the same day.
- 3-doses of each drug are administered over 3-days.
- 4-inpatient days are required for 3-day dosing.
- Cycles are administered at 3-weekly intervals.

Table 26 outlines the medication costs for second-line chemotherapy with ifosfamide and etoposide, and Table 27 presents the administration costs.

Table 26: Second-line chemotherapy unit costs

Therapy	Dose	Number of cycles	Number of doses/ cycle[1]	Unit cost[2]/ dose for a 1.5m patient	Assumptions
Ifosfamide	2.8g/m^2/day	5	3	£118	Net price 1g vial = £27.03; 2g vial = £45.49
Etoposide	100mg/m^2/day	5	3	£29	Etoposide 20 mg/mL, net price 5mL vial = £12.15, 10mL vial = £29.00, 25mL vial = £60.75

[1]As for EURAMOS 1 study
[2]BNF 56, September2008

Table 27: Inpatient unit costs for second-line chemotherapy

Description	Frequency	Unit cost
In-patient visit to deliver second-line chemotherapy treatment (first visit)	1	£430[1]
In-patient visit to deliver subsequent doses of second-line treatment.	3	£255[2]

NHS Reference Costs 2006-07
[1]SB14Z: Inpatient chemotherapy: Deliver complex chemotherapy, including prolonged infusional treatment at first attendance
[2]SB15Z: Inpatient chemotherapy: Deliver subsequent elements of a chemotherapy cycle

10.5.4.2 Palliative care for Disease-Progression

The economic model assumes that patients progress to palliative care if still in disease progression after second-line chemotherapy. Expert opinion (personal communication, Dr Ian Lewis) advises that care can be daily or weekly, depending on the level of need. Patients experience 4-8 weeks of major symptoms requiring opiate based pain treatment by intravenous infusion and some may be given oxygen treatment, either at home or in hospital. Patients are generally entered into a clinical trial and although the clinical trial drugs are free, it is estimated that the cost of nursing and medical staff due to the intensive resources required for the trial, is approximately £10,000/patient.

No evidence could be found to quantify the resource utilisation for palliative care for patients with osteosarcoma in the UK. To address this evidence gap, a literature search was undertaken in Pubmed to assess UK specific costs for palliative care in childhood cancers. No evidence was identified and the search was broadened to include evidence of non-childhood cancers in the UK. Five studies were identified[108,109,110,111,112]. Three studies were rejected; two did not provide costing information[108,109] and one focused on a comparison of types of opioids[111].

Guest et al.[110] estimated the expected cost of palliative care for terminally-ill cancer patients in the UK after switching from weak to strong opioids, to be in the range £2,500-£4,000 based on 1995/1999 prices. A range of £1,500-£6,000 was determined based on a sensitivity analysis, depending on the length of survival. The key cost drivers were hospice care, hospitalisation, general practitioner consultations and specialist nursing visits. Neither the choice of opioid, nor managing constipation impacted substantially on the expected cost. The expected daily cost per patient was reported to be in the range £22-£82. Approximately 67% of the costs were incurred by the UK NHS, with the remainder incurred by voluntary and charitable sectors. This study was informed by the UK Palliative Care Advisory Committee.

A more recent study by Guest et al.[112] 2006 estimated the palliative care treatment costs for specific cancers: breast, colon, lung, uterus, ovary, prostate and stomach for patients ≥30 years old. The mean NHS cost of palliative care resource use ranged from £1,816 for colon cancer to £4,789 for ovarian cancer. The primary cost driver was hospitalisation which accounted for 35-77% of the total costs. The authors estimated that if non-NHS resources were included i.e. resources funded by the voluntary and charitable sector, then hospice care and specialist nurse visits would add a further £5,000 and £200 onto the cost of palliative care, respectively.

For the economic evaluation, the cost of palliative care for patients in disease progression is assumed to be the average of the mean NHS cost across all cancers i.e. £3,094 (2000/2001 prices). Using the Consumer Price Index (CPI), these prices were adjusted to 2006 prices to correspond with the year chosen for NHS references costs to give an estimate for mean palliative care costs of £3403 and a range of £1,997-£5,367.

Palliative care and second-line chemotherapy costs were assumed to be incurred in the first 6-months after the maintenance phase. Patients surviving beyond 6 months with disease progression did not incur any further costs. Hearing loss adverse events in Disease Progression

Within 6-months of completion of the maintenance phase, patients experiencing hearing loss have a hearing aid fitted and a post-fitting assessment. Thereafter, patients are assumed to have annual follow up visits with the audiology department, until the end of 4-years post-maintenance phase when a replacement hearing aid is fitted. Annual assessments continue after the replacement fitting.

10.5.5 Recurrence State

A transition to the Recurrence state is conditional on a patient having no evidence of disease prior to recurrence. Therefore, transitions to this state are always from the Disease-Free state. Patients suspected of having a relapse from

their routine chest X-ray performed during the DF state are typically asymptomatic. Patients stay in the recurrence state for one cycle only. In this state they incur diagnostic costs and costs of additional surgery or chemotherapy.

10.5.5.1 Diagnostics

A complete reassessment of the patient is performed when recurrence is suspected and diagnostic tests are performed on an outpatient basis (personal communication Dr Ian Lewis). Only the cost of diagnostic tests for confirmed recurrences are included. The following tests are performed over two outpatient visits:

- CT scan.
- Isotope bone scan.
- MRI of the primary and other tumour sites.
- Blood tests, which are assumed to be included in the cost of an outpatient visit.
- Insertion of a central line. It is assumed that at the end of the maintenance phase all central lines relating to adjuvant chemotherapy and MEPACT treatment are removed. Therefore recurrences occurring after maintenance treatment require reinsertion of a central line, which is performed during an inpatient overnight stay.

10.5.5.2 Surgery and second-line chemotherapy at Recurrence

As recurrence was an endpoint in study INT-0133, information pertaining to a patient's disease-free/disease progression status after recurrence (with the exception of death) was not collected consistently in the study. Only information on withdrawal and death status together with the site of recurrence were collected for these patients. Table 5 presents a summary of the site of disease recurrence in study INT-0133 indicating that approximately 50% of patients had pulmonary metastases only. The literature was therefore used to inform on further assumptions regarding resource and outcomes post-recurrence. Ferrari et al.[44] report 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 i.e. similar to study INT-0133. A total of 125 patients had lung metastases only, 93 (75%) achieved surgical remission after surgery alone (69%) or surgery and chemotherapy with high dose ifosfamide (31%).

Of the 37 patients who had 'other than lung metastases' alone, 21 (57%) achieved surgical remission after surgery alone (38%) or surgery and chemotherapy with high dose ifosfamide (62%).

Of the 48 patients not achieving surgical complete remission, there was insufficient information to assess the frequency of surgery and/or second-line chemotherapy. For lung metastases, the same rates of surgery and second-line chemotherapy are assumed. For 'other than lung metastases' it was assumed that the 14 unaccounted patients who received chemotherapy alone were in this group (88%) and the remaining 12% received surgery alone. Second-line chemotherapy was assumed to be the same as for disease progression i.e. ifosfamide and etoposide administered on an inpatient basis for an average of 5 cycles with:

- Both treatments being administered on the same day.
- 3-doses of each drug being administered over 3-days.
- 4-inpatient days being required for 3-day dosing.
- Cycles being administered at 3-weekly intervals.

Table 28 outlines the costs associated with recurrence diagnosis and surgery. Two outpatient visits for diagnostic evaluation and a further 3-day elective inpatient stay for surgery are assumed. These costs are applied for each patient at the point of recurrence in the model.

Table 28: Recurrence diagnostic and surgery resources and unit costs

Diagnosis	Frequency	Unit cost	Total cost applied to the economic model
CT scan	1	£100[1]	£108
MRI	1	£278[2]	£247
Isotope bone scan	1	£183[3]	£183
Outpatient visits	2	£189[4]	£378
Inpatient visit for central line insertion	1	£2,281[5] (<18 years) £3,481[5] (>19 years)	£2,281
Surgery			
Salvage surgery (pulmonary) (3-day inpatient stay)	1	£1,809[6] *3	£5,426
Salvage surgery (non-pulmonary) (3-day inpatient stay)	1	£2,056[6] *3	£6,168

[1]NHS Reference Costs 2006-07 (Code: RA11Z, Computerised Tomography Scan, two areas, no contrast)
[2]NHS Reference Costs 2006-07 (Code: RA02Z, Magnetic Resonance Imaging Scan, 2-3 areas, no contrast)
[3]NHS Reference Costs 2006-07 (Code: RA36Z, Nuclear Medicine, Category 2)
[4]NHS Reference Costs 2006-07 (Outpatient specialty code 370, Medical Oncology, attendance without treatment)
[5]NHS Reference Costs 2006-07 (Code: EA36B and EA36Z: Catheter 18 years and under and Catheter 19 years and over)
[6]The unit cost of pulmonary salvage surgery is sourced from Reference Costs 2006-07. It is equal to an average of three elective inpatient HRGs (DZ09A, DZ09B, DZO9C: Pulmonary Embolus procedures) with respective unit costs of £2,209, £2,230 and £987.
[7]The unit cost of non-pulmonary salvage surgery is sourced from Reference Costs 2006-07. It is equal to an average of three elective inpatient HRGs (HD36A, HD36B, HD36C: 'Pathological Fractures or Malignancy of Bone and Connective Tissue) with respective unit costs of £3,052, £1,793 and £1,322.

10.5.6 Post-Recurrence: Disease-Progression

The estimates for survival post-recurrence are taken from Ferrari et al.[44]. In patients who failed to achieve complete surgical remission, post-recurrence survival did not differ according to the site of first recurrence but was influenced by the use of chemotherapy. The post-recurrence 1-year survival rate was 53% for patients who received chemotherapy versus 12% for those who did not. Within 2 years, all patients were dead. As the number of patients receiving chemotherapy was not transparent for the group of patients with non-surgical remission[44], survival assumptions were based on Figure 1, Plot D[44]. Post-recurrence survival rates at 1 year, 18 months and 2 years were assumed to be 0.4, 0.18 and 0 respectively, implying a death rate of 60% in year 1, 82% in year 2 and 100% in year 3.

Assuming a fixed rate with respect to time: the instantaneous event rate (death rate of 82% at year 2) = -Ln (1-0.82)/4 = 0.429. The 6-month probability of dying is then assumed to be: 1-exp (-0.429*1) = 0.349. This 6-month probability is assumed for the 18-month period post-recurrence. Thereafter, at 2 years post-recurrence all patients are assumed to have died.

Patients are assumed to have palliative care when in the Post-Recurrence: Disease-Progression state. As all patients die within 18-months (3 cycles) in this state, this has been set up as a 3-tunnel state. Palliative care costs are incurred at the point of death in the model.

10.5.7 Post-Recurrence: Disease-Free (surgical remission)

The estimates for survival post-recurrence are taken from Ferrari et al.[44]. In patients who achieved complete surgical remission, post-recurrence survival was influenced by both relapse site and the length of the relapse-free interval (≤24 or >24 months). The 5-year post-recurrence survival rates were reported as 20% and 60% for recurrences occurring within ≤24 and >24 months, respectively.

10.5.7.1 *Probability of death Post-Recurrence*

Recurrences occurring at ≤24 months

A survival rate of 20% at 5 years (≈ ten/6 monthly cycles) corresponds to a death rate of 80%. Assuming a fixed rate with respect to time, the instantaneous event rate = -Ln (1-0.8)/10 = 0.161. Then the 6-month probability of dying is assumed to be: 1-exp (-0.161*1) = 0.1487. This 6-month probability is assumed for the period of recurrence until the end of the model horizon.

Recurrences occurring at >24 months

A survival rate of 60% at 5 years (≈ ten / 6 monthly cycles) corresponds to a death rate of 40%. Assuming a fixed rate with respect to time, the instantaneous event rate = -Ln (1-0.4)/10 = 0.0511. Then the 6-month probability of dying is assumed to be: 1-exp (-0.0511*1) = 0.0498. This 6-month probability is assumed for the period of recurrence until the end of the model horizon.

10.5.7.2 Routine monitoring Post-Recurrence for patients in surgical remission

Routine monitoring post-recurrence is assumed to be the same as routine monitoring for the Disease-Free state. Patients are assumed to have palliative care prior to dying in the Post-Recurrence: Disease-Free state and these costs are incurred in the model at the point of death.

10.5.8 Starting states: patient allocation

The number and proportion of patients entering the maintenance phase and starting in the Disease-Free and Disease-Progression states are summarised in Table 29.

Table 29: Patients entering the maintenance phase of study INT-0133

Treatment group	Patients entering maintenance phase	Patients disease-free post-surgery	Patients with evidence of disease post-surgery	Proportion of patients starting in Disease-Free state	Proportion of patients starting in Disease-Progression state
MEPACT	303	298	5	0.983498	0.016502
No MEPACT	301	299	2	0.993355	0.006645

10.5.9 Handling of withdrawals

The transition probabilities based on the INT-0133 data also included transition probabilities from the non-absorbing states (Disease-Free, Disease-Progression and Recurrence) to Withdrawal i.e.

- Disease-Free $\rightarrow$ Withdrawal
- Disease-Progression $\rightarrow$ Withdrawal
- Recurrence $\rightarrow$ Withdrawal

10.5.9.1 Disease-Free state

On the advice of expert opinion, patients who transitioned from the Disease-Free state to Withdrawal were reallocated to: Disease-Progression or Recurrence based on the transition probabilities in the same cycle. Reallocation to Recurrence was based on the probability of Disease-Free ->Recurrence in the

same cycle. Reallocation to Disease-Free was based on the sum of the probabilities of (Disease-Free ->Recurrence + Disease-Free ->Death + Disease-Free ->Withdrawal),ensuring that the transition probabilities from the Disease-Free state summed to 1. Patients were assumed to continue through the model using the established transition probabilities for those patients who did not withdraw.

10.5.9.2 Disease-Progression State

Patients who withdrew in the Disease-Progression state were assumed to transition to the Disease-Progression state and continue through the model using the established transition probabilities for those patients who did not withdraw. It is noted that no patients commencing in the Disease-Progression state transitioned to the Disease-Free state.

10.5.9.3 Recurrence

As recurrence was an endpoint in study INT-0133, information pertaining to a patient's 6-monthly Disease-Free/Disease-Progression status after recurrence was not standardly recorded. Only Withdrawal and Death status were recorded for these patients. The literature was, therefore, used to inform the assumptions regarding resource and outcomes post-recurrence for all patients who had a recurrence and no withdrawals (see Sections 6 & 7).

10.5.10 Derivation of the utility estimates

10.5.10.1 EQ 5D survey in osteosarcoma patients

The EQ 5D survey in a UK treatment centre (St James Hospital, Leeds) was intended as the primary source of utility data for the economic model. Table 30 presents the characteristics of the 22 patients included in the survey.

Table 30: EQ 5D survey-Osteosarcoma patient characteristics (n=22)

Characteristic	Number (range)	Percentage
Gender:		
Male	15	68%
Female	7	
Current age:		
<10 years	1	5%
11-18 years	6	27%
19-30 years	13	59%
>30 years	2	9%
Age at diagnosis:		
<10 years	7	32%
10-14 years	6	27%
14-18 years	7	32%
>18 years	2	9%
Currently on treatment	0	0%
Previously experienced a recurrence	4	18%
Surgery received:		
Limb (leg) Amputation*	4	18%
Limb-salvage surgery**	21	95%
Other surgery***	6	27%

*3 patients also received limb-salvage surgery. 1 patient received an above knee amputation
** Primarily endoprosthetic replacement with/without leg lengthening.
*** Primarily one or more thoracotomies,

10.5.10.2 Review of NICE Assessment Group independent cancer model utilities

The NICE HTA review identified 6 cancer technology appraisals not performed as a single technology appraisal, thereby including the possible development of an independent economic model by the NICE Assessment Group. Utilities from this source were assumed overall to be the most robust or reliable for the specific appraisals as they were generated following consideration of a wide set of information available to the Assessment Group including manufacturer submissions, publications and other sources. Not all non-STA appraisals contained an independent model (some, particularly the earlier appraisals, contained only reviews of the manufacturer model). In addition, for some appraisals the utilities used for cancer health states were not clearly specified or available (e.g. due to commercial in confidence restrictions, or the Assessment Group report not being accessible via the NICE website). In the six published or ongoing appraisals selected the utilities were sufficiently clearly specified in the

Assessment Group reports for the exercise (available from the NICE website). The included Assessment Group reports were[113,114,115,116,117,118].

A limitation was that none of the technology appraisals considered bone tumours or childhood cancer and so the utilities were not directly relevant. However, they have been applied, with some adjustments based on the EQ 5D survey in patients, to fill gaps in the utility data needs for the economic model. The primary and most robust source of utility data for the model comes from the EQ 5D survey.

The details of the six technology appraisals and the individual utility estimates are presented in Table 31. The individual disease states from the Assessment Group reports were grouped into disease-free, disease progression/recurrence and disease progression/late stage disease (to death) categories. The average of the utilities for each category of health state was then calculated, as shown in Table 32. For the technology appraisals and utilities that were included there is likely to be a degree of selection bias. However, the utilities identified represent plausible values and, where direct values from the osteosarcoma EQ 5D survey are absent, are reasonable to use for defined health states (with adjustments) in the MEPACT economic model. The utilities have been subject to sensitivity analysis.

Table 31: Cancer technology appraisals included in the NICE HTA review

Technology Appraisal (TA)	Health states (HS)	Mean utility weight	Utility weight [range] and SD	Utility Method	Assessment Group Report Source & patient group covered in TA
TA70- Imatinib for 1st line treatment of chronic myeloid leukaemia in chronic phase. Oct 2003	Chronic phase – on imatinib [stable/benign] Chronic phase – on interferon-α Accelerated phase – all treatments Blast phase [progression to death]	0.85 0.71 0.73 0.52	SD=0.1925 SD=0.2658 SD=0.204 SD=0.424	Stated as patient based values provided in manufacturer submission.	Dalziel et al, 2003 *Typical age for CML is 45-55, but also in younger 30+, rarely below 20.*
TA100 - The use of oxaliplatin and capecitabine for the adjuvant treatment of colon cancer. April 2006	On adjuvant chemotherapy (without side effects) On adjuvant chemotherapy (with side effects) In remission On palliative chemotherapy	0.70 0.63 0.92 0.24	SE=0.036 SE=0.036 SE=0.05 SE=0.041	Published estimates: Standard Gamble in 81 patients with colorectal cancer; Health Utilities index (HUI) in 173 patients (40 advanced)	Pandor et al, 2005 *Highest incidence in age 75+, with cases 45-75 years also*
TA101 - docetaxel in combination with prednisone or prednisolone for the treatment of hormone refractory metastatic prostate cancer. June 2006	Metastatic disease (12 months before death)	0.538	N/A	EQ 5D in 1237 patients from published cost-utility study	Collins et al, 2005 *Typical patient age is >75 years*
TA118 - The use of bevacizumab and cetuximab for the treatment of metastatic colorectal cancer. Jan 07	Progression-free disease Progressive disease	0.80 0.60	N/A N/A	Assessment group adjustment of published utilities using standard gamble technique in 30 oncology nurses	Tappenden et al, 2006 *Highest incidence in age 75+, with cases 45-75 years also*

Technology Appraisal (TA)	Health states (HS)	Mean utility weight	Utility weight [range] and SD	Utility Method	Assessment Group Report Source & patient group covered in TA
TA121 - Carmustine implants and temozolomide for the treatment of newly diagnosed high-grade glioma, June 2007	Stable malignant glioma Progressive malignant glioma	0.89 0.73	[0.525, 1] SD=0.1284 [0.125, 0.995] SD=0.2067	Standard Gamble using Sheffield Value of Health Panel (n=36)	Garside et al, 2005 *Typical age of patients 70-74, although also occurs in children 5-9 years*
TA in development - Bevacizumab, sorafenib, sunitinib and temsirolimus for renal cell carcinoma. 2008	PFS first-line treatment good prognosis PFS second-line treatment poor prognosis Disease progression first- line treatment good prognosis Disease progression secondline treatment poor prognosis	0.78 0.60 0.70 0.45	SE=0.01 SE=0.02 SE=0.06 SE=0.04	EQ 5D in clinical trials	Thompson Coon et al, 2008 *Incidence highest in age >65's in men and >55's in women, with cases mostly in >40 year population.*

Table 32: Average utility by category of health state from the NICE HTA review

Health state category	Utilities relevant for category (from Table 31)*	Average utility for health state category
Disease-free	TA70 HS1 (0.85), TA100 HS3 (0.92), TA118 HS1 (0.80), TA121 HS1 (0.89), TA in development HS1 (0.79)	0.85
Disease progression/recurrence	TA70 HS3 (0.73), TA118 HS2 (0.60), TA121 HS2 (0.73); TA in development HS3	0.69
Disease progression/late phase (to death)	TA70 HS4 (0.52); TA100 HS4 (0.24), TA101 HS1 (0.54); TA in development HS4 (0.45)	0.44

*Excluded utilities from Table 31 were: TA70 HS2 (utility likely to be heavily influenced by side effects of treatment); TA100 HS1 & 2 (non-specificdisease states, couldn't readily be categorised); TA in development HS2 (health state couldn't readily be categorised).

Table 33: Economic model assumptions

Number	Description	Assumption	Justification	Source
1	MEPACT	The average surface area of a patient receiving MEPACT is 1.5m^2 and therefore only one vial is required for each dose administration.	Average body surface estimate for: Children: 1.14m^2 Adolescents: 1.42m^2 Young adults 1.7m^2	Personal communication Dr Ian Lewis
2	MEPACT	1 hour pharmacy preparation time is required for the preparation of MEPACT.		Expert opinion
3	MEPACT	Approximately 30% of MEPACT doses will require an extra outpatient visit.	It is expected that approximately 70% of doses can be administered on the same day as other adjuvant chemotherapy agents i.e. doxorubicin, cisplatin, methotrexate and ifosfamide.	Expert opinion /INT-0133
4	MEPACT	Patients receive on average 36-40 doses of MEPACT.	Not all patients received 48 MEPACT doses in maintenance phase	Table 2 (taken from INT-0133)
5	Amputation and limb-salvage	25% of patients will have an amputation and 75% limb-salvage.	UK rates	Lewis et al.[26]
6	Treatment-emergent adverse events	Treatment differentiating AEs included in the economic evaluation are: Fever/influenza symptoms infusion/reactions Hearing loss, Grade 3 or 4	MEPACT clinical data	INT-0133 and Phase II study (Section 6.7)
7	Routine Monitoring	After the adjuvant chemotherapy, an expected cost for routine monitoring is applied to each patient.	Routine monitoring reflects UK clinical practice and is assumed to cease at the time of recurrence to reflect a change in the pattern of care.	Personal communication (Dr Ian Lewis)
8	Disease Progression	Patients are assumed to receive ifosfamide and etoposide as second-line chemotherapy.		Personal communication (Dr Ian Lewis), EURAMOS I study

9	Palliative care	Palliative care is assumed to commence at the point of disease progression, post-adjuvant chemotherapy.		
10	Recurrence	At time of recurrence, patients are categorised as either having “Lung metastases” only or “Other than lung metastases” with an assumed probability of 0.5.	INT-0133 estimates are: MEPACT No MEPACT Lung Met. 53% 47% Other 47% 53%	Literature suggest estimates of 0.75% Ferrari et al.[44]
11	Recurrence	75% of patients with lung metastases and 57% with other than lung metastases achieve Disease-Free status after surgery.	Ferrari et al,[44]	
12	Costs	Any costs incurred more than 1 year post-treatment are discounted at a rate of 3.5%.		
13	Utilities	Utilities for health states – see Table 10 in Section 7.2.8 Disutility of 18% for hearing loss (MEPACT adverse event)	Derived from osteosarcoma patients, and other cancers adjusted for Published estimate in cancer. Identified as only additional adverse event that would impact on patient quality of life	EQ 5D survey in osteosarcoma patients,[103] NICE HTA review EQ 5D survey [107], Expert opinion

Table 34: Overview of patient status during each 6-month cycle, post commencement of 9-month maintenance phase

		Cycle of 6 months (Counts), Cycle 1 of 9-month duration																							
	State	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
MEPACT	Disease	5	4	4	2	2	2	2	1	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0
	Recurrences	4	16	15	10	6	6	5	4	0	0	1	0	0	1	0	0	0	0	0	0	0	0	0	0
	Post-Recurrence	0	3	15	23	29	31	28	27	28	24	22	18	17	16	16	14	13	10	9	5	3	1	0	0
	Deaths	3	3	5	9	4	5	9	4	4	4	2	5	0	0	1	0	1	1	0	0	0	0	0	0
	Withdrawals	3	2	2	2	4	5	9	9	11	11	13	18	10	9	12	19	8	19	14	23	11	9	14	3
	Disease-Free	288	269	251	239	229	217	203	193	181	170	156	139	130	121	109	92	84	67	54	35	26	19	6	3
	Total N	303	297	292	285	274	266	256	238	225	210	195	180	157	147	138	125	106	97	77	63	40	29	20	6
No MEPACT	Disease	2	2	2	2	2	2	1	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Recurrences	8	21	19	11	6	8	6	4	2	0	1	1	1	0	0	0	0	0	0	0	0	0	0	0
	Post-Recurrence	0	5	18	27	31	29	31	28	30	25	16	14	12	13	11	10	9	4	3	1	1	1	1	0
	Deaths	4	4	10	10	8	8	5	7	1	6	9	2	2	1	1	0	0	3	0	0	0	0	0	0
	Withdrawals	3	3	1	3	4	1	8	13	6	11	10	12	11	11	7	16	13	17	15	23	14	8	4	4
	Disease-Free	284	259	237	223	212	203	191	176	169	159	149	137	126	114	108	93	81	66	52	31	17	9	5	2
	Total N	301	294	287	276	263	251	242	229	209	202	185	166	152	139	127	119	103	90	70	55	32	18	10	6

For each cycle, “Total N” represents the number of patients starting in the cycle and the other counts represent the number of patients transitioning to that state in the next cycle