NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

SPECIFICATION FOR MANUFACTURER/SPONSOR SUBMISSION FOR SINGLE TECHNOLOGY APPRAISAL (STA)

VELCADE® (BORTEZOMIB) FOR THE TREATMENT OF MULTIPLE MYELOMA PATIENTS AT FIRST RELAPSE

Contents

Executive Summary

Background to Multiple Myeloma (MM)

- Multiple myeloma (MM) is a rapidly progressing, incurable haematological cancer. As well as reducing life expectancy, MM causes significant morbidity. Typically, the symptoms are painful, distressing and disabling, and include lytic bone lesions leading to pathological fractures of the long bones and vertebral collapse, renal failure, anaemia, and neutropenia leading to serious and recurrent infections.

Background to VELCADE

- VELCADE which has a unique mechanism of action was developed following the scientific research into the regulation (via the proteasome) of intra-cellular signalling proteins which control cell proliferation; this research was awarded the Nobel prize for chemistry in 2004 (1)

- VELCADE, a first in class proteasome inhibitor, targets specific biological pathways in myeloma cells, disrupting normal intra-cellular protein regulation, leading to apoptosis (programmed cell death).

- VELCADE received its initial licence in 2004 for the treatment of relapsed and refractory MM. In April 2005, based on the clinical results from the phase III APEX trial, VELCADE received an extension of its licence to allow use as a mono-therapy for the treatment of progressive MM in patients who have received at least one prior therapy (at first-relapse) and who have already undergone or are unsuitable for bone marrow transplantation.

- The use of VELCADE within its licensed indications for the treatment of patients at first relapse has been endorsed by the UK Myeloma Forum (UKMF) and British Committee for Standards in Haematology (BCSH) in the recently published BCSH position paper (2).

- In UK clinical practice, many clinicians consider using VELCADE in combination with dexamethasone because of the synergistic relationship observed between these two agents (3-5). This practice is reflected in the design of a proposed protocol extension within the independent MRC Myeloma IX trial (6, 7), in which the combination of VELCADE and dexamethasone is included as treatment for patients at first relapse. It is also a recommendation of the BCSH position paper. Within the SmPC for VELCADE, guidance is given with respect to the combination use with dexamethasone.

Clinical results for VELCADE

- The Phase III, randomised controlled APEX trial was designed to evaluate the efficacy and safety of VELCADE as a monotherapy agent compared with High Dose Dexamethasone (HDD) in patients with MM who had received one to three lines of prior therapy (8, 9).

- APEX is the largest study performed in relapsed MM patients to date, involving a total of 669 patients in 93 major cancer centres in 12 European and North American countries. In the UK a total of 51 patients were recruited in 7 centres.

- HDD was considered the most appropriate comparator because it is a licensed effective monotherapy agent for the treatment of MM and was endorsed by the regulatory authorities when designing the APEX trial. Newer experimental compounds continue to be evaluated against HDD (10-12).

- The clinical superiority of VELCADE compared to HDD became apparent during the APEX trial to such a degree that the independent data monitoring committee (IDMC) following a predetermined interim analysis deemed it unethical to continue with the APEX trial after 8.3 months follow-up. They also recommended that patients in the HDD arm should be offered the opportunity to receive VELCADE treatment as soon as possible.

- Overall, VELCADE demonstrated efficacy in first relapse MM patients that was superior to the conventional chemotherapy, HDD, in terms of rapid response rates, extended survival and delayed time to disease progression (8).

- One-year survival was significantly prolonged in patients receiving VELCADE compared to HDD (p=0.003). VELCADE-treated patients experienced a 41% decreased risk of death in the first year of treatment (hazard ratio 0.57, p=0.001).

- Because of the high crossover rate, 62% of HDD patients received VELCADE in APEX (9), it is difficult to determine the precise difference in terms of survival advantage for VELCADE compared to HDD. VELCADE nevertheless continues to demonstrate a significant survival advantage with an estimated median survival difference of 6.1 months at 22 months follow-up.

- Quality of life of patients treated with VELCADE was superior to HDD.

- Adverse events with VELCADE were manageable, generally reversible and predominantly mild to moderate in severity.

- Combination of VELCADE with dexamethasone enhances response rates providing a highly efficacious combination treatment option. This synergistic effect was observed in the Phase II SUMMIT and CREST trials (3, 4). Within the CREST trial adding dexamethasone to VELCADE in patients who achieved an inadequate response to VELCADE alone boosted response rates from 50% to 62% (3). In UK clinical practice, many clinicians consider starting VELCADE in combination with dexamethasone, or add dexamethasone to VELCADE monotherapy non-responders, typically after two cycles.

- In the APEX trial, the majority of patients (85%) who responded to treatment did so by the third cycle. Despite this, within the rigorously controlled setting of the APEX trial non-responding patients were allowed to continue treatment with VELCADE. It is now clear that using VELCADE in patients that are not responding to treatment after three cycles would increase drug costs for little additional benefit. Therefore, an appropriate strategy within routine clinical practice would be to continue treatment in those patients responding to treatment (up to a maximum of eight cycles as per SmPC) and stop in those patients not responding. Economic analyses (discussed below) indicate that it is more cost-effective to stop treatment in non-responders after three cycles.

Cost-effectiveness of VELCADE

- A modelling approach, built around current UK clinical practice has been adopted to evaluate the economic benefits of VELCADE compared to HDD for the treatment of MM at first relapse. The model uses VELCADE clinical data from the

APEX trial, supplemented with peer reviewed published data, to address analytical challenges associated with early termination of this study.

- In the context of UK decision-making, the APEX trial has a number of limitations that impact its applicability for cost-effectiveness analysis. The early termination of the trial, as well as the use of VELCADE according to a clinical trial protocol does not fully reflect current clinical practice in the UK.

- The model has been designed to be able to consider the impact on survival and cost-effectiveness of strategies such as combination therapy with HDD and withdrawal of treatment from VELCADE non-responders.

- The basecase economic modelling result demonstrates that VELCADE as a single agent results in an incremental mean discounted survival gain of 9.9 months compared to HDD (11.2 months undiscounted).

- The cost per life-year gained (LYG) with VELCADE monotherapy compared to HDD at 1st relapse was £30,750.

- However, if a rule is implemented whereby non-responders stop treatment after three cycles, the cost per LYG with VELCADE treatment versus HDD is £28K. VELCADE acquisition costs are reduced by over £5K in this analysis compared to basecase.

- Combination of VELCADE and HDD increases the (discounted) survival advantage from 9.9 months to 11.0 months, at marginal additional cost. The cost per LYG in this analysis is £28K.

- These results demonstrate that the cost per LYG for VELCADE was between £28K and £31K depending on the scenario tested.

- The most cost-effective strategy to use within routine clinical practice would be to limit VELCADE non-responders to three cycles of treatment and continue treatment in responders for a maximum of eight cycles in line with the recommendations in the SmPC.

Conclusions

- VELCADE, a first in class proteasome inhibitor is an effective treatment option for patients at 1st relapse of MM. In the APEX trial treatment with Velcade has been found to be clinically effective in terms of maximising depth and duration of response and increasing survival (59% improvement at 1-year) compared to HDD.

- A lifetime survival analysis conducted as part of the cost-effectiveness model shows an incremental (discounted) survival benefit with VELCADE of 9.9 months versus HDD at first relapse. The economic model shows that the cost per LYG versus HDD is between £28K and £31K. The cost per LYG is lowest when treatment is withdrawn from patients who fail to respond after 3 cycles.

1 Background

The purpose of the background section is to summarise and contextualise the decision problem. It should contain the following information.

1.1 Summary of decision problem [maximum 600 words]

The purpose of this section is to summarise the decision problem and state the key factors that are addressed in the submission:

1. intervention

VELCADE® (bortezomib) is a novel first in class proteasome inhibitor which specifically and reversibly targets an intra-cellular structure known as the proteasome. The research into the proteasome, and its role in regulation of key intra-cellular signalling proteins [which subsequently led to the development of VELCADE] was awarded the Nobel Prize for Chemistry in 2004 (1). Through inhibition of a single target, the proteasome, it can affect numerous biological pathways including cell cycle regulation and apoptosis. Proteasome inhibition has been shown to be particularly effective in treating multiple myeloma (MM).

2. population, including subgroups

The population covered in this submission are MM patients at first relapse and beyond. MM is a debilitating, incurable disease which has a poor prognosis and is universally fatal. The median age at diagnosis is 65 years with one-year survival rates of approximately 60% and five-year survival rates of approximately 25% (13, 14). In the absence of treatment, MM is slightly more common in males than females (14, 15), and the incidence rate among Afro-Carribeans is higher than for Caucasians of European descent (16).

3. relevant comparator(s)

HDD is an appropriate comparator because it is a licensed monotherapy agent with proven efficacy in first relapse patients, which is commonly used in clinical practice in the UK. HDD was the comparator agreed with the FDA and EMEA as the basis for regulatory approval of the APEX trial. In clinical practice, at first relapse, there is not full consensus as to which treatments to use, and therefore treatment choices tend to be dependant upon the clinical condition of the individual patient. With the exception of HDD, and now VELCADE, there are no other currently licensed treatments available for treatment of MM following first relapse.

4. outcomes

The outcomes addressed in this submission are clinically meaningful to the treatment of first relapse within MM:

- Response Rates (overall, time to achieving and duration of)
- Time to disease progression

- Survival (overall and one-year)
- Quality of life

5. key issues.

The key issues to be considered are:

1. Meeting the clinical challenges in MM

MM is an incurable disease. The aim of treatment is to reduce morbidity and to extend survival for as long as possible. A major problem is that all patients will eventually relapse following treatment. Following relapse, treatment options become increasingly limited, and there is an urgent unmet clinical need for new and effective therapeutic agents to be available. Following initial treatment with standard chemotherapy agent's patients frequently become refractory to further courses of chemotherapy. VELCADE, because of its novel mechanism of action can be effective in such patients.

2. VELCADE evidence base

The phase III randomised, controlled APEX trial is the largest study performed in relapsed MM patients to date, involving a total of 669 patients in 93 major cancer centres in 12 European and N American countries including the UK (8).

The Independent Data Monitoring Committee terminated the APEX trial prematurely after 8.3 months follow-up, when the predetermined interim analysis showed superior efficacy with VELCADE compared to HDD. Although ethically and clinically unavoidable, the early termination of the APEX trial and the subsequent cross-over of patients from the HDD arm to VELCADE treatment presents a number of methodological challenges in terms of quantifying the precise benefits (including overall survival and duration of response) accruable to VELCADE compared to HDD and other incremental health outcomes and associated costs for use in economic evaluation, which are necessary to inform clinical decision-making.

The main objective of the APEX study was to evaluate the clinical efficacy and safety profile of VELCADE as a single agent. The study design, choice of comparator and selection of outcome measures were guided by the requirements of regulatory agencies such as the EMEA, FDA and MHRA. Whilst the APEX trial is internally valid, there are some elements of this regulatory trial design which impact on its external validity. In particular, some elements of the study design do not now reflect the use of VELCADE in the UK.

In particular, a major impact on the health economic determination is that within the APEX study patients who did not respond to VELCADE were allowed to continue on treatment. However, in UK clinical practice, many cancer networks have developed guidelines limiting the number of cycles of VELCADE in patients not responding (2). The benefits of this approach are numerous in that patients are not unnecessarily exposed to cancer treatments and potential associated adverse events and from an economic perspective, this approach would be expected to minimise costs and ensure a more efficient use of resources.

A second factor which needs to be considered is that in the UK, clinicians prefer to treat all stages of MM with combination therapy. The rationale is that an effective combination of synergistic agents can increase response rates and have the potential to prolong survival relative to monotherapy. In UK clinical practice, VELCADE is frequently used in combination with dexamethasone. This treatment strategy has been recommended in clinical practice guidelines and by clinicians. Regulatory

constraints have meant that the APEX trial only assessed VELCADE as a single agent.

In undertaking the health economic evaluation of VELCADE, we believe it is important not only to consider the available evidence from carefully controlled randomised clinical trials, but also to consider the impact of both the combination synergy with Dexamethasone, and also the clinical application of a "stopping rule" in non-responders.

1.2 Description of technology under assessment

6. Give the brand name, approved name and where appropriate, therapeutic class.

Brand name: VELCADE®

Approved name: Bortezomib

Therapeutic Class: Antineoplastic agent

7. Does the technology have a UK marketing authorisation/CE marking for the indications detailed in this submission? If yes, please give the date it received it. If no, please state current UK regulatory status, with relevant dates (for example, date of application and/or expected approval dates).

Yes. This was received on the 20th of April 2005.

8. Does the technology have regulatory approval outside of the UK?

Yes. VELCADE has been approved in 62 countries worldwide.

9. If the technology has not been launched, please supply the anticipated launch date for the UK.

N/A

10. Is the technology subject to any other form of Health Technology Assessment either in the UK or elsewhere? If so, what is the timescale for completion?

This submission is for the use of VELCADE in relapsed MM patients who have received at least one prior therapy (first relapse and later).

UK
The Scottish Medicines Consortium (SMC) will be reviewing VELCADE "mono-therapy for the treatment of progressive MM in patients who have received at least 1 prior therapy and who have already undergone or are unsuitable for bone marrow transplantation". We plan to make a submission to the SMC soon.

Canada
Submissions have been made to both the Ontario Drug Board (ODB) and to Quebec for relapsed and refractory disease (not the indication in this submission)

It is likely that a decision on the Quebec submission will be available by June 2006. The ODB does not follow pre-set timelines for submission review.

Australia
Submissions have been made to the Pharmaceutical Benefits Advisory Committee (PBAC) for relapsed and /or refractory disease. The decision is expected by end of April 2006

11. What is the principal mechanism of action of the technology?

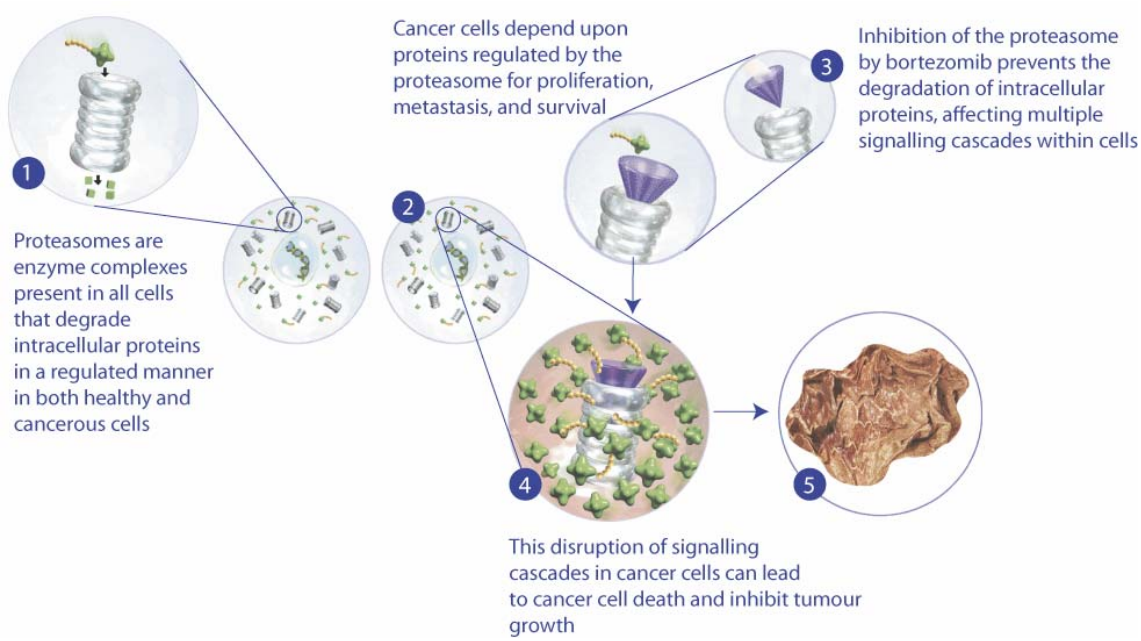
VELCADE is the first of a novel class of anticancer compounds known as proteasome inhibitors. Its development followed a research programme into the ubiquitin proteasome pathway in the regulatory processes of eukaryotic cells, which was awarded the 2004 Nobel Prize for Chemistry. The Nobel Committee specifically mentioned the development of VELCADE as an important outcome of their work. The development of VELCADE involved the collaboration of up to 100 academic and clinical centres throughout the world. This collaborative model has become the paradigm for the development of other targeted therapies and has allowed for the rapid translation of research in the molecular genetics of cancer to novel therapies.

Mechanism of Action

- VELCADE was designed to specifically and reversibly target an intracellular structure called the proteasome.
- Proteasomes are cylindrical, multi-enzyme complexes present in all cells that degrade proteins in a regulated manner.
- Cancer cells depend upon proteins regulated by the proteasome for proliferation, metastasis and survival.
- Inhibition of the proteasome prevents degradation of intracellular proteins, affecting multiple signalling cascades within cells.
- This disruption of signalling cascades in the cell can lead to cancer cell death and inhibit tumour growth.

These steps are summarised graphically in Figure 1 below

Figure 1: Overview of the Antineoplastic Activities of VELCADE



Multiple Effects of Proteasome Inhibition

The proteasome is a single target that affects multiple pathways important for cancer. Inhibiting protein degradation by the proteasome has the potential to drive cancer cells to apoptosis, prevent metastasis, overcome treatment resistance, and interfere with the interaction of cancer cells and their microenvironment. Proteasome inhibition has been shown to be particularly effective in treating MM.

VELCADE confounds cancer cells in numerous ways. Some of the best characterised pathways influenced by proteasome inhibition involve:

- **Gene transcription**: VELCADE prevents gene expression of many proteins involved in tumour cell progression, treatment resistance to cancer therapies, and tumour survival.
- **The cell cycle:** VELCADE can stop cancer cells from dividing by promoting a build-up of proteins that regulate the cell cycle. High levels of these proteins within the cell produces confounding signals leading to programmed cell death (apoptosis).
- **Angiogenesis:** VELCADE inhibits the growth of new blood vessels (angiogenesis) which supply the tumour with oxygen and nutrients.
- **Apoptosis:** VELCADE alters the production of chemicals crucial for the survival of cancer cells.

VELCADE, MM and the Tumour Microenvironment

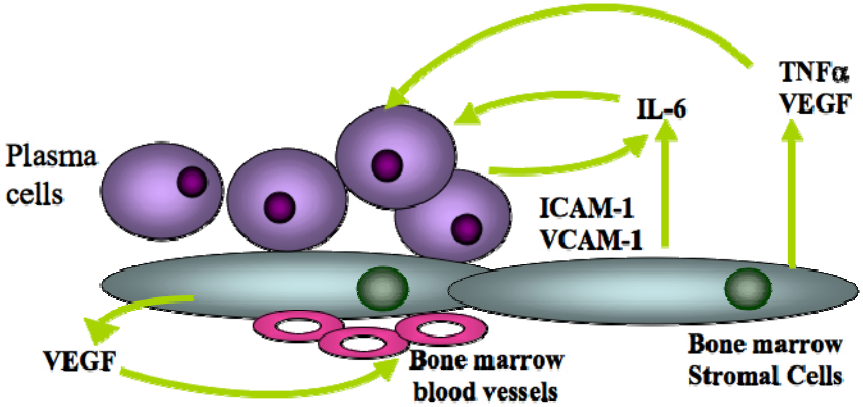
By affecting multiple biological pathways, VELCADE can directly target the tumour's microenvironment in the bone marrow. When MM cells migrate to bone, signalling occurs between the tumour cells and the bone marrow stromal cells. Both the MM cells and bone marrow stromal cells express adhesion molecules, such as Intracellular Adhesion Molecule-1 (ICAM-1), that increases their ability to adhere to each other.

Furthermore, adhesion molecules transduce signals through cells. The adhesion itself then sets in place a series of signals that triggers stimulation of the release of other molecules from both MM cells and bone marrow stromal cells that are important for MM growth and survival including IL-6, Vascular endothelial growth factor (VEGF) and TNF-α:

- High levels of IL-6 have been linked to growth and survival of MM cells (17), resistance to treatments such as radiation and dexamethasone (through inhibition of apoptosis), and disease progression.
- VEGF induces blood vessel development which provides tumour cells with a source of nutrients and a means to eliminate metabolic waste.
- Thus, interaction between MM cells and bone marrow stromal cells fosters a microenvironment conducive to MM cell growth.

Proteasome-mediated degradation regulates many of the proteins involved in the interactions between MM cells and the bone marrow stromal cells. Thus, proteasome inhibition mediated by VELCADE has the potential to block the effects of these proteins (Figure 2).

Figure 2: The MM Tumour MicroEnvironment (Adapted from (18))



Normal Cells Survive the Effects of VELCADE

Traditional chemotherapeutic agents affect many normal cells in addition to the malignant cells they are supposed to destroy. Although cancer cells are more susceptible to proteasome inhibition than normal cells, the effects of inhibition on certain host cells can lead to clinically predictable (and reversible) toxicities (for instance a transient thrombocytopenia following temporary inhibition of megakaryocyte function). Such effects on normal cells may sometimes limit the dose tolerated by a patient, however algorithms exist (see SmPC) to enable appropriate dose reduction and management. Clinical practice has also determined that recovery usually follows.

The 72-hour time period between VELCADE doses allows normal cells to recover from the effects of proteasome inhibition, whilst cancer cells undergo apoptosis, most probably because key intra-cellular protein regulatory mechanisms have been disrupted to a greater degree than host cells. In vitro experiments have empirically determined that MM cells are 100 to 1000 times more sensitive to VELCADE than normal freshly isolated peripheral blood leukocytes.

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

Powder for solution for injection, bortezomib (as a mannitol boronic ester), single 3.5 mg vial pack

13. What is the acquisition cost of the technology (minus VAT)? 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. For devices, provide the list price and average selling price.

£762.38 for 3.5 mg vial.

14. What are the (proposed) main indication(s)?

VELCADE is indicated as mono-therapy for the treatment of progressive MM in patients who have received at least 1 prior therapy and who have already undergone or are unsuitable for bone marrow transplantation.

The SmPC for VELCADE provides details for the use of VELCADE in combination with dexamethasone. This combination is used frequently in the UK.

15. 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 recommended starting dose of VELCADE is 1.3 mg/m^2 body surface area twice weekly for two weeks (days 1, 4, 8, and 11) followed by a 10-day rest period (days 12-21). This 3-week period is considered a treatment cycle. The SmPC allows for patients to be treated for up to 8 cycles, however the length of therapy will vary depending upon response (see SmPC in Appendix 1).

16. What other therapies, if any, are likely to be prescribed as part of a course of treatment?

Combination therapy is commonly used at all stages of MM. An effective combination of synergistic agents can increase response rates and have the potential to prolong survival. In clinical practice, dexamethasone is frequently used in combination with VELCADE either at the start of therapy or during treatment when patients are not responding to VELCADE monotherapy. This approach is used to enhance the response to VELCADE. The synergistic relationship between dexamethasone and VELCADE, has been demonstrated in patients with relapsed and refractory disease (3, 4) and in treatment naïve patients (5). Clinical trials have reported that adding dexamethasone to VELCADE in patients who achieved an inadequate response to VELCADE alone can boost responses from 50% to 62% in relapsed, refractory MM patients (3); and can achieve a 90% response rate in treatment-naïve patients (5).

The ability to enhance VELCADE responses, at a minimal incremental cost with dexamethasone, in a disease that is traditionally difficult to treat is a promising strategy. The superior efficacy demonstrated has led to the proposed inclusion of VELCADE-dexamethasone combination within a protocol extension for the Myeloma IX study following a patient's first relapse (6, 7). The Myeloma IX study may be considered as a strong indicator of the future direction of MM treatment in the UK.

Patients receiving VELCADE treatment may also require standard MM supportive therapies, including bisphosphonates, antidiarrhoeals, anti-emetics and blood transfusions.

17. 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? If yes, provide details.

As with all antineoplastic agents, regular monitoring of standard laboratory values is recommended for patients on VELCADE, including full blood count (FBC), liver function test (LFT), urea & electrolytes (U&E), renal function tests and standard observations.

Peripheral neuropathy is a common symptom associated with MM (19) as well as a treatment-related adverse event associated with specific regimens such as vinca alkaloids (20) and thalidomide treatment (21). Peripheral neuropathy has also been reported as a treatment-related adverse event associated with VELCADE. In order to minimise the severity of peripheral neuropathy with VELCADE treatment, dose modification guidelines have been developed and are included within the Summary of Product Characteristics (Appendix 1). Evidence from the APEX trial shows that resolution or improvement in the severity of peripheral neuropathy occurs when SmPC recommendations are followed (22).

Platelet count should be monitored regularly for signs of thrombocytopenia, and platelet support administered according to local guidelines.

18. For pharmaceuticals, please provide a Summary of Product Characteristics (SPC) or draft SPC as an appendix to the submission.

The Summary of Product Characteristics is available in Appendix 1.

19. For devices, please provide the (anticipated) CE marking, including the indication for use, (draft) technical manual and details of any different versions of the same device, as an appendix to the submission.

Not Applicable

20. What is the current usage of the technology in the NHS? Include details of use in ongoing clinical trials. (Max 300 words)

VELCADE is an established treatment for relapsed and refractory MM in the UK, and has been accepted for use for this indication by the Scottish Medicines Consortium (SMC) and the All Wales Medicines Strategy Group (AWMSG). Following fast-track regulatory approval, an extension to the VELCADE licence occurred in April 2005 to include treatment of first relapse in MM patients. VELCADE is a widely used treatment option for the management of patients experiencing a first relapse throughout Europe, although in the UK access to funding is inconsistent, with "post-code prescribing" creating an inequity of access for NHS patients in England and Wales. This situation is illustrated in the map in Appendix 2 which highlights both the areas where VELCADE has been approved clinically and also the extent of funding currently available.

Future research with VELCADE in MM is focused on investigating the use of VELCADE in newly diagnosed MM patients (ie before first relapse), and also as combination therapy with treatments other than dexamethasone. There are many clinical trials ongoing throughout the world that are addressing these questions. Clinical trials ongoing or planned in the UK are summarised in Appendix 3.

1.3 Context

21. Please provide a brief overview of the disease and current treatment options.

Multiple myeloma (MM) is a haematological cancer arising from plasma cells (antibody producing cells) in the bone marrow. It is the second most common haematological cancer in England and Wales. The annual incidence of MM in England and Wales is presented in Table 1.

Table 1: The Annual Incidence of MM in the UK by sex, 2001(14)

	England	Wales	Total
Male	1528	161	1685
Female	1331	125	1456
Total	2859	286	3145

MM occurs throughout the body at multiple sites. The most commonly affected areas are the bone marrow and in locations such as the spine and pelvis, rib cage and skull. In some patients, the plasma cells may aggregate to form solid tumours called plasmacytomas.

The malignant plasma cells produce and secrete paraprotein (M protein), monoclonal immunoglobulins that are the hallmark of MM. The abnormal MM cells only produce dysfunctional paraprotein at the expense of normal, infection-fighting antibodies. Paraprotein concentration is a good indicator of MM burden and is a primary measure of disease response to treatment. MM patients will be familiar with their paraprotein levels and will use the measurement to track their disease progress.

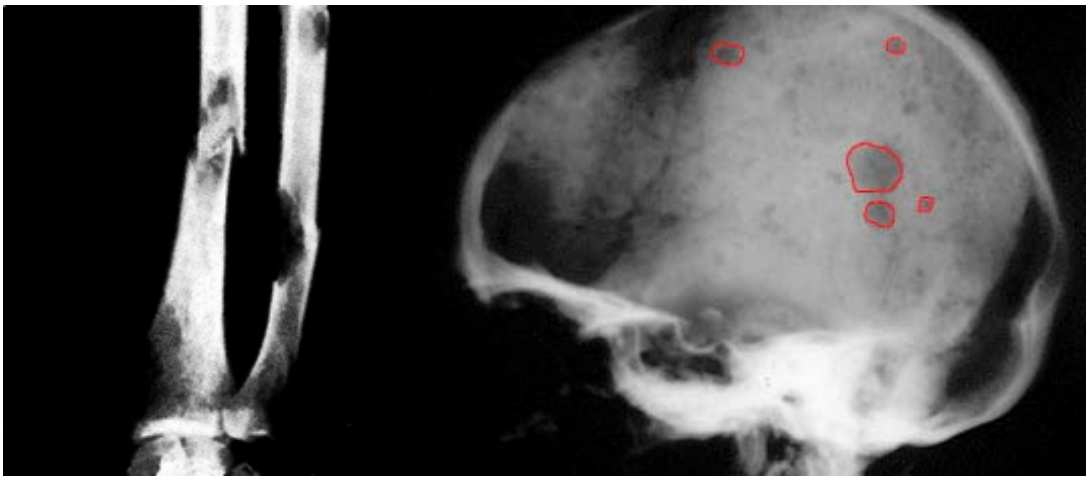
Symptoms

Patients with MM commonly experience the following symptoms and complications:

- **Bone pain and skeletal dysfunction:** Severe bone pain and skeletal dysfunction is caused by invasion of bone by MM cells. Bone pain is present at diagnosis in almost 60% of patients (23), with more than 50% presenting with vertebral fractures (24). Furthermore, generalised osteopenia is present in 60% patients, of which only 5% will have no associated lytic lesions (24).

  Skeletal dysfunction manifests itself as diffuse osteoporosis, lytic bone lesions (Figure 3), hypercalcaemia, pathological fractures of the long bones (figure 3) and vertebrae leading to vertebral collapse causing loss of height, neurological, and severe respiratory sequelae.

Figure 3: X-Rays of a Long Bone and Skull Showing MM Bone Lesions and Fracture



- **Anaemia:** MM patients commonly experience decreased red blood cell counts due to bone marrow replacement by MM cells and the suppressive effects of cytokines secreted by the tumour.

- **Infection:** Patients are at an increased risk of infection due to inadequate production of functional antibodies and subsequent impairment of the immune response.

- **Renal insufficiency:** The two main causes are accumulation of paraprotein in the kidneys, and hypercalcaemia. Paraprotein build up in the kidneys can reduce its ability to dispose of excess salt, fluid and body wastes leading to renal insufficiency and eventually to renal failure.

- **Hyperviscosity:** Accumulation of paraprotein in the blood causes increased viscosity (hyperviscosity). This can cause circulatory problems such as a deep vein thrombosis, or other cardiovascular symptoms.

- **Bleeding problems:** Commonly a result of platelet dysfunction caused by paraprotein coating the cells or due to thrombocytopenia caused by MM cells overcrowding the bone marrow. Fifteen to thirty percent of patients with MM have excessive bleeding or bruising.

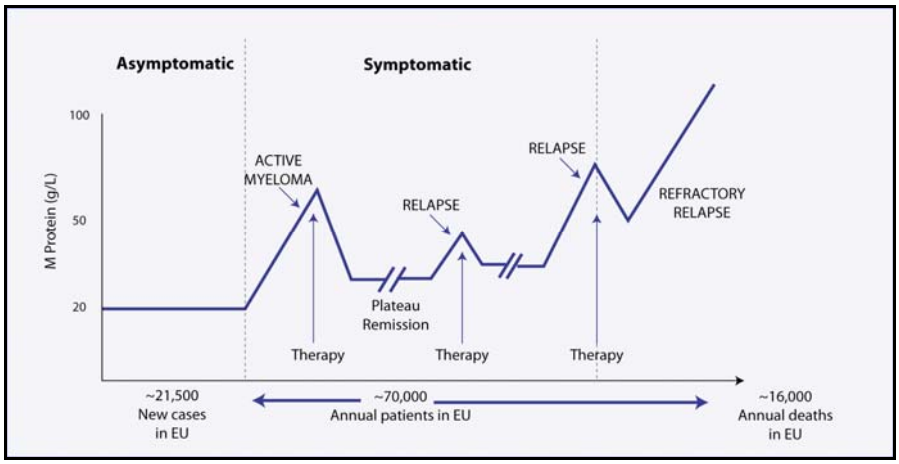
- **Neurological symptoms:** Often caused by compression of the spinal cord nerves following vertebral collapse, or by peripheral neuropathy caused either

de novo, or as a result of treatment. Strokes may occur consequent to hyperviscosity.

Treatment

At diagnosis, symptomatic MM is heterogeneous and the course and response to treatment are affected by many disease and patient variables including disease stage, prognostic factors, patient age and performance status. The clinical course of MM is characterised by periods of treatment separated by frequent relapses (Figure 4).

Figure 4: A Depiction of the Clinical Course of MM



Although responses to therapy are common, repeated relapses are inevitable. Treatment, therefore, is centred on a sequence of drug therapies aimed at achieving durable responses and delaying relapse. Eventually, all patients have disease relapse that is refractory to further therapy.

There is currently no UK consensus on the “gold standard” treatment options for MM at first relapse (25). Over the last few years there has been an increase in the number of novel agents under development for MM and as a consequence published guidelines are unable to keep abreast of all these latest therapeutic developments.

A trial that best represents the current positioning of treatments for MM is the randomised Phase III, National Cancer Research Institute (NCRI) supported MRC Myeloma IX study (6, 7). The recruitment of patients to this trial has been rapid reflecting how closely it matches UK clinical practice (1157 patients enrolled since May 2003 out of total planned recruitment of 1600 patients involving 130 centres within the UK). Patients in Myeloma IX are treatment-naïve and receive either an intensive regimen (where patients receive either cyclophosphamide, vincristine, adriamycin and dexamethasone (CVAD) or cyclophosphamide, thalidomide and dexamethasone (CTD), Figure 5) or a non-intensive regimen (melphalan-prednisone (MP) or CTD attenuated (CTDa), Figure 6).

The Myeloma IX trial protocol is currently being amended to include the combination of VELCADE plus dexamethasone for patients who are at first relapse, or patients who do not respond to 2 cycles of intensive therapy (primary refractory patients). This is a strong indicator of evolving UK clinical practice with VELCADE-dexamethasone being considered a good treatment option at first relapse.

Figure 5: Myeloma IX Intensive Regimen

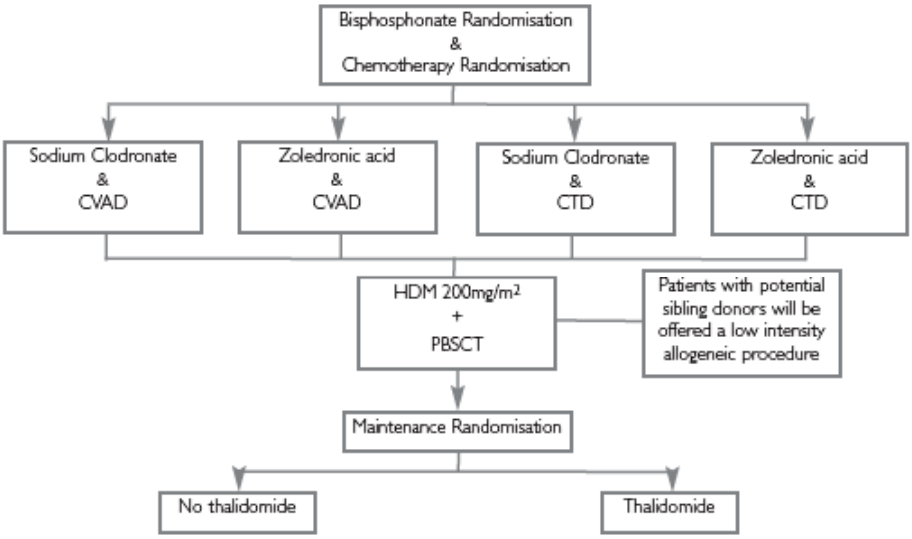
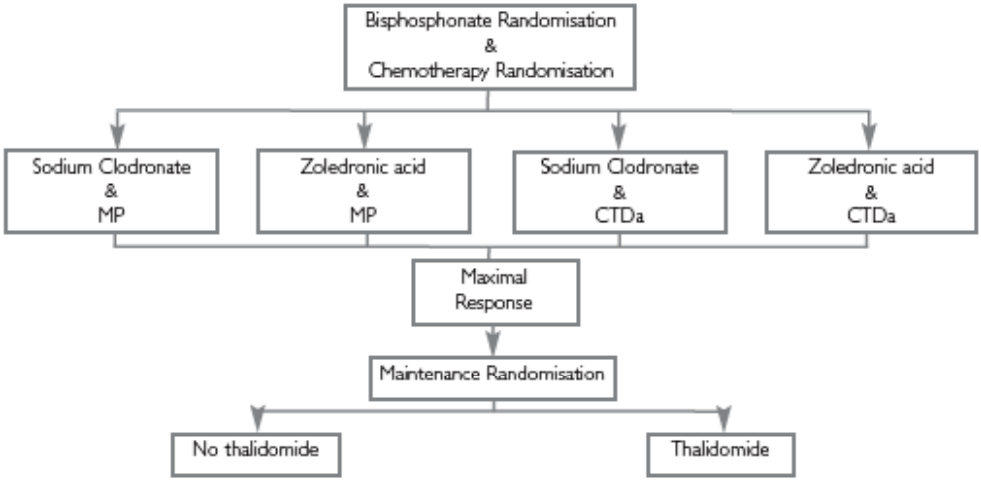


Figure 6: MRC Myeloma IX Non-Intensive Regimen



22. What was the rationale for the development of the new technology? (Max 200 words)

As outlined in our response to question 11, the proteasome pathway plays a key role in cancer cell growth and survival. VELCADE was developed to specifically target the proteasome thereby interfering with these processes and killing cancer cells.

Preclinical studies revealed a unique profile with pro-apoptotic and anti-tumour activity *in vitro* and *in vivo*, and a Phase I study revealed significant activity in multiple myeloma with 9 of 9 evaluable patients exhibiting evidence of clinical benefit including one durable complete remission (26). These initial results of significant activity in MM were confirmed later in subsequent phase II and III studies (3, 4, 8).

23. What is the suggested place in therapy for this technology with respect to treatments currently available?

VELCADE is indicated for the treatment of MM patients at first (and subsequent) relapse. The use of VELCADE at first (and subsequent) relapse has been approved by both the European and U.S. regulatory authorities.

The combination of VELCADE with dexamethasone, guidance for which is given within the SmPC for VELCADE, results in higher response rates compared to VELCADE monotherapy and provides evidence that combination treatment is currently a more effective way of using VELCADE (3, 4).

Clinical trial evidence, clinical guidelines, the Myeloma-IX trial design and clinical opinion all support the use of VELCADE in combination with dexamethasone as a means to optimise response rates.

In line with the SmPC, VELCADE responders should continue to receive treatment up to a maximum of eight cycles. In the APEX clinical trial, 85% of responders responded before or during the 3rd VELCADE cycle. For patients who do not respond, it is prudent to discontinue treatment as this reduces patient exposure to potential side-effects and maximises cost-effectiveness. Economic analyses detailed in section 3.2 of this submission suggest that it is most cost-effective to discontinue treatment in non-responders after approximately three cycles.

24. Describe any current variation in services and/or uncertainty about best practice, including cost effectiveness. (Max 100 words)

Despite published guidelines, the nature of the clinical course of myeloma means that there is no definitive pathway and as such no consensus in the UK, for the treatment of MM at first relapse. However, recent advances including the a BCSH position paper supporting the use of VELCADE in first relapse patients, and the proposed inclusion of VELCADE-dexamethasone combination for first relapse patients in Myeloma IX, give a strong indication of emerging consensus view among UK clinicians that VELCADE is considered a first relapse option.

This position also reflects a move towards European practice where the use of VELCADE at first relapse is much more common than currently within the UK, due to funding constraints and the fact that a formal and independent cost effective evaluation has not yet been reported by NICE.

The absence of guidance from NICE has led to a striking disparity in access to funding for VELCADE in the NHS, has created inequity of access for NHS patients, and has limited clinical uptake of a potentially valuable new therapy by clinicians (Appendix 2).

25. Provide details of any relevant guidelines or protocols.

The UK MM Forum and The Nordic MM Study Group Guidelines on the Diagnosis and Management of MM 2005 (25)

The United Kingdom MM Forum (UKMF) Guideline on the Diagnosis and Management of MM has recently been updated in cooperation with the Nordic MM Study Group (NMSG) and published as an approved Guideline on the British Committee for Standards in Haematology (BCSH) website (25).

Over the last few years, there has been a rapid development of new treatments for MM with the result that the periodically published guidelines are unable to keep abreast and reflect all the available licensed treatments on offer for relapsed disease.

The positioning of VELCADE within the UKMF guideline does not reflect its current licensed indication, because these guidelines were published prior to April 2005 when VELCADE received its current licence extension to treat patients with MM at first relapse.

Subsequently however, the UKMF in collaboration with the BCSH have published a position paper on the use of VELCADE for the treatment of MM at first relapse which supersedes the positioning of VELCADE in the UKMF guidelines and endorses its use as an effective treatment at first relapse (2). In this position statement the UKMF and BCSH advise that:

"VELCADE is currently approved for the treatment of multiple myeloma patients who have received at least 1 prior therapy and who have already undergone or are unsuitable for transplantation. Given the strength of this data the UK myeloma forum and British Committee for Standards in Haematology believe that bortezomib should be available for prescription by UK haematologists according to its licensed indication in patients with relapsed myeloma"

1.4 Comparator(s)

26. Describe the relevant comparator(s) and provide a justification for your selection. In some cases, comparisons with more than one comparator or combination-therapy comparators will be necessary. The Institute considers the most relevant comparators to be those that the new technology is attempting to displace from UK practice.

VELCADE targets specific biological pathways in MM and remains active against myeloma cells even after patients have become refractory to previous treatments. This in addition to its demonstrated activity at first relapse means that VELCADE is an important treatment option for clinical use.

In terms of evaluating the efficacy of VELCADE as a single agent within the APEX trial, the following criteria in terms of appropriate comparator had to be met in order for regulatory approval of the APEX trial design by the FDA and EMEA to be granted:

- Effective licensed monotherapy agent.
- Have proven efficacy in first relapse patients.

HDD is the only agent that met these criteria when the APEX trial was designed in 2000

From a UK clinical practice perspective, there is currently no UK consensus on best practice for the treatment of MM at first relapse, although recent guidelines and the proposed use of VELCADE at first relapse in the Myeloma IX study give clear indication as to the emerging consensus for the use of VELCADE under these circumstances (25). Both HDD and thalidomide as single agents and as part of a combination strategy are also commonly used in the UK for treatment of relapsed MM.

However, there are a number of factors, which preclude thalidomide from being considered an appropriate comparator to VELCADE. These are listed below:

- Thalidomide is not licensed for MM or any other indication within the UK.
- There is no UK consensus on appropriate dosing schedule and duration of treatment for thalidomide (27). Therefore making it impracticable to compare the benefits of thalidomide with VELCADE.

Comparison from a perspective of published trials is also problematic since different clinical end points are reported in differing trials with none reporting response criteria in accord with the stringent EMBT criteria used within the VELCADE studies.

27. What are the main differences in the indications, contraindications, cautions, warnings and adverse effects between the proposed technology and the main comparator(s)? (100 word maximum)

Table 2: Comparison of VELCADE and Dexamethasone SPC Recommendations

	VELCADE (8, 28)	Dexamethasone (Decadron) (8, 29)
Indications	Mono-therapy for the treatment of progressive MM in patients who have received at least 1 prior therapy and who have already undergone or are unsuitable for bone marrow transplantation.	Treatment for certain endocrine and non-endocrine disorders….including MM.
Contraindications	Severe hepatic impairment	Systemic fungal infections Live virus vaccines
Cautions/warnings	Patients with renal failure, hepatic impairment, high risk for hypotension, risk factors for heart disease, high tumour burden, amyloidosis and pre-existing neuropathy or haematological toxicity should be treated with caution (please refer to SPC)	Standard precautions for corticosteroid therapy including caution in patients post myocardial infarction, cerebral malaria, renal insufficiency, hypertension, diabetes, congestive heart failure, liver failure and glaucoma (please refer to SPC)
Adverse Effects (8)	Gastrointestinal (diarrhoea, nausea, vomiting, constipation) Peripheral Neuropathy Thrombocytopenia Fatigue	Diarrhoea Fatigue Anaemia Insomnia Dyspnoea

2 Clinical evidence

2.1 Identification of studies

28. Describe the strategies used to retrieve relevant clinical data both from the published literature and from unpublished data held by the company. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used should be provided.

Specify:

29. the specific databases searched and service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- **Medline**
- **Embase**
- **Medline (R) In-Process**
- **The Cochrane Library**

A comprehensive, systematic literature search was carried out to identify randomised controlled clinical trials that assessed the use of VELCADE as a single agent in the treatment of multiple myeloma patients at first relapse.

The following databases were searched using DataStar Web:

- MEDLINE (1951 to date)
- MEDLINE In Process (Latest 8 weeks)
- EMBASE (1974 to date)

The Cochrane Library was searched using the website search engine at: http://www3.interscience.wiley.com/cgi-bin/mrwhome/106568753/HOME?CRETRY=1&SRETRY=0

30. the date the search was conducted

The search was conducted on Wednesday 8th February 2006

31. the date span of the search

The date span of the search is as indicated for the databases in question 29. The total date span was 1951 to date.

32. the complete search strategies used, including all the search terms: Textwords (free text), Subject Index Headings (e.g. MeSH) and the relationship between the search terms (e.g. Boolean)

Table 3: MedLine and MedLine-In-Process Search Strategy

No	SEARCH STRATEGY	NOTES
1	Multiple-myeloma.DE. OR plasmacytoma#.DE. OR paraproteinemias#.DE.	MeSH specific disease descriptors
2	Myelom$ OR multiple ADJ myeloma OR plasmacytom$ OR plasmocytom$ OR MGUS OR monoclonal ADJ gammopathy ADJ of ADJ undetermined ADJ significance	Free-text disease search
3	1 OR 2	
4	Bortezomib OR VELCADE OR ps341 OR ps-341 OR ps ADJ '341' OR proteasome ADJ inhibit$5	Free-text product search
5	Randomized-controlled-trial.PT. OR comparative-study.PT.	Publication type search

	OR meta-analysis.PT. OR controlled-clinical-trial.PT.	
6	Controlled-clinical-trials#.DE. OR randomized-controlled-trials#.DE. OR double-blind-method.DE. OR control-groups.DE. OR cross-over-studies.DE. OR meta-analysis.DE. OR random-allocation.DE. OR single-blind-method.DE.	MeSH specific clinical trial design search
7	(intervention OR clinical$) NEAR (trial$ OR study OR studies) AND (random$ OR placebo$ OR rct$ OR (control OR controls OR controlled) WITH (trial$ OR study OR studies) OR (cross ADJ over OR crossover OR parallel OR prospectiv$) WITH (trial$ OR study OR studies) OR (singl$ OR doubl$ OR trebl$ OR tripl$) WITH (blind$ OR Mask$))	Free text clinical trial design search
8	5 OR 6 OR 7	
9	3 AND 4 AND 8	
10	9 LG=EN AND HUMAN=YES	Restricting English language and human studies only.

Table 4: EMBASE Search Strategy

ID	SEARCH STRATEGY	NOTES
1	Multiple-myeloma.DE. OR malignant-plasmacytoma#.DE. OR plasmacytoma.DE. OR myeloma.DE. OR myeloma-cell.DE. OR monoclonal-immunoglobulinemia.DE. OR paraproteinemia#.DE.	EMTREE specific disease descriptors
2	Myelom$ OR multiple ADJ myeloma OR plasmacytom$ OR plasmocytom$ OR MGUS OR monoclonal ADJ gammopathy ADJ of ADJ undetermined ADJ significance	Free-text disease search
3	1 OR 2	
4	Bortezomib.de.	EMTREE product search
5	Bortezomib OR VELCADE OR ps341 OR ps-341 OR ps ADJ '341' OR proteasome ADJ inhibit$5	Free-text product search
6	4 OR 5	
7	Randomized-controlled-trial.DE. OR comparative-study#.DE. OR drug-comparison#.DE. OR controlled-study#.DE. OR randomization#.DE. OR double-blind-procedure.DE. OR single-blind-procedure.DE. OR triple-blind-procedure.DE. OR parallel-design.DE. OR crossover-procedure.DE. OR meta-analysis#.DE.	Publication type search
8	(intervention OR clinical$) NEAR (trial$ OR study OR studies) AND (random$ OR placebo$ OR rct$ OR (control OR controls OR controlled) WITH (trial$ OR study OR studies) OR (cross ADJ over OR crossover OR parallel OR prospectiv$) WITH (trial$ OR study OR studies) OR (singl$ OR doubl$ OR trebl$ OR tripl$) WITH (blind$ OR Mask$))	Free text clinical trial design search
11	7 OR 8	
12	3 AND 6 AND 11	
13	12 LG=EN AND HUMAN=YES	Restricting English language and human studies only.

Cochrane Library Search Strategy

As the search engine for the Cochrane Library was not as sophisticated as Datastarweb, a simple search strategy for all records relating to VELCADE was performed and the myeloma specific articles were manually selected.

Table 5: Cochrane Library Search Strategy

ID	Search	Hits
#1	VELCADE in All Fields or bortezomib in All Fields or ps-341 in All Fields or ps 341 in All Fields or proteasome inhibitor in All Fields in all products	25
#2	myeloma in All Fields or multiple myeloma in All Fields or plasmacytoma in All Fields or plasmocytoma in All Fields or MGUS in All Fields in all products	1086
#3	(#1 AND #2)	13

Company Literature Database (LMD) Search Strategy

As this database is managed by the Johnson & Johnson, the compound name for VELCADE was used in the strategy (JNJ-26866138-AAA*)

JNJ-26866138-AAA* and ((((monoclonal gammopathy of undetermined significance) or (MGUS)) or (HAEMATOLOGICAL-MALIGNANCY OR CANCER-RELAPSED OR CANCER-REFRACTORY OR PLASMACYTOMA or MULTIPLE-MYELOMA)) and published and HUMAN and ENGLISH-LANGUAGE and (ACTIVE-CONTROLLED or META-ANALYSIS or RANDOMIZED or DOUBLE BLIND or PLACEBO-CONTROLLED or CROSS-OVER or SINGLE-BLIND or META-ANALYSIS or PARALLEL))

Search Results

Database	References Identified
Medline	16
Embase	238
Medline In Process	4
Cochrane Library	13
Company database	28

Duplicates

Removal of duplicates from the Medline, Medline-In-Process and Embase was performed automatically by Datastar Web.

Criterion	Number of records
Combine databases	258
Drop duplicates	13
Unique records	245

References identified through the Cochrane Library and in-house database searches were manually checked against the 245 unique records from Medline, Embase and Medline-In-Process. There were 2 duplicate records in the Cochrane Library search, and 3 in the In-house database search. Making the total number of records for evaluation 283.

33. details of any additional searches, for example searches of company databases (include a description of each database)

The abstracts from the American Society of Hematology and the American Society of Clinical Oncology were searched manually for relevant articles.

A Company literature management database (LMD) was also searched.

34. the inclusion and exclusion criteria

Trials that were included had the following characteristics:

- Clinical studies
- Randomised controlled trials, meta-analyses or systematic reviews
- Comparing VELCADE with another therapy or placebo
- Enrolled MM patients at first relapse
- English language

Trials were excluded if they had the following characteristics:

- Non-systematic reviews or editorials
- Animal or in vitro studies
- Enrolled treatment-naïve MM patients
- Trials involving only patients who were at second relapse and beyond.
- Enrolled patients aged 12 years or younger

35. the data abstraction strategy.

The abstracts of the 257 articles identified by the literature search were individually checked to see if they contained appropriate efficacy data, and to eliminate inappropriate papers. To be considered applicable for the clinical effectiveness section, publications were required to meet some or all of the following criteria, according to the guidance below:

Answer either yes, no, or unknown for each question depending on the information provided in the abstracts and/or titles.

Any combination of results including a “no” shall be categorised as “exclude”

Any combination of “yes” and “unknown” or “yes” alone requires the publication to be included, and a full text publication will be obtained.

If the results are all “unknown” then the publication will be included

Criteria		Yes	No	Unknown
1	The study is in humans			
2	The study is a randomised controlled trial/systematic review/ meta-analysis			
3	The study contains a population of patients with first relapse MM			
4	The study compares treatment with VELCADE monotherapy with either placebo or another comparator.			
5	The study is English language			
6	Patients are aged over 12 years			
9	The study has more than 20 patients enrolled			

2.2 Study selection

2.2.1 Complete RCT list

36. Provide a list of all RCTs that compare the intervention with other therapies, including placebo. The list must be complete and will be validated by searches conducted by the assessors.

Where data from a single study have been drawn from more than one source (e.g. a poster and a published report) and/or where trials are linked (e.g. an open-label extension to an RCT), this should be made clear.

The results from the data abstraction exercise reveals that the only RCT that compares VELCADE with other therapies, including placebo, in MM patients at first relapse is the Phase III APEX study. Initial and updated data from the APEX study have been published in full as well as in abstract and poster form at various international conferences. Sub-analyses from the APEX study have also been published

Initial APEX Data Analysis

Primary Publication:

- Richardson PG, Sonneveld P, Schuster MW, Irwin D, Stadtmauer EA, Facon T, et al. Assessment of Proteasome Inhibition for Extending Remissions (APEX) Investigators. Bortezomib or high-dose dexamethasone for relapsed multiple myeloma. N Engl J Med. 2005 Jun 16;352(24):2487-98

Conference presentations (same data as primary publication)

- P. Richardson, P. Sonneveld, M. W. Schuster, D. Irwin, E. A. Stadtmauer, T. Facon, et al. Bortezomib vs. Dexamethasone in relapsed multiple myeloma:

a phase 3 randomized study. Presented at the Annual Society of Clinical Oncology (ASCO) 2004: Abstract 6511

- P. Richardson, P. Sonneveld, M.W. Schuster, D. Irwin, E.A. Stadtmauer, T. Facon, et al. Bortezomib versus dexamethasone for the treatment of patients with relapsed multiple myeloma: a randomized phase 3 trial. The apex study group. Poster presented at the European Haematology Association 2004, Geneva, Switzerland: Abstract 305
- Paul Richardson, P. Sonneveld, M. Schuster, D. Irwin, E. Stadtmauer, T. Facon, et al Bortezomib Demonstrates Superior Efficacy to High-Dose Dexamethasone in Relapsed Multiple Myeloma: Final Report of the APEX Study. Blood 2004; 104(11): Abstract 336.5
- APEX (Assessment of Proteasome inhibition for Extending remissions) trial: phase III randomized, multicenter, placebo-controlled trial to evaluate the efficacy and safety of bortezomib versus dexamethasone in patients with recurrent or treatment-resistant multiple myeloma. Clin Adv Hematol Oncol. 2003 Mar;1(3):190. [No authors listed]

Updated APEX Data Analysis

- Paul Richardson, P. Sonneveld, M. Schuster, D. Irwin, E. Stadtmauer, T. Facon, J. Harousseau, D. Ben-Yehuda, S. Lonial, H. Goldschmidt, D. Reece, J. San Miguel, J. Blade, M. Boccadoro, J. Cavenagh, W. Dalton, A. Boral, D. Schenkein, K. Anderson. Bortezomib Continues Demonstrates Superior Efficacy Compared with High-Dose Dexamethasone in Relapsed Multiple Myeloma: Updated Results of the APEX Trial. Blood 2005 106, issue 11: Abstract 2547

APEX Sub-Analyses

Osteoblast Activation Analysis

- Zangari M, Esseltine D, Lee CK, Barlogie B, Elice F, Burns MJ, et al. Response to bortezomib is associated to osteoblastic activation in patients with multiple myeloma. Br J Haematol. 2005 Oct;131(1):71-3.

High-Risk and Elderly Patient Sub-Analysis

- P. G. Richardson, P. Sonneveld, M. W. Schuster, D. Irwin, E. A. Stadtmauer, T. Facon, et al. Safety and efficacy of bortezomib in high-risk and elderly patients with relapsed myeloma. Presented at ASCO 2005: Abstract 6533
- P.G. Richardson, P. Sonneveld, M.W. Schuster, D. Irwin, E.A. Stadtmauer, T. Facon, et al. Bortezomib is significantly more effective than high-dose dexamethasone in high-risk and elderly patients with relapsed myeloma: an APEX subgroup analysis. Poster presented at the European Haematology Association 2005, Geneva, Switzerland: Abstract 413 *(Same data as abstract above)*

Quality of Life Sub-Analysis

- S. J. Lee, P. G. Richardson, P. Sonneveld, M. Schuster, D. Irwin, J. Massaro, B. et al. Health-related quality of life (hrql) associated with bortezomib compared with high-dose dexamethasone in relapsed multiple myeloma (MM): results from APEX study. Poster presented at ASCO 2005: Abstract 6535

- S. Lee, P.G. Richardson, P. Sonneveld, M. Schuster, D. Irwin, J. Massaro, et al. Health-related quality of life of patients with relapsed multiple myeloma receiving bortezomib versus high-dose dexamethasone in the APEX trial. Poster presented at the European Haematology Association 2005, Geneva, Switzerland: Abstract 284 *(Same data as abstract above)*

No Prior Therapies Sub-Analysis

- P. Sonneveld, P.G. Richardson, M.W. Schuster, D. Irwin, E.A. Stadtmauer, T. Facon, et al. Bortezomib is more effective than high-dose dexamethasone at first relapse and provides better outcomes when used early rather than as later salvage therapy in relapsed multiple myeloma. Poster presented at the European Haematology Association 2005, Geneva, Switzerland: Abstract.

Peripheral Neuropathy in APEX

- J.F. San Miguel, P. Richardson, P. Sonneveld, M. Schuster, D. Irwin, E. Stadtmauer, et al. Frequency, Characteristics, and Reversibility of Peripheral Neuropathy (PN) in the APEX Trial. Blood 2005 106, issue 11: Abstract 366

Haematological Toxicities in APEX

- Sagar Lonial, P. Richardson, P. Sonneveld, M. Schuster, D. Irwin, E. Stadtmauer, T. et al. Hematologic Profiles in the Phase 3 APEX Trial. Blood 2005 106, issue 11: Abstract 3474

Pharmacogenomics in APEX

- G. Mulligan, C. Mitsiades, B. Bryant, F. Zhan, W. Cheng, S. Eschrich, et al. Pharmacogenomics (PGx) Research in the APEX Randomized Multicenter International Phase 3 Trial Comparing Bortezomib and High-Dose Dexamethasone (Dex). Blood 2005 106, issue 11: Abstract 3491

Other relevant studies

- Miles Prince, Michael Adena, Dell Kingsford Smith, Judy Hertel. Efficacy of Single-Agent Bortezomib Versus Thalidomide in Patients with Relapsed or Refractory Multiple Myeloma: A Systematic Review. □□ Blood 2005 106, issue 11: Abstract 5160

2.2.2 Relevant RCT list

37. List all randomised trials that compare the technology directly with the main comparator(s). If there are none, state this.

Where data from a single study have been drawn from more than one source (e.g. a poster and a published report) and/or where trials are linked (e.g. an open-label extension to an RCT), this should be made clear.

The results from the data abstraction exercise revealed only one RCT compares VELCADE with other therapies, including placebo, in MM patients at first relapse. This RCT is the Phase III APEX study. Initial and updated data from the APEX study have been published in full as well as in abstract and poster form at various

international conferences. Sub-analyses from the APEX study have also been published

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- Paul Richardson, P. Sonneveld, M. Schuster, D. Irwin, E. Stadtmauer, T. Facon, et al Bortezomib Demonstrates Superior Efficacy to High-Dose Dexamethasone in Relapsed Multiple Myeloma: Final Report of the APEX Study. Blood 2004; 104(11): Abstract 336.5
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No Prior Therapies Sub-Analysis

- P. Sonneveld, P.G. Richardson, M.W. Schuster, D. Irwin, E.A. Stadtmauer, T. Facon, et al. Bortezomib is more effective than high-dose dexamethasone at first relapse and provides better outcomes when used early rather than as later salvage therapy in relapsed multiple myeloma. Poster presented at the European Haematology Association 2005, Geneva, Switzerland: Abstract.

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38. Please provide details of relevant ongoing studies from which additional evidence is likely to be available in the next 6–12 months.

There are no ongoing studies from which additional evidence will be available in the next 6 to 12 months.

39. A flow diagram of numbers of number of studies included and excluded at each stage should be provided as per the QUORUM statement.

2.3 Summary details of RCTs

40. As a minimum, the summary should include information on the following aspects of the study but the list is not exhaustive. Where there is more than one RCT please tabulate the information.

The clinical development programme for VELCADE began with a series of phase I trials initiated in October 1998 that were designed to define its toxicity profile and determine the appropriate dose and schedule for phase II development. The phase I studies were notable for the anti-tumour activity observed. In particular, six of 13 patients with MM (or related plasma cell dyscrasias) had evidence of tumour reduction, including one patient with a durable complete remission (26).

Two phase II studies (SUMMIT and CREST) were designed to establish the efficacy of VELCADE in MM and to further evaluate the safety profile (3, 4). Based on the results of these studies, VELCADE underwent an accelerated approval process with regulatory authorities in both the USA (FDA) and Europe (EMEA), and was approved under exceptional circumstances (30, 31). VELCADE was approved by the FDA under subpart H rule, which allows a drug to be approved if a surrogate endpoint (such as time to progression) is deemed a reasonable predictor of clinical benefit. The aim of the Phase III study, APEX, was to compare the efficacy of VELCADE as a monotherapy to a conventional chemotherapy.

The studies summarised in this submission are tabulated in Appendix 4.

2.3.1 Methods

41. Describe the trial design (e.g. degree and method of blinding and randomisation) and interventions.

Study Design

The APEX study was an international, randomised, open-label trial, designed to evaluate the efficacy and safety of VELCADE compared with HDD in patients with MM who had received 1-3 lines of prior therapy. It was conducted at 93 major cancer centres in 12 countries, including the United States, Europe, Canada and Israel. Seven centres in the UK were involved in this study. The study enrolled 669 patients, of whom 657 received at least one dose of study drug. This makes APEX the largest study performed in relapsed MM to date.

APEX was open-label because a blinded design was not feasible, appropriate or ethical for two reasons. Firstly, VELCADE is administered as an IV bolus, whilst HDD is an oral preparation and to give placebo IV bolus injections was deemed unacceptable. Secondly, each treatment has characteristic adverse event profiles such that the blind would not be able to be maintained. To reduce selection bias, patients were assigned to treatment randomly. Randomisation and stratification also served to balance subjects among treatment groups with regard to baseline and demographic characteristics. Patients were assigned to receive VELCADE or HDD by random allocation at a 1:1 ratio. Both arms were also balanced in terms of duration of therapy and frequency of tumour assessments. Patients who progressed on HDD at any time during the study were allowed to receive VELCADE therapy in a companion crossover study.

To further ensure subject balance between treatment groups, randomisation was stratified by three key variables (Table 6):

- Number of lines of prior therapy (1 vs. > 1)
- Refractoriness to prior therapy. (Time to progression after last therapy; ≤ 6 months vs .> 6 months)
- Baseline serum β_2-microglobulin concentration (≤2.5 mg/dL vs. >2.5 mg/dL)

Table 6: Study/Treatment Group Assignment (32)

Treatment	No. of Previous Treatment Regimens	Timing of PD / Relapse Relative to Most Recent Treatment Regimen	Screening β_2-microglobulin (mg/L)
VELCADE 1.3 mg/m^2/dose or HDD 40 mg	1	During / within 6 months after	>2.5
			≤ 2.5
		>6 months after	>2.5
			≤ 2.5
	>1	During / within 6 months after	>2.5
			≤ 2.5
		>6 months after	>2.5
			≤ 2.5

Stratification factors were balanced between treatment arms, but the number of subjects enrolled in each stratum was not controlled.

An interactive voice recognition system (IVRS) was utilised to assign treatment. The IVRS provided immediate telephone access for the study centres to randomly assign patients at a 1:1 ratio to either VELCADE or HDD. Patients were required to begin treatment within 72 hours after randomisation. The randomisation number assigned through the IVRS was to be documented in the source documents and the patient's case record form.

Interim Analysis

A single interim analysis was conducted for time to progression (TTP), based on the method of O'Brien and Fleming (33). This test was to be performed when half of the total required number of events had occurred (a total of 231 patients having PD).

Interventions

The rationale for HDD as a comparator is described in Section 1.4.

2.3.2 Population

42. Provide details of the inclusion and exclusion criteria and describe the patient characteristics at baseline. Highlight any differences between study groups.

Inclusion Criteria

To be eligible, patients had to be previously diagnosed with MM, to have measurable disease and to require second-, third- or fourth-line therapy because of progressive disease. Other inclusion criteria were:

- At least 18 years of age.
- Voluntary written informed consent.
- Use of an acceptable method of contraception for the duration of the study. Women were required to be post-menopausal, surgically sterilised, or to have a negative pregnancy test.
- Karnofsky performance status ≥60%.
- Life-expectancy >3 months.
- Adequate liver function as defined by a serum aspartate transaminase or alanine transaminase ≤ 2.5 x upper limit of normal and total serum bilirubin ≤ 1.5 x upper limit of normal.
- Adequate renal function as defined by calculated or measured creatinine clearance ≥ 20 mL/min.
- Platelet count ≥ 50 x 10^9/L, Hb ≥ 7.5 g/dL and an absolute neutrophil count ≥ 0.75 x 10^9/L without transfusion or colony stimulating factor support
- Corrected serum calcium <14 mg/dL (3.5 mmol/L).

Exclusion criteria

Patients who had previously been exposed to VELCADE were excluded from the trial, as were patients who had previously received HDD and were determined to be refractory. This was important to ensure that there was no trial bias based on previous exposure to dexamethasone. Other exclusion criteria included:

- Nitrosoureas within 6 weeks or other chemotherapy, clarithromycin, interferon or radiation therapy within 3 weeks of enrolment
- Corticosteroids within 3 weeks before enrolment
- Immunotherapy or antibody therapy within 8 weeks before enrolment
- Plasmapheresis or major surgery within 4 weeks prior to enrolment
- Allergy to compounds containing boron or mannitol
- Peripheral neuropathy ≥ Grade 2 as measured by the NCI Commnon Toxicity Criteria (CTC)
- NYHA Class III or IV heart failure, uncontrolled angina, severe uncontrolled ventricular arrhythmias or electrocardiographic evidence of acute ischaemia or active conduction system abnormalities, or myocardial infarction within 6 months or enrolment.
- Cardiac amyloidosis
- Treated for another cancer within 5 year prior to enrolment (excluding MM, basal cell carcinoma or cervical cancer in situ)
- Patient had poorly controlled hypertension, diabetes mellitus, or other serious medical or psychiatric illness
- Patient was known to be human immunodeficiency virus (HIV)-positive.

- Patient was known to be hepatitis B surface antigen-positive or had known active hepatitis C infection.
- Patient had an active systemic infection requiring treatment.
- If female, patient was pregnant or breast-feeding.
- Patient was enrolled in another clinical research study and/or was receiving an investigational agent for any reason.

Baseline Patient and Disease Characteristics

Table 7 shows patient characteristics for the study subjects for both VELCADE and HDD treatment groups. The two treatment groups were comparable with regards to several baseline disease characteristics, including amount of serum and urine M-protein present, proportion of patients with abnormal skeletal survey findings and with plasmacytomas, serum calcium, C-reactive protein and β_2-microglobulin levels, renal function, and refractoriness to prior therapy

Table 7: Baseline Demographic and Disease Characteristics, Overall and by Treatment Group (N=669)

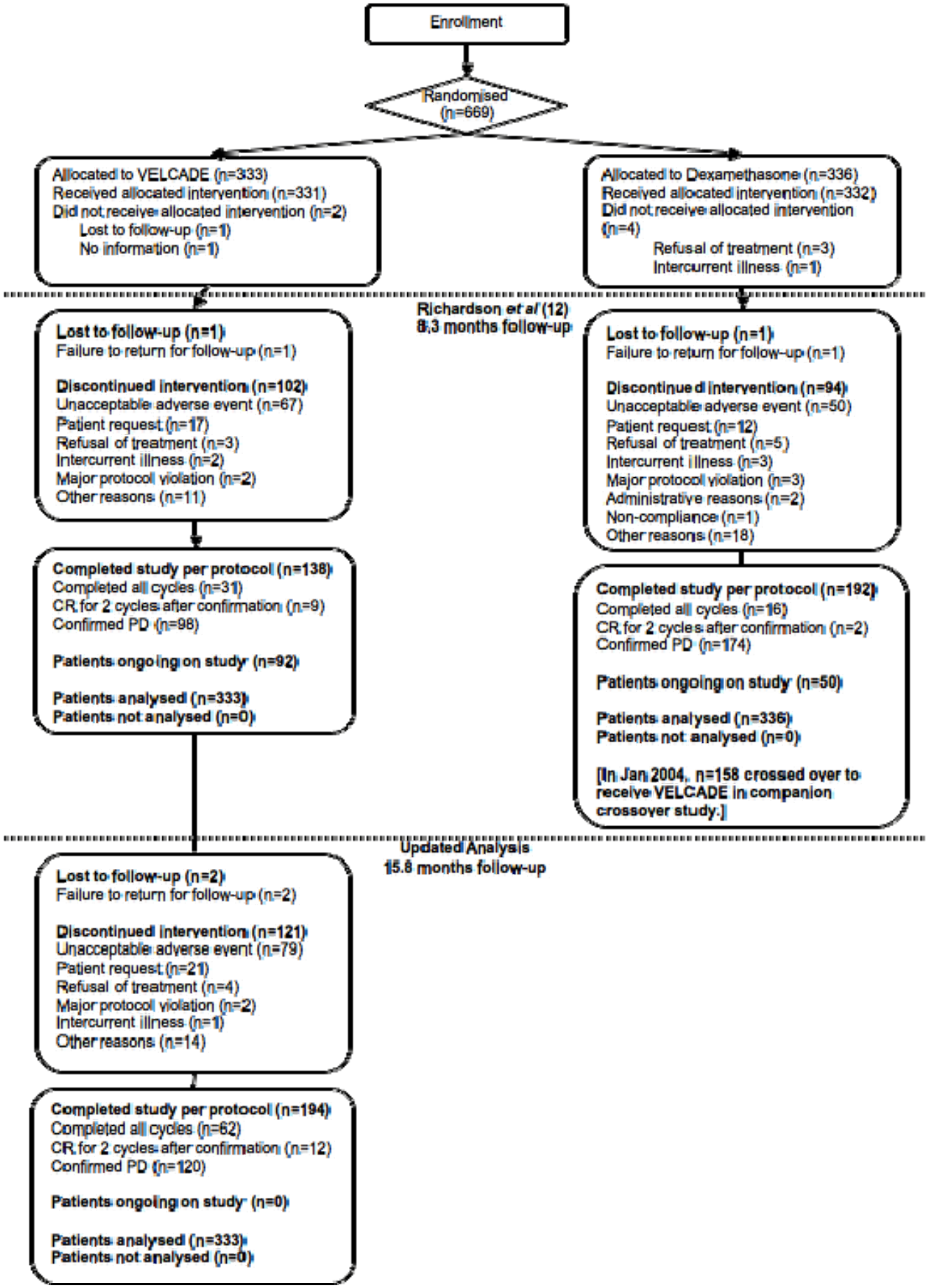
Characteristic / Statistic	VELCADE (N = 333)	HDD (N = 336)	Total (N = 669)
Sex [Male n (%); Female n (%)]	188 (56); 145 (44)	200 (60); 136 (40)	388 (58); 281 (42)
Age years [Median]	62	61	62
KPS ≥60 [n (%)]	304 (94)	312 (96)	616 (95)
KPS ≥80, n/N (%)	280 (87)	271 (83)	551 (85)
MM type [IgG, IgA, B-J, Other %)]	60, 23, 12, 5	59, 24, 13, 3	60, 23, 13, 4
Years since diagnosis, [Median]	3.5	3.1	3.3
Abnormal Skeletal Survey %	85	86	85
Plasmacytomas %	10	7	8
Corrected Serum Ca mmol/L [Median]	2.3	2.3	2.3
Hb, median (g/L)	108.0	109.0	109.0
Plt median (x 10^9/L)	192	188	189
Plt<75×10^9/L n (%)	21 (6)	15 (4)	36 (5)
≥ G1 hypercalcaemia [n (%)]	23 (7)	24 (7)	47 (7)
β_2M >2.5 mg/L [n (%)]	244 (75)	257 (79)	182 (77)
β_2M >5.5 mg/L [n (%)]	81 (25)	101 (31)	501 (28)
CRP (Median)	4.0	4.0	4.0
CrCl ≤60 ml/min [n (%)]	110 (33)	111 (35)	221 (34)
Prior lines of therapy [Median (Min, Max)	2.0 (1, 7)	2.0 (1, 8)	2.0 (1, 8)

1 prior line of therapy (%)	40	35	38
Prior steroids (%)	98	99	98
Prior alkylating agents (%)	91	92	91
Prior anthracyclines (%)	77	76	77
Prior thalidomide (%)	48	50	49
Received at least 2/3/4 of the above (%)	98/82/34	99/84/35	98/83/35
Prior stem cell transplant/high-dose therapy (%)	67	68	67

KPS - Karnofsky Performance Scale; B-J - Bence-Jones; Hb - haemoglobin; Plt - Platelet ;G1 - Grade 1; β_2M - β-$_2$-microglobulin; CRP - C-reactive protein; CrCl: creatinine clearance

2.3.3 Patient numbers

43. Provide details of the numbers of patients eligible to enter the trial, randomised, and allocated to each treatment. Provide details of patients who crossed over treatment groups and dropped out from the trial. This information should be presented as a CONSORT flow chart.


Enrollment
Randomised (n=669)
Allocated to VELCADE (n=333)
Received allocated intervention (n=331)
Did not receive allocated intervention (n=2)
Lost to follow-up (n=1)
No information (n=1)
Allocated to Dexamethasone (n=336)
Received allocated intervention (n=332)
Did not receive allocated intervention (n=4)
Refusal of treatment (n=3)
Intercurrent illness (n=1)
Richardson et al (12)
8.3 months follow-up
Lost to follow-up (n=1)
Failure to return for follow-up (n=1)
Discontinued intervention (n=102)
Unacceptable adverse event (n=67)
Patient request (n=17)
Refusal of treatment (n=3)
Intercurrent illness (n=2)
Major protocol violation (n=2)
Other reasons (n=11)
Lost to follow-up (n=1)
Failure to return for follow-up (n=1)
Discontinued intervention (n=94)
Unacceptable adverse event (n=50)
Patient request (n=12)
Refusal of treatment (n=5)
Intercurrent illness (n=3)
Major protocol violation (n=3)
Administrative reasons (n=2)
Non-compliance (n=1)
Other reasons (n=18)
Completed study per protocol (n=138)
Completed all cycles (n=31)
CR for 2 cycles after confirmation (n=9)
Confirmed PD (n=98)
Patients ongoing on study (n=92)
Patients analysed (n=333)
Patients not analysed (n=0)
Completed study per protocol (n=192)
Completed all cycles (n=16)
CR for 2 cycles after confirmation (n=2)
Confirmed PD (n=174)
Patients ongoing on study (n=50)
Patients analysed (n=336)
Patients not analysed (n=0)
[In Jan 2004, n=158 crossed over to receive VELCADE in companion crossover study.]
Updated Analysis
15.8 months follow-up
Lost to follow-up (n=2)
Failure to return for follow-up (n=2)
Discontinued intervention (n=121)
Unacceptable adverse event (n=79)
Patient request (n=21)
Refusal of treatment (n=4)
Major protocol violation (n=2)
Intercurrent illness (n=1)
Other reasons (n=14)
Completed study per protocol (n=194)
Completed all cycles (n=62)
CR for 2 cycles after confirmation (n=12)
Confirmed PD (n=120)
Patients ongoing on study (n=0)
Patients analysed (n=333)
Patients not analysed (n=0)

2.3.4 Outcomes

44. Provide details of the outcomes investigated and the measures used to investigate those outcomes. This may include therapeutic outcomes and patient-related outcomes such as assessment of quality of life, social outcomes etc. and any arrangements to measure concordance. Where appropriate, also provide details of the principal outcome measure(s) including details of length of follow-up, timing of assessments, scoring methods, evidence of validity and current status of the measure (e.g. approval by professional bodies, licensing authority, etc.).

Primary Efficacy Outcome

The primary efficacy variable was time to disease progression (TTP), which was chosen due to its accepted correlation with survival and because of its clinical relevance.

TTP was defined as the duration from the date of randomisation until the date of first documented evidence of progressive disease (PD) (or relapse for patients who experienced a complete response (CR)). The date of PD was determined as the date of the first indication of progression (e.g., sufficient elevation of M-protein or new skeletal event).

Patients were to be evaluated every 3 weeks during treatment. Patients who completed treatment before development of PD or who prematurely discontinued treatment for any other reason (e.g., adverse events) were to be evaluated for PD every 3 weeks until the end of the treatment period (39 weeks) and every 6 weeks thereafter.

Secondary Efficacy Outcomes:

Secondary endpoints included:

- Response rate and duration
- Overall and one-year survival
- Time to new skeletal events
- Incidence of Grade 3/4 infection
- Safety
- Quality of life
- Pharmacogenomics

Response Rate

Responses were based on the rigorous European Group for Blood and Marrow Transplant (EBMT) criteria, which are summarised in table 8 (34), with the full detailed response criteria available in Appendix 4. A new response category, near

complete response (nCR), was defined as a 100% reduction in serum M protein concentration but with residual protein detectable by immunofixation (CR^{IF+}). This was included because of its relevance to practicing physicians and its use in other recent MM studies. All responses were determined by a computer-programmed SAS algorithm that was developed by the sponsor and validated by an Independent Review Committee (IRC).

Table 8: Summary of the EBMT Criteria (Adapted from reference (34))

	M Protein	Urinary light chain	PCs, marrow	Plasmacytoma	Skeletal Disease	Calcium
CR	None (IF neg)	None (IF neg)	<5%	None	Stable	Normal
PR	≥50% ↓	≥ 90% ↓□or <200 mg/24h	N/a	≥ 50% ↓ (size)	Stable	N/A
MR	≥25% ↓□	50-89 % ↓ but ≥ 200mg/24h	N/a	≥ 25% ↓ (size)	Stable	N/A
PD	>25% ↑ or min 5 g/L	>25% ↑ or ≥ 200mg/24h	>25% ↑□	New or ↑ size	New or ↑ size	↑□
Requires two determinations 6 weeks apart. Stable disease (SD): Not meeting criteria for MR or PD						

CR: Complete response; PR: partial response; MR: minimal response; PD: progressive disease; IF: immunofixation

The EBMT response criteria were developed specifically to assess patient response versus perceived “gold standard” MM treatment – the stem cell transplant. As such, the criteria are the most rigorous response criteria that have been used in MM clinical trials to date. Furthermore, evidence from high-dose therapy followed by stem cell transplant indicates that achieving a CR is a significant prognostic factor for survival (35). The SUMMIT and CREST Phase II clinical trials were two of the first studies to assess response to a pharmacological therapy using these criteria (3, 4). Caution is therefore required in attempting to undertake comparisons to these results to other MM studies as they are likely to define CR using different (less stringent) criteria.

In order to assess disease response, blood samples were collected for serum protein electrophoresis with quantitation of immunoglobulins and M-protein and immunofixation. Urine samples for protein electrophoresis, M-protein quantitation, and immunofixation were also collected. All patients had bone marrow aspirate and biopsy performed at the time of screening and at the time of the first documentation of CR. In addition, skeletal surveys and other radiographs were performed as required. Patients who had confirmed CR continued the study drug (VELCADE or HDD) for 2 treatment cycles after confirmation of CR and could then discontinue the study drug.

Time to Response

Time to first response was defined as the duration of time from date of first administration of study treatment to the date of first evidence of confirmed disease response.

Duration of Response

Duration of response, calculated from the date of the first evidence for a confirmed response to the date of first documented evidence of PD (or relapse for patients who experience CR), was to be calculated for patients who achieved CR or PR.

Survival

Survival was assessed from the duration in months from the date or randomisation to the date of death.

Quality of Life (QoL) (36)

In the APEX study, quality of life was measured using the EORTC QLQ-C30 questionnaire and a neuropathy-specific assessment tool, the FACT/GOG-Ntx. Whilst these measures are not specifically developed for MM, both are widely accepted validated generic cancer instruments. Health related QoL data were collected prospectively at baseline and at weeks 6, 12, 18, 24, 30, 36 and 42, or until discontinuation of protocol treatment. Data were analysed based on modified intention-to-treat analysis; 44 of 642 patients were excluded due either to absent baseline data or lack of follow-up QoL data (36)

Time to New Skeletal Event

Development of new selected skeletal events [e.g., new fractures (excluding vertebral compression or rib fractures), irradiation of or surgery on bone, or spinal cord compression] was assessed from randomisation through to death.

Incidence of Grade 3/4 Infections

≥Grade 3 infections, as assessed by the National Cancer Institute Common Toxicity Criteria (NCI CTC) Version 2, from randomisation through the End of Treatment visit, 30 days after the last dose of study medication.

Follow-up and Timing of Assessments

Patients were evaluated at scheduled visits in up to 4 study periods:

1. **Pre-Treatment:** This period included screening and baseline visits
2. **Treatment**: All patients attended the study centre on a 3-week basis (Weeks 3, 6, 9, 12, 15, 18, 21, 24, 27, 30, 33, 36, and 39; and the End of Treatment visit (Week 42), which will be a minimum of 30 days following the final dose).

   During the Treatment Period, all patients who permanently discontinued study drug, whether prematurely or as scheduled, completed an End of Treatment visit a minimum of 30 days after the last study drug dose. Ideally, patients who discontinued study drug for reasons other than confirmed Progressive Disease (PD) were to continue attending scheduled study centre visits on an every 3-week basis until Week 39 or development of confirmed PD.
3. **Short-Term Follow-Up**: After completion of the Treatment Period, patients who had not experienced confirmed PD were to attend Short-Term Follow-Up visits every 6 weeks until development of confirmed PD.
4. **Long-Term Follow-Up**: After development of confirmed PD, patients were to be followed for the occurrence of selected skeletal events and for survival during the Long-Term Follow-Up Period every 3 months via telephone or office visit.

2.3.5 Statistical analysis and definition of study groups

45. State the primary hypothesis or hypotheses under consideration and statistical analysis used in testing hypotheses. Also provide details of the power of the study and a description of sample size calculation

including assumptions. Provide details of how the analysis took account of patients who withdrew (e.g. a description of the intention-to treat analysis including censoring methods; whether a per-protocol analysis was undertaken). Provide details of any subgroup analyses that were undertaken.

Primary Objective

The primary efficacy objective was to determine whether VELCADE provided benefit to patients with relapsed or refractory MM relative to treatment with HDD, as assessed by significant prolongation of time to disease progression (TTP) and supported by improvement in selected measures of clinical benefit (development of Grade 3 or worse infections, and development of new skeletal events).

Secondary Objective

Secondary efficacy objectives were to:

- Determine whether treatment with VELCADE prolonged survival time (overall and one-year) relative to treatment with HDD.
- Assess the potential superiority of VELCADE to HDD, as determined by the rates of CR and PR to treatment

Time to event data were summarised for the 2 treatment groups by 25th, 50th (median), and 75th percentiles with associated 2-sided 95% confidence intervals, as well as percent of censored observations.

Formal statistical hypothesis tests of the superiority of VELCADE to HDD were to be performed, with all tests conducted at the 2-sided, 0.05 level of significance.

Sample Size Calculation

The parameters used in calculations for sample size determination were: two-sided α = 0.05 (significance level of the statistical test), β = 0.20 (corresponding to power of 80%), an estimated median TTP of eight months for HDD (37) and 10.4 months for VELCADE (ratio of median TTP of 1.30 for VELCADE relative to HDD), a patient accrual period of nine months, and a planned analysis 14 months after the last patient accrued. The exponential form of the survival function was used, and no losses to follow-up were accounted for in the calculations (it was assumed nearly all patients would provide data for TTP). Based on this calculation, the total number of events required was 458. The O'Brien-Fleming adjustment (33) for the planned single interim analysis results in an increase of 0.8%, or 462 events. An estimated total of 620 patients, 310 assigned to VELCADE and 310 assigned to HDD, was required in order to obtain the 462 events.

ITT Analyses

The Intent-to-Treat (ITT) population was defined as all patients who were randomised to treatment; patients in this population were analysed according to the treatment to which they were randomised. All available data for TTP and survival was collected and analysed for these patients, including survival data collected after termination from the study (i.e., after development of PD). Safety analyses were based on patients who received at least one dose of study drug, but according to the treatment actually received (Safety Population). Patients who had inadequate data post-

baseline to assess efficacy according to the criteria for response were considered treatment failures for analysis of rates of response.

Interim Analysis

A single interim analysis was conducted for TTP, based on the method of O'Brien and Fleming (33). This test was to be performed when half of the total required number of events has occurred (a total of 231 patients having PD). This was anticipated to occur when half of the enrolled patients had completed 14 months of the study (including the Treatment and Short-Term Follow-Up periods), at approximately 18.5 months after the first patient was enrolled. Statistical significance was to be declared at the interim analysis if the log-rank p-value was ≤0.005, and, failing this, at the final if the p-value was ≤0.048.

If a significant difference between treatment groups in time to progression was seen, then it was considered likely that the study would be stopped at the interim stage so that patients receiving the less effective therapy would have the option to receive the more effective therapy.

Procedures for Handling Missing Data

All available efficacy and safety data were to be included in data listings and tabulations. No imputation of values for missing data was to be performed, with the exception of QOL subscales. Missing items for a given multi-item scale were handled by using the average of the remaining items to replace the missing items, as long as at least half of the items were not missing.

Patients who were treated with study drug but had no follow-up for safety were not to be included in safety analyses, because their inclusion would only serve to dilute percentages of patients with adverse events or laboratory toxicities.

Censoring

TTP: Patients who started alternate therapy, were lost to follow-up or died before documentation of PD were censored at the last documented visit date at which study assessments were performed before start of alternate therapy and indicated that the disease was stable.

Since TTP is not available for patients who refuse treatment, these data were censored at the time of randomisation.

Duration of Response: As for time to progression.

Survival: Patients who are lost to follow-up are censored at the date they were last known to be alive

Sub-Group Analyses

Analyses of time to progression, survival, response rate, time to response and duration of response were conducted for patient subgroups based on stratification factors, including number of prior lines of therapy (one or more than one based on the sponsor-derived computer algorithm), β_2-microglobulin level (≤ 2.5 and >2.5 mg/L) and whether or not the patient was refractory to the last prior therapy. Subgroup analyses also were conducted based on age at randomisation (<65 and ≥65 years) and sex.

In addition, a review of baseline prior high-dose steroid data revealed that some patients who may have been refractory to dexamethasone were enrolled into the

study in error. As these patients would not be expected to respond to HDD, or to have a more short-lived response, a sensitivity analysis was conducted excluding these patients from the analysis.

2.4 Critical appraisal

46. For each of the following methodological topics, choose the description that best fits each trial. If there is more than one trial, tabulate the responses, highlighting any 'commercial in confidence' data. Your results will be validated by the assessor.

2.4.1 Randomisation

47. Which of the following best describes the randomisation?

C) A secure randomisation method was used, where the randomisation sequence was kept away from the clinical area and administered by staff not directly involved in patient care.

2.4.2 Adequacy of follow-up

48. Which of the following best describes the adequacy of follow-up?

B) There were some drop-outs with no assessment of trial outcome(s) in the subjects who dropped out, and drop-out rates were (approximately) equivalent in treated and control groups.

There was a low frequency of drop-outs in the trial

2.4.3 Blinding of outcomes assessment

49. Which of the following best describes the blinding of the outcomes assessment?

B) The observer(s) were kept fully blinded to treatment assignment, or the measurement technique was not subject to observer bias (e.g. measurement of bone mineral density or survival).

As discussed in Question 41, the trial was not blinded, however, efficacy assessments were predominantly objective and laboratory-based and were not interpretation driven.

2.4.4 Other

50. Was the design parallel-group or cross-over? Indicate for each cross-over trial whether a carry-over effect is likely.

The design was parallel group.

Patients on the HDD arm who experienced progressive disease at any point throughout the study were permitted to receive VELCADE in a companion crossover study. After the interim analysis on Dec 3 2003, the IDMC recommended that all patients randomised to HDD (regardless of whether their disease had progressed) be given the opportunity to receive VELCADE in the companion cross-over study.

51. Was the trial conducted in the UK (or were one or more centres of the multinational trial located in the UK)? If not, where was the trial conducted and is clinical practice likely to differ from UK practice?

The trial was conducted at 93 major cancer centres in 12 countries, including the United States, Europe, Canada and Israel. Seven centres in the UK were involved in this study contributing a total of 51 patients.

52. How do the subjects included in the trial compare with patients who are likely to receive the drug in the UK? Consider factors known to affect outcomes in the main indication such as demographics, epidemiology, disease severity, setting.

The baseline characteristics of the 669 patients randomised in the APEX study are typical of MM patients who have received between one and three prior lines of therapy. There were 51 UK patients enrolled in the trial and these patients did not differ from the overall cohort. There is no reason why MM patients throughout England and Wales would differ from this cohort and no reason why the health benefits and adverse events described in the study would not be applicable to patients in routine clinical practice in England and Wales.

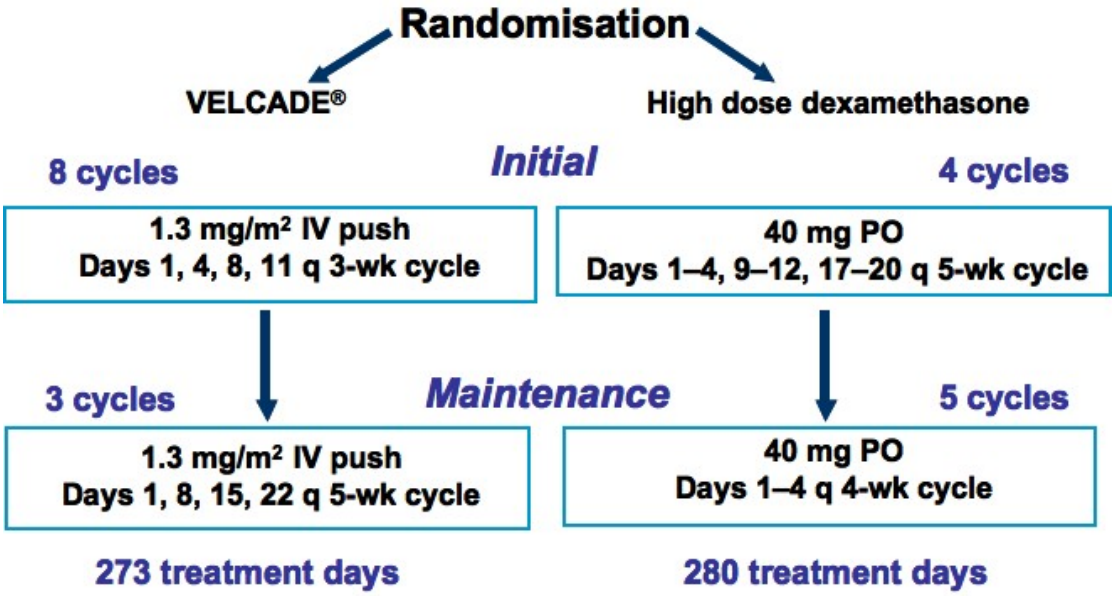
53. For pharmaceuticals, what dosage regimens were used in the trial? Are they within those detailed in the Summary of Product Characteristics?

VELCADE was administered at a dose of 1.3 mg/m^2 on days 1, 4, 8 and 11 with a 10-day rest period, constituting a 21-day cycle for eight cycles; followed by a maintenance phase with treatment at a dose of 1.3 mg/m^2 on days 1, 8, 15, 22 of a 35 day cycle for 3 cycles.

HDD was administered at a dose of 40 mg/day orally on days 1-4, 9-12 and 17-20 of a 35-day cycle for four cycles. This was followed by a maintenance phase of treatment on days 1-4 of a 28-day cycle for 5 cycles.

The dosage regimens are summarised in Figure 7.

Figure 7: Dose Regimens in the APEX Trial



Rationale for Dosing Regimens

In this study, patients assigned to VELCADE were to receive initial therapy followed by maintenance therapy with VELCADE.

The VELCADE dose selected for the initial therapy, 1.3 mg/m^2, and 3-week treatment schedule (VELCADE on Days 1, 4, 8, and 11 followed by a 10-day rest period) is the regimen currently licensed.

The VELCADE regimen selected for maintenance therapy (VELCADE administered once per week for 4 weeks (on Days 1, 8, 15, and 22) followed by a 13-day rest period) was selected based on results from a Phase 1 study conducted in patients with advanced solid tumours, primarily prostate cancer (38). It is important to note that the all patients achieved their responses during the initial 8 cycles of therapy.

The dose and regimen of HDD selected for this study were based on those commonly used in clinical practice, per published literature, either alone or as part of a combination chemotherapeutic regimen (37, 39-42).

The duration of HDD treatment selected for this study was not specified in the literature cited. An international advisory panel of MM clinicians (convened December 2001) confirmed that it is typical in clinical practice to administer HDD according to the schedule selected for this clinical study, i.e., four 5-week treatment cycles of HDD 40 mg administered on Days 1-4, 9-12, and 17-20 followed by five 4-week treatment cycles of HDD 40 mg administered on Days 1-4. During the protocol design process, the HDD treatment schedule selected was endorsed by ~60 MM clinicians selected as investigators for this international clinical study.

In addition, the duration of therapy and the duration of induction and maintenance therapy was reasonably balanced between the two treatment arms.

54. What was the median (and range) duration of follow-up in the trial?

Median: 21.9 months (9)
Range: 0 to 35.6 months

2.5 Results of the comparative randomised trials

55. Provide the results for all relevant outcome measure(s). If there is more than one trial, tabulate the responses, highlighting any 'commercial in confidence' data. The information may be presented graphically to supplement text and tabulated data. Data from intention-to-treat analyses should be presented wherever possible.

For each outcome:

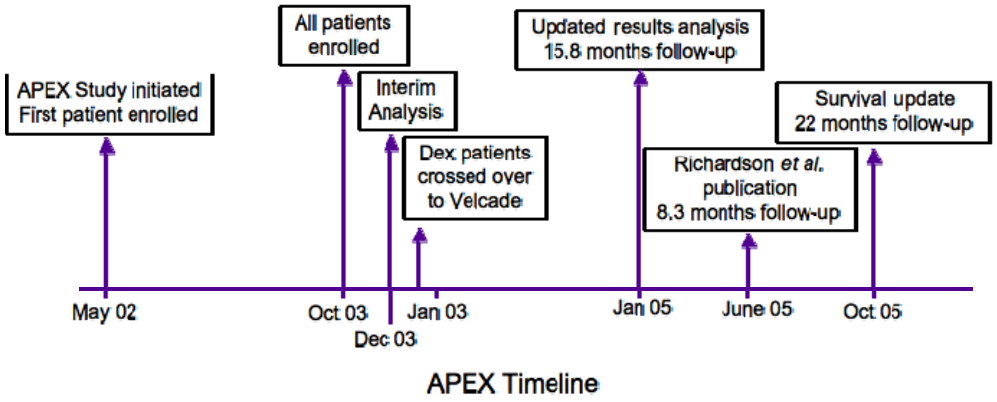
- describe the unit of measurement
- report the size of the effect; for dichotomous outcomes, the results ideally should be expressed as both relative risks (or odds ratios) and risk (or rate) differences. For time-to-event analysis, the hazard ratio is an equivalent statistic
- provide a 95% confidence interval
- provide the number of patients included in the analysis
- state whether 'intention-to-treat' was used for the analysis
- discuss and justify definitions of any clinically important differences.

EFFICACY ANALYSES

There have been three analyses of the APEX clinical data.

- The results of the first analysis at 8.3 months follow-up reported by Richardson *et al*. (8) have been published in the New England Journal of Medicine (NEJM).
- The second analysis at 15.8 months follow-up has now been completed. Some of these data were published at the 47th Annual meeting of the American Society of Haematology (ASH) in 2005 (9)
- The final analysis was an update to the survival results only at 22 months follow-up which has been presented at the 47th Annual meeting of the American Society of Haematology (ASH) in 2005 (9).

Figure 8: Timelines for the APEX study



APEX Timeline

Interim Analysis

As outlined in section 2.3.5, a pre-planned interim analysis was conducted on 3 December 2003 involving a total of 254 PD events at 8.3 months follow-up. By that time, a total of 669 patients were enrolled in the study.

The results demonstrated a significant efficacy benefit in patients treated with VELCADE including:

- A highly significant 58% difference increase in TTP for patients on the VELCADE arm ($p<0.001$)
- A significantly improved overall survival ($p=0.04$)

Based on the superiority of VELCADE monotherapy, the independent data monitoring committee (IDMC) deemed it unethical to continue with the study and recommended that all patients randomised to HDD should be offered the opportunity to be treated with VELCADE as soon as possible in a companion study.

The members of the IDMC were chosen with advice from consultants and thought leaders in the field. The IDMC consisted of 4 Oncologists and 1 statistician, all members were free of conflicts of interest that could be substantially affected by the outcome of the trial.

Accordingly on 15th December 2003, the HDD arm was halted and patients were allowed to cross-over to receive VELCADE. Data for TTP and response were censored before December 15, 2003. Safety analyses, including survival, were censored before 14 January 2004. These results have been published by Richardson and co-workers in the New England Journal of Medicine (NEJM) (8). The median follow-up time for this analysis was 8.3 months.

Updated Analysis

At the time of the NEJM publication, a total of 142 of 669 patients were ongoing in this study, including 92 patients assigned to VELCADE and 50 patients assigned to HDD. All 142 subjects who were ongoing have subsequently completed study participation (ie, completed all cycles of therapy or discontinued from the study).

An important consequence of allowing patients in the HDD arm the opportunity to crossover to receive VELCADE prior to disease progression is that comparative statistical analyses after this date were limited to survival endpoints only. These results were presented at the 47th Annual Meeting of the American Society of

Haematology (ASH) in December 2005 (9). The median follow-up time for these analyses was 22 months

All other planned statistical comparisons between VELCADE and HDD groups were not possible after 15 December 2003. Updated results for response evaluations and time to progression for patients assigned to the VELCADE arm were presented at the 47th Annual Meeting of the American Society of Haematology (ASH) in December 2005 (9). The cut-off date for these analyses was 30 January 2005 with a median follow-up time of 15.8 months.

IMPLICATIONS OF THE APEX RESULTS

Important Features of the APEX trial

- APEX is the largest trial to be conducted in relapsed MM to date.
- APEX is the first trial to demonstrate a survival advantage of a monotherapy agent over a conventional therapy
- The APEX trial was terminated early when a predetermined interim analysis established the superior efficacy of VELCADE compared to HDD in terms of time to progression, response rate and survival.

Implications of the Early Closure of the APEX Trial

The early termination of the APEX trial has three important implications for interpretation of the results:

- At the time of study closure, the median follow-up was 8.3 months and there were 142 patients ongoing in the study. As such, there was a high level of censoring in both the VELCADE and HDD arms for the TTP and survival analyses.
- The design of APEX allowed for any HDD patient experiencing disease progression to be offered VELCADE therapy. At interim analysis (median follow-up 8.3 months), 44% of HDD patients had crossed over to receive VELCADE. This would have the likely effect of reducing the observed efficacy differences between the two arms. Despite this, a significant difference was observed and the trial was closed early. Updated survival results (median follow-up 22 months) included >62% of HDD patients who had crossed over to receive VELCADE. Despite this, the survival advantage afforded to patients in the VELCADE arm is highly significant.
- Because of the very high level of crossover from HDD to VELCADE, extended follow-up efficacy results other than survival are only available for patients allocated to the VELCADE arm.

EFFICACY OUTCOMES

Primary and secondary efficacy analyses were conducted on data from all 669 patients randomised in this study, i.e. on the ITT population. All 663 patients who received at least one dose of study treatment were included in the Safety Population.

Responses were assessed using the rigorous EBMT criteria previously described in section 2.3.4 (34). A total of 627 patients comprised the response population, including patients who received at least one dose of study treatment and had measurable disease at baseline.

8.3 MONTHS FOLLOW-UP (Richardson *et al.* (8))

Time to Disease Progression (TTP)

- VELCADE was associated with a 78% increase in the time to disease progression compared to HDD (hazard ratio = 0.55; p<0.001)

Survival

- Overall survival was significantly prolonged for patients in the VELCADE treatment group compared to patients in the HDD group with a hazard ratio of 0.57 (p=0.0013).

- One-year survival was also significantly prolonged in patients receiving VELCADE compared to HDD (p=0.003) with VELCADE patients experiencing a 41% decreased risk of death in the first year of treatment (hazard ratio 0.57, p=0.001).

- Of note, these analyses include data from the 44% of HDD patients (147/330) who crossed over to the companion study to receive VELCADE after experiencing progressive disease on HDD prior to the interim analysis. Despite this, the survival advantage with VELCADE is still statistically significant.

Response To Therapy

- The overall response rate (defined as CR+PR) was significantly higher for patients treated with VELCADE than for those treated with HDD (38% vs. 18%; p < 0.001). There were also significantly more patients achieving a complete or near complete response in the VELCADE treatment group (13% of compared to 2%; p<0.001).

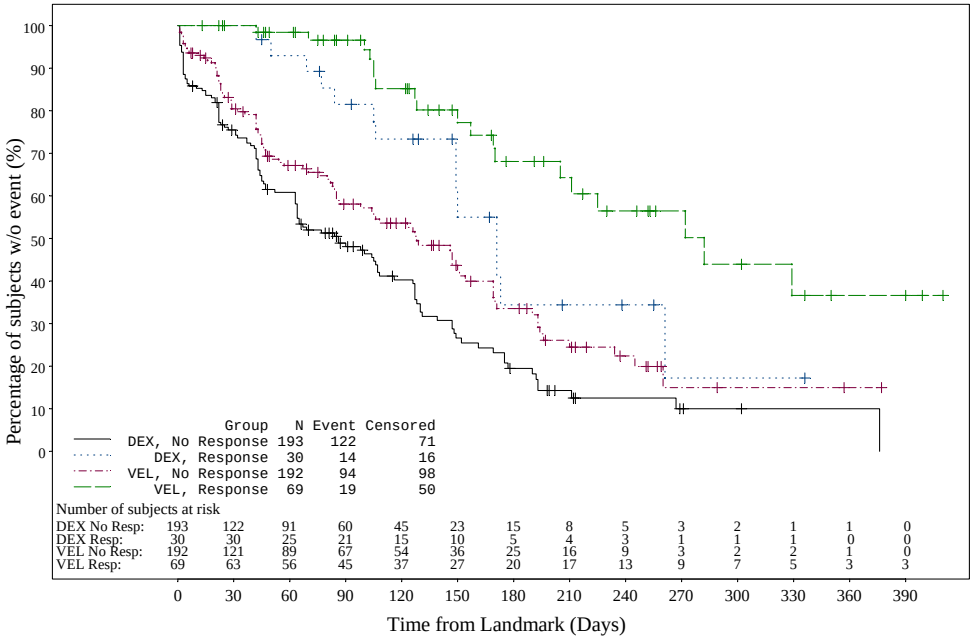
- VELCADE is associated with a rapid time to response. The median time to first response was 43 days (within the first two cycles of therapy). The median time to first response for HDD-treated patients was also 43 days.

- As well as having a rapid time to response, VELCADE responses are also durable. Responses to VELCADE lasted longer than HDD responses (8 months vs 5.6 months). Furthermore, complete responses were more durable than partial responses for VELCADE (9.9 months vs 7.8 months). There were too few complete responses in the HDD arm to perform this evaluation.

- Patients who responded to VELCADE with either a complete or partial response (CR or PR) also achieved better outcomes in terms of delaying the time to progression of MM (32).

- Response to VELCADE was associated with a significantly prolonged TTP compared to patients responding to HDD (Figure 9) (32).

Figure 9: Landmark Analysis: Time to Disease Progression By Response Status at Landmark (Final Analysis: Landmark at 6 Weeks) (32)



- The association between disease response and outcomes is consistent with previous data in newly diagnosed MM patients (35, 43, 44).

UPDATED ANALYSES (9, 32)

Time to Disease Progression (TTP)

After 15.8 months follow-up, the results confirm those of Richardson *et al.* (Table 9)

Table 9: Time to Disease Progression (ITT Population; N=669)

Richardson *et al.* (8) (8.3 months follow-up)				**Updated Analysis (9) (15.8 months follow-up)**
VELCADE Median TTP, months (95% CI)	**HDD** Median TTP, months (95% CI)	**Hazard Ratio** (95% CI)	**p-Value**	**VELCADE** Median TTP, months (95% CI)
n=333 6.2 (4.9, 6.9)	n=330 3.5 (2.8, 4.2)	0.55 (0.44, 0.69)	< 0.001	n=333 6.2 (5.5, 6.9)

Survival

The Richardson *et al.* results are confirmed following 22 months follow-up in the updated survival analysis.

Overall survival remains significantly longer in VELCADE treated patients compared to HDD (hazard ratio = 0.77; p=0.0272). Median survival is 29.8 months and 23.7

months in the VELCADE and HDD groups respectively. This represents a 6-month improvement in median survival for patients randomised to VELCADE.

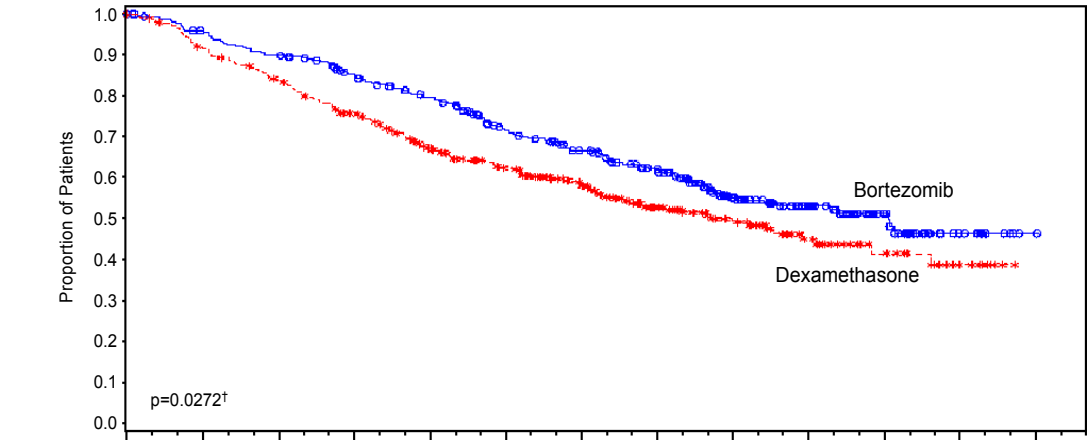
Importantly, the HDD arm includes 208 patients (62%) who crossed over to receive VELCADE in the companion study, either as a result of developing progressive disease on HDD before the interim analysis (n=152), or at the time of the interim analysis (n=56). This is an underestimation of the fraction of HDD patients who have crossed over to receive VELCADE, since it is known that some HDD patients treated in the US have subsequently received commercial VELCADE off protocol.

Despite the high crossover rate, VELCADE continues to demonstrate a significant survival advantage (Figure 10; Table 10).

Figure 10: Updated Kaplan-Meier Survival Curve

(ITT Population; n=669; 22 months follow-up)

(adapted from (9))



* Patients remaining after the indicated timepoint

† p-value from log-rank test

Table 10: Summary of Overall and 1-Year Survival

(ITT Population; N=669; 22 months follow-up)

	Richardson *et al.* (8) (8.3 months follow-up)		Survival Update (9) (22 months follow-up)	
	Overall Survival Months Median (95% CI)	**1-Year Survival (%)**	**Overall Survival Months Median (95% CI)**	**1-Year Survival (%)**
VELCADE (n=333)	16.6 (16.6, NE)	80	29.8 (23.2, NE)	80
HDD (n=330)	NE (NE, NE)	66	23.7 (18.7, 29.1)	67
Hazard Ratio (95% CI)	0.57 (0.40, 0.81)	-	0.77 (0.61, 0.97)	-
p-value	0.0013	0.003	P=0.0272	0.0002

Response Rates

At 15.8 months follow-up, the response rates have improved, with the overall response rate to VELCADE increasing to 43% (9% CR, 7% nCR, 28% PR) (Table 11)

Table 11: Summary of Overall Response Rates

	Richardson *et al.* (8) (8.3 months follow-up)			Updated Analysis (9) (15.8 months follow-up)
	VELCADE (n=315)	**HDD (n=312)**	**p-Value**	**VELCADE (n=315)**
ORR (CR+ PR), n(%)	121 (38)	56 (18)	<0.001	135 (43)
CR, n(%)	20 (6)	2 (<1)	<0.001	27 (9)
nCR, n(%)	21 (7)	3 (<1)	<0.001	21 (7)
PR, n(%)	80 (25)	51 (16)	<0.001	87 (28)

ORR – overall response rate; CR – complete response; nCR – near complete response PR – partial response

Achieving a complete or partial response by EBMT criteria is a significant outcome in MM. Patients achieve a 50 to 100% reduction in paraprotein accompanied by improvements in other significant disease parameters such as stabilisation of skeletal disease, 50 to 100% reduction in the size of any plasmacytomas, and in some cases normalisation of their serum calcium levels. At this stage of MM, such complete and partial response rates are rarely achieved with a monotherapy agent.

Response rates for HDD are lower than those previously reported in the published literature. This difference relates to the different methods of assessing responses in the trials. In previous HDD studies, responses were assessed using a percent reduction in paraprotein alone, not taking other clinical parameters into account. In the APEX study, responses were assessed using the more stringent EBMT criteria where responses are measured by confirmed paraprotein reduction in both serum and urine as well as other clinical parameters such as reduction in plasmacytomas and stabilisation of bone disease.

Time to Response

Response to VELCADE treatment within the APEX trial was rapid with the majority of patients (85%) responding to treatment by the third cycle (Table 12) (32).

Table 12: Percentage of Responders by Treatment Cycle (32)

	Response by cycle		
Cycle	**Incident**	**Cumulative**	**Proportion**
1	57	57	42.2%
2	36	93	68.9%
3	22	115	**85.2%**
4	8	123	91.1%
5	6	129	95.6%
6	3	132	97.8%
7	0	132	97.8%
8	3	135	100.0%
9	0	135	100.0%
10	0	135	100.0%
11	0	135	100.0%
Total	135		

Duration of Response (DoR)

The durable duration of response was confirmed following 15.8 months follow-up (table 13)

Table 13: Duration of Response (ITT Population, N=669)

	Richardson *et al.* (8) 8.3 months follow-up		Updated Analysis (9) 15.8 months follow-up
	VELCADE	**HDD**	**VELCADE**
CR + PR			
N	121	56	135
Median DoR, months (95% CI)	8 (6.9, 11.5)	5.6 (4.8, 9.2)	7.8 (6.9, 9.1)
CR			
N	20	2	27
Median DoR, months (95% CI)	9.9 (6.1, NE)	NE (6.2, NE)	9.9 (6.3, 17.9)
PR			
N	101	54	108
Median DoR, months (95% CI)	7.8 (6.9, 11.5)	5.6 (4.3, 9.2)	7.6 (6.2, 9)

Efficacy Summary

- As a result of the superior efficacy experienced by VELCADE patients, an independent data monitoring committee deemed it unethical to continue with the study and recommended that all patients randomised to HDD should be offered the opportunity to be treated with VELCADE as soon as possible.
- Overall survival was significantly prolonged in VELCADE patients compared to HDD (16.6 months vs NE, hazard ratio 0.57, p=0.0013). At 22 months follow-up survival in VELCADE patients has reached a median of 30 months.
- VELCADE was associated with a 41% reduction in the risk of death in the first year of treatment.
- Survival benefits were seen despite a significant proportion of HDD patients crossing over to receive VELCADE.
- VELCADE prolongs time to disease progression by 78% (hazard ratio = 0.55; ($p<0.001$)) compared to HDD.
- Overall response rate was significantly higher for VELCADE patients ($p<0.001$). Response rates of 43% are rarely seen with a monotherapy agent at this stage of MM.
- VELCADE is associated with a rapid time to response, with the majority of patients responding by cycle 3.
- In patients not responding to VELCADE there is minimal, if any, additional benefit of continuing treatment after cycle 3.
- Response to VELCADE is also durable, with duration of response increasing the higher the quality of response.
- VELCADE responders experienced a longer time to disease progression than non-responders and dexamethasone responders.
- The APEX trial confirms the clinical superiority of VELCADE as a single-agent treatment compared to HDD.

QUALITY OF LIFE (QoL)

Quality of life in MM patients is poor, mainly due to the debilitating symptoms associated with the disease. In particular, QoL is impacted by continuous pain resulting from bone lesions and persistent fatigue. Responding to MM agents will reduce tumour burden and can improve some of the disease associated symptoms. However, other symptoms such as bone pain may not be impacted. For example, a complete response measured by the stringent EBMT response criteria will achieve stabilisation of bone disease and calcium levels, rather than resolving this devastating symptom.

At baseline, the two treatment groups were comparable on demographic and clinical characteristics, neurotoxicity score, and on most EORTC scores (Global Health, Physical, Role, Social and Cognitive Functioning, Appetite, Constipation, Dyspnoea, Financial Impact, Nausea, and Pain) (36). There was substantial missing data (from 12.5% at week 6 to 75.6% at week 42), primarily due to premature closure of the study and disease progression. Extensive statistical analyses were undertaken to correct for potential bias related to the missing data. The *a priori* primary end point for the QoL analyses was the Global Health Status scale of the EORTC. All other scales and symptom scores were considered secondary end points. The P values were adjusted for multiple comparisons by the Hochberg-Benjamini method.

Using generalised estimating equations (GEE) of multiply imputed datasets, a significant difference over the 42 weeks in favour of VELCADE was found for the primary end point of Global Health (P= 0.0005), as well as the secondary end points of Physical, Role, Cognitive, and Emotional Functioning (adjusted P values < 0 .05) and the symptom items of Total Neurotoxicity, Nausea, Dyspnoea, Sleep, Diarrhoea, and Financial Impact (adjusted P values < 0.05) (Table 14) (36). There was no QoL domain for which HDD was superior to VELCADE over time. Using alternative methods to adjust for potential informative censoring, both a Sun and Song analysis and a Pattern-Mixture model analysis supported the GEE conclusions.

Table 14: GEE Analysis Over 42 Weeks Multiply Imputed Data

EORTC Component Scores	Raw P-Value	Adjusted P-Value
Global Health	0.0005	-
Physical Function	0.0215	0.0430
Role Fuction	0.0179	0.0418
Cognitive Function	0.0001	0.0007
Emotional Function	0.0301	0.0468
Social Function	0.0770	0.0898
EORTC Symptom Scores		
Fatigue	0.0742	0.0898
Nausea	0.0133	0.0372
Pain	0.0621	0.0869
Dyspnoea	0.0023	0.0107
Sleep	0.0001	0.0007
Appetite	0.6693	0.7208
Constipation	0.8720	0.8720
Diarrhoea	0.0059	0.0207
Financial Impact	0.0291	0.0468

* P values adjusted using the Hochberg Benjamini sequential testing procedure.

Quality of Life Summary

- Quality of life in MM patients is poor due to the significant clinical and psychological burden of the disease.
- Debilitating symptoms impacting quality of life include persistent fatigue and constant pain
- VELCADE was found to be superior to dexamethasone in all QoL domains.

SUBGROUP ANALYSES

A number of sub-analyses were undertaken to assess the benefit of VELCADE monotherapy across a range of patient factors commonly associated with poor prognosis and inadequate outcomes. The analyses demonstrated that VELCADE was superior to HDD across all groups of patients. In particular the sub-analyses revealed that the efficacy of VELCADE improves the earlier it is used in the MM treatment pathway.

a) Earlier Vs Later VELCADE

Analyses were conducted for patients who had received only one prior line of therapy (251 of 669 patients, 38%) and for patients who had received more than one prior therapeutic line (417 of 669 patients, 62%) (data were missing for number of prior therapies for one patient).

Patients at an earlier stage of their disease (1 prior therapy) achieved better overall outcomes than later stage patients (>1 prior therapy). This was consistent for both the VELCADE and dexamethasone groups.

Furthermore, VELCADE continued to achieve superior outcomes compared to dexamethasone regardless of the number of prior treatments patients had received.

At 8.3 months follow-up, compared with patients at second relapse and beyond, patients at first relapse achieved:

- Prolonged TTP (7.0 months Vs. 4.9 months)
- Extended overall and one year survival (89% 1-year survival Vs. 73%)
- Higher response rates (45% Vs 34%).

These results were confirmed at the updated analysis. The full results from this subgroup analysis are summarised in Appendix 5.

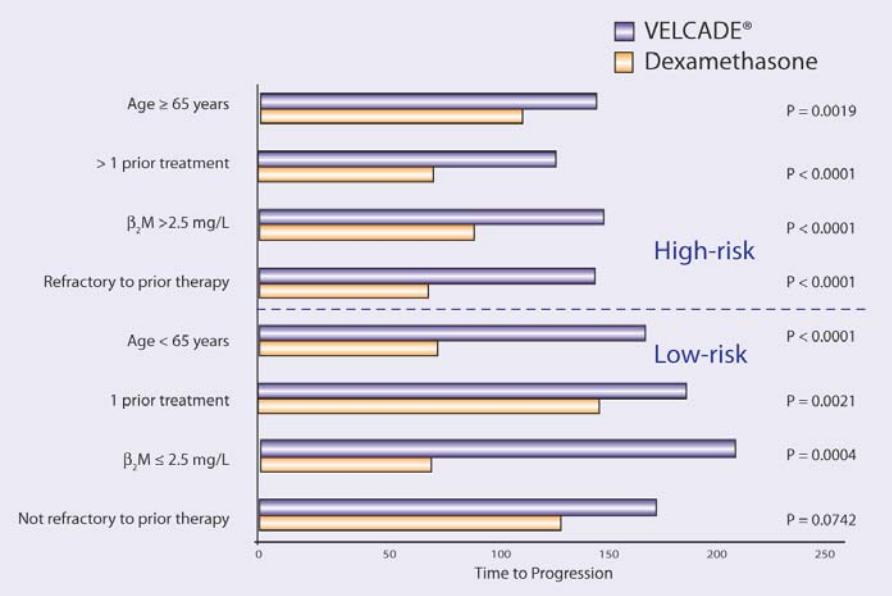
This subgroup analysis suggests that the efficacy of VELCADE is higher in patients at an earlier stage of their disease. Patients at first relapse achieve better outcomes with VELCADE treatment compared to those at second relapse and beyond.

b) Poor Prognosis Patients

Several factors, if present at diagnosis, are predictive of a poorer prognosis in MM patients. These include increasing age, raised serum β_2-microglobulin levels, an increasing number of prior therapies and refractoriness to therapy.

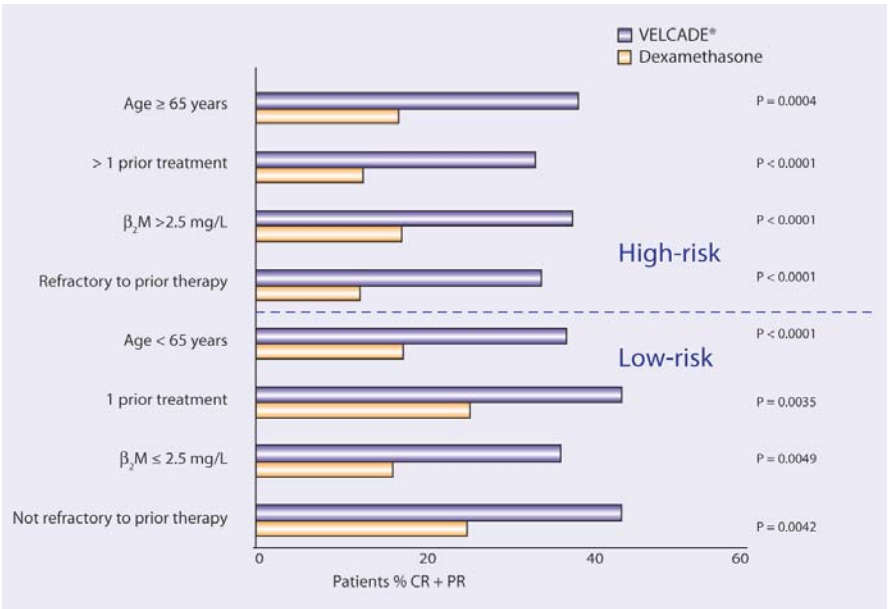
A sub-analysis of the safety and efficacy of VELCADE in high-risk patients (defined as age > 65 years, >1 prior therapy, refractory to prior therapy or serum β_2-microglobulin level >2.5 mg/L) from the APEX study, showed that the efficacy advantage of VELCADE was maintained in both high-risk and low-risk patients (45) (Figures 11 and 12).

Figure 11: TTP in high-risk and low-risk patients (ITT Population; N=669)(45)



The efficacy advantage in terms of overall response rate (CR+PR) was also maintained across both the high-risk and low-risk patient sub-groups (Figure 11) (45).

Figure 12: Overall response (CR + PR) rates in high-risk and low-risk patients (ITT Population)(45)



In the sub-analysis, VELCADE was associated with a significantly increased overall survival (P<0.05) compared with HDD in all subgroups, except in patients younger than 65 years of age. In this sub-group, the overall survival for patients younger than 65 years of age, while not statistically significant (P = 0.097), favours VELCADE, with a hazard ratio of 0.68, representing a 47% higher risk of death for the HDD arm (45).

The subgroup analysis suggests that the efficacy of VELCADE is consistent across all patients with relapsed or refractory MM, irrespective of their risk status. The sub-analysis also demonstrates that patients at an earlier stage of their disease (1 prior therapy) achieve better overall outcomes compared to patients at a later stage of treatment (> 1 prior therapy). Further results on this sub-analysis can be found in Appendix 5.

c) HDD Refractory

A review of baseline prior high-dose steroid data revealed that some patients who may have been refractory to dexamethasone were enrolled into the study in error. A total of 60 (9%) of the 669 patients randomised into the study were determined to be refractory to dexamethasone, including 32 (10%) of 333 VELCADE patients and 28 (8%) of 336 HDD patients.

As these patients would not be expected to respond to HDD, or to have a more short-lived response, a sensitivity analysis was conducted excluding these patients from the analysis; results were also provided for the 60 patients determined to be dexamethasone-refractory. Endpoints analysed included TTP, survival, and response.

All results for those 609 patients determined not to be refractory to dexamethasone were consistent with those in the overall population. Further results of this sub-analysis can be found in Appendix 5.

Subgroup Analysis Summary

- Patients receiving VELCADE at an earlier stage of their disease (1 prior line of therapy) achieve better outcomes than more heavily pre-treated patients (>1 prior line)
- VELCADE produces consistent outcomes in high risk patients compared to low risk patients supporting the use of VELCADE treatment in all relapsed MM patients.
- When the 28 dexamethasone-refractory patients in the dexamethasone arm are excluded from the analysis, VELCADE remains superior to dexamethasone across all efficacy measures.

56. Where interim trial data are quoted this should be clearly stated along with the point at which data were taken and the time remaining until completion of that trial. Analytical adjustments should be described to cater for the interim nature of the data.

This has been discussed in the response to Question 54

57. If the trial measures a number of outcomes, discuss whether and how an adjustment was made for multiple comparisons in the analysis.

58. Other relevant data that may assist in interpretation of the results may be included, such as adherence to medication and/or study protocol.

OTHER SUPPORTIVE DATA

The clinical benefits of VELCADE monotherapy have been observed in the relapsed and refractory setting, in patients who have experienced two or more relapses. Two published phase II studies, SUMMIT and CREST, provide additional evidence for the efficacy of VELCADE in MM. The studies also give an indication to the synergy between VELCADE and dexamethasone. In both studies, adding dexamethasone to VELCADE in suboptimal responders boosted response rates, even in patients who were previously refractory to corticosteroid therapy. An overview of the key findings of SUMMIT and CREST are presented below. The full references can be found in Appendix 6.

SUMMIT

SUMMIT was a phase II, open-label trial designed to assess the efficacy and safety of VELCADE in patients with relapsed MM who were refractory to their most recent treatment (4). A total of 202 patients were recruited. The patients were heavily pre-treated (median previous lines of therapy = 6: range 2-15 lines of therapy). The prognosis for such patients was very poor, with a median expected survival of 6-9 months (4).

Methodology

Patients received VELCADE at a dose of 1.3 mg/m^2 on days 1, 4, 8 and 11 of a 21 day cycle and could receive up to 8 cycles. As with the APEX study, responses were assessed using the stringent EBMT criteria (34). Patients with progressive disease (PD) after 2 cycles, or stable disease (SD) after 4 cycles were eligible for the addition of dexamethasone to the treatment regimen. Dexamethasone (20mg) was administered on the day of and the day after bortezomib administration (days 1, 2, 4, 5, 8, 9, 11 and 12 of a 21 day cycle).

Results

Response Rates

- Of 193 evaluable patients, CR or nCR was observed in 19 (10%) patients. In 12 patients, this was their best response achieved to any therapy they had received.
- 35% had a CR, PR or MR with VELCADE alone, and a further 24% achieved stabilisation of their disease. Given that patients were experiencing progressive disease at enrolment, stable disease is a clinically meaningful outcome. Such response rates are rarely observed in late stage, refractory MM.

- A landmark analysis of survival showed a significant association between responder status and ultimate survival (p=0.007).

Time to Progression and Duration of Response

- The median TTP with VELCADE alone more than doubled compared to the TTP on patients' last prior therapy before enrolment (p=0.01).
- Responses to VELCADE were durable, with overall responses (CR + PR + MR) lasting a median of 12 months, and complete or near complete responses lasting 15 months.

Survival

- The expected median survival of heavily pre-treated, late stage, refractory MM patients is 6 to 9 months (4). After being treated with VELCADE, patients in the SUMMIT study survived for a median of 17 months (28).
- Patients who responded to VELCADE survived significantly longer than all other patients (p=0.007)

Dexamethasone Combination

- Eighteen percent of patients who received concomitant dexamethasone due to inadequate response went on to achieve a minimal or partial response. In six of these patients, the disease had previously been refractory to corticosteroids.

Table 15: Summary of Efficacy Results from the SUMMIT trial

Response Analyses	**N=193**
Overall Response Rate (CRa +PR+MR) (95% CI)	35% (28.0 - 41.9)
Complete remission [a] (90% CI)	10% (6.5 – 14.1)
Stable disease	24%
Time to Event Analyses	**N=202**
Median DoR (CR or PR or MR) (months) (95% CI)	12 (5.7 – NE)
Median TTP – All Patients (days) (95% CI)	6.9(5.1 – 9.2)
Median Overall Survival – All Patients (months)	17
a CRIF- + CRIF+ Note: Responses subsequent to the use of dexamethasone are excluded NE = not estimable	

Quality of Life (QoL)

- Patients enrolled on the SUMMIT trial had very progressive disease and their baseline EORTC QLQ-C30 scores were in the same range as those of cancer patients with advanced solid tumours.
- Data on patient's self-reported QoL from 143 patients revealed maximal improvements from baseline in mean global QoL score and disease symptoms, including pain and fatigue, with the greatest improvements seen in the complete and partial responders.

- Statistically significant differences for the change in patient's self-reported QoL scores were obtained within the CR+PR responder groups (46).

SUMMIT Summary

- The SUMMIT study demonstrated significant efficacy in a heavily pre-treated, difficult to treat patient population.
- In 12 of the 19 complete responders, this was the best response they had ever had to therapy
- Responses were durable with CR lasting for 15 months
- Survival reached 17 months in a population expected to survive 6 to 9 months.
- Clinical efficacy was accompanied by an improvement in quality of life
- Adding dexamethasone to VELCADE boosted outcomes in 18% of VELCADE non-responders, 6 of whom had been previously refractory to corticosteroids

CREST Trial

Overview

CREST was a prospective, randomised, multicentre, open-label phase II study designed to assess the efficacy of two different doses of VELCADE in patients with MM who had failed to respond to or relapsed following first line therapy (median number of prior therapies was 3, range 1 to 7) (3).

Patients were randomised into two groups: group A included 27 evaluable patients, who were treated with 1.0 mg/m^2 VELCADE using the same schedule as the SUMMIT study and group B included 26 evaluable patients who received 1.3 mg/m^2 doses. Both groups were treated for a maximum of eight cycles. The guidelines for addition of Dexamethasone were the same as for SUMMIT.

Results

Response

- Overall response rates of 33% and 50% were reported for 1.0 mg/m^2 and 1.3 mg/m^2 groups respectively following single agent VELCADE
- Addition of dexamethasone to inadequate responders boosted overall response rates to 44% and 62% (Table 16)
- Although not statistically powered for comparison, the 1.3 mg/m^2 dose achieved numerically higher response rates than the 1.0 mg/m^2 dose. The SmPC recommendations are to start with a dose of 1.3 mg/m^2 and reduce it to 1.0 mg/m^2 in the case of toxicity.

Table 16: Overall Response Rates for VELCADE alone and VELCADE plus dexamethasone

	VELCADE 1.0mg/m^2 (n = 27)		VELCADE 1.3mg/m^2 (n = 26)	
	VELCADE alone	**VELCADE ± dexamethasone**	**VELCADE alone**	**VELCADE ± dexamethasone**
ORR (CR + PR + MR), %	33	44	50	62
CR + PR, %	30	37	38	50
CR + nCR, %	11	19	4	4
PR, %	19	19	35	46
MR	4	7	12	12
ORR – Overall Response Rate, CR - Complete Response, PR – Partial Response, nCR – near Complete Response, MR – Minimal Response				

Survival

- The median overall survival had not been reached in the 1.3 mg/m^2 group, and was 26.7 months in the 1.0 mg/m^2 group.
- The median duration of follow-up for the observational period was 9.5 months in the 1.0 mg/m^2 dose group and 8.1 months in the higher dose group.

CREST Summary

- An overall response rate of 50% and 33% was achieved following a starting dose of 1.3 mg/m^2 and 1.0 mg/m^2 VELCADE respectively
- Adding dexamethasone to VELCADE boosted response rates in non-responders in both dosing groups.
- Patients experiencing toxicity at a starting dose of 1.3 mg/m^2 can be treated effectively at 1.0 mg/m^2 whilst reducing the risk of adverse events.

2.6 Meta-analysis

59. Where more than one study is available consideration should be given to undertaking a meta-analysis. The following steps should be used as a minimum.

- **Perform a statistical assessment of heterogeneity. If the visual presentation and/or the statistical test indicate the trial results are heterogeneous, try to provide an explanation for the heterogeneity.**

- **Statistically combine (pool) the results for both relative risk reduction and absolute risk reduction using both the fixed effects and random effects models (giving four combinations in all).**
- **Provide an adequate description of the methods of statistical combination and justify their choice.**
- **Undertake sensitivity analysis where appropriate**
- **Tabulate and/or graphically display the individual and combined results.**

There is only one randomised controlled Phase III trial available assessing the efficacy of VELCADE in MM patients at first relapse. As such performing a meta-analysis is not relevant.

2.7 Indirect/mixed treatment comparisons

60. In circumstances where there are no RCTs that directly compare the technology with the comparator(s) of interest consideration should be given to using indirect/mixed treatment comparisons. Give a full description of the methodology used and provide a justification for the approach.

Not applicable

2.8 Comparative safety

61. Give a brief overview of the safety of the technology compared to the comparator(s). Give incidence rates if appropriate.

Evidence from comparative trials and regulatory summaries is preferred; however, findings from non-comparative trials may sometimes be relevant. For example, they may demonstrate a relative lack of adverse effects commonly associated with the comparator or the occurrence of adverse effects not significantly associated with other treatments.

If any of the main trials are primarily designed to assess a safety outcome (for example, they are powered to detect significant differences between treatments with respect to incidence of an adverse effect) these should be reported here in the same detail as described previously (section 3) for efficacy trials.

A total of 663 patients received at least one dose of study drug and are included in the safety population (331 in the VELCADE group, and 332 in the HDD group).

RICHARDSON, *ET AL*: 8.3 MONTHS FOLLOW-UP (8)

In the APEX trial, the safety profile of VELCADE was similar to that reported in the published Phase II studies (SUMMIT and CREST). The safety profile for HDD was consistent with other clinical trial data reported to date. (3, 4, 8) (Table 18).

Overall, the adverse events associated with VELCADE treatment were mild to moderate (grades one or two) in severity, and were expected and manageable.

Certain adverse events were more prominent in the VELCADE group (Table 15) including gastrointestinal events, thrombocytopenia and peripheral neuropathy. Grade 3 adverse events were reported in 61% of VELCADE-treated patients and in 44% of HDD patients. The most common Grade 3 adverse events (reported by more than 10% patients) were thrombocytopenia, anaemia and neutropenia in patients receiving VELCADE; and anaemia in HDD patients. Both groups had similar rates of Grade 4 toxicities (14% VELCADE; 16% HDD).

A total of 121 patients (37%) in the VELCADE group had adverse events necessitating discontinuation of treatment. These events included peripheral neuropathy (8%), and thrombocytopenia, gastrointestinal disorders, fatigue, hypercalcaemia and spinal cord compression (2%). In the HDD group, 96 patients discontinued due to adverse events (29%), which included psychotic disorder, hyperglycaemia, or thrombocytopenia (2% each).

There were 8 deaths considered possibly related to study drug: four in the VELCADE group (3 from cardiac causes and one from respiratory failure) and four in the HDD group (three from sepsis, and one sudden death of unknown cause).

UPDATED ANALYSIS: 15.8 MONTHS FOLLOW-UP

After 15.8 months follow-up, adverse events commonly reported with VELCADE (>10% patients) were the same as those reported by Richardson et al. Only slight, if any, differences in the incidences of these commonly reported adverse events were seen. It is notable that despite increased VELCADE exposure through the updated reporting period, only 1 commonly reported adverse event (paraesthesias and dysesthesias) increased in incidence by >2% through the updated reporting period.

Table 17: Adverse Events During Treatment Reported by 15% or More of Patients Receiving VELCADE or HDD, including Grade 3 or 4 Events [8.3 Months Follow-up]

Event	Treatment Group					
	VELCADE (n=331)			HDD (n=332)		
	Total n (%)	Grade 3 n (%)	Grade 4 n (%)	Total n (%)	Grade 3 n (%)	Grade 4 n (%)
Diarrhoea	190 (57)	24 (7)	0	69 (21)	6 (2)	0
Nausea	190 (57)	8 (2)	0	46 (14)	0	0
Fatigue	140 (42)	17 (5)	1 (<1)	106 (32)	12 (4)	0
Constipation	140 (42)	7 (2)	0	49 (15)	4 (1)	0
Peripheral neuropathy	120 (36)	24 (7)	2 (1)	29 (9)	1 (<1)	1 (<1)
Vomiting	117 (35)	11 (3)	0	20 (6)	4 (1)	0
Pyrexia	116 (35)	6 (2)	0	54 (16)	4 (1)	1 (<1)
Thrombocytopenia	115 (35)	85 (26)	12 (4)	36 (11)	18 (5)	4 (1)
Anaemia	87 (26)	31 (9)	2 (1)	74 (22)	32 (10)	3 (1)
Headache	85 (26)	3 (1)	0	43 (13)	2 (1)	0
Anorexia	75 (23)	9 (3)	0	14 (4)	1 (<1)	0
Cough	70 (21)	2 (1)	0	35 (11)	1 (<1)	0
Paraesthesia	68 (21)	5 (2)	0	27 (8)	0	0
Dyspnoea	65 (20)	16 (5)	1 (<1)	58 (17)	9 (3)	2 (1)
Neutropenia	62 (19)	40 (12)	8 (2)	5 (2)	4 (1)	0
Rash NOS	61 (18)	4 (1)	0	20 (6)	0	0
Insomnia	60 (18)	1 (<1)	0	90 (27)	5 (2)	0
Abdominal pain	53 (16)	6 (2)	0	12 (4)	1 (<1)	0
Bone pain	52 (16)	12 (4)	0	50 (15)	9 (3)	0
Pain in limb	50 (15)	5 (2)	0	24 (7)	2 (<1)	0
Muscle cramps	41 (12)	0	0	50 (15)	3 (1)	0

Time to First Skeletal Event (TSE) and Rate of ≥ Grade 3 Infections

TSE and the rate of ≥ Grade 3 infections were assessed as secondary endpoints in the APEX study.

The TSE and rate of Grade 3 or higher infections did not differ significantly between the two treatment groups. The median time to a first skeletal event could not be estimated in either group, and the hazard ratios were not significantly different (p=0.32) (8). Note that the low rate of skeletal events in both treatment groups is

likely due to the requirement that all patients receive intravenous bisphosphonates during the study and the short follow-up time relative to this endpoint.

The proportion of patients with Grade 3 or higher infections was 13% in the VELCADE group and 16% in the HDD group (p=0.19) (8).

It is important to note that the protocol recommended that patients not receive prophylactic antibiotic treatment. However, despite this recommendation, approximately one-third of patients in the HDD group (112 of 332, 34%) and 9% (29 of 331 patients) of patients in the VELCADE group included in the safety population received prophylactic treatment with sulfonamides/trimethoprim during the study (32).

Peripheral Neuropathy

Peripheral neuropathy can occur in MM patients as a result of the disease itself or as a side effect of various commonly used therapies including thalidomide and vinca alkaloids. The neuropathy associated with these agents is often cumulative and can be irreversible. In the APEX study, 38% of patients reported symptoms of peripheral neuropathy at baseline (32).

The updated analysis of the APEX trial (15.8 months follow-up) reported that 36% (n=120) VELCADE patients developed worsening or new symptoms of peripheral neuropathy, which was Grade 3 or higher in 9% (n=30) (22). Evidence from the Phase II trials indicates that VELCADE-associated peripheral neuropathy can be readily managed through reducing the dose of VELCADE (47), as such, patients on the APEX trial who developed peripheral neuropathy whilst receiving VELCADE were managed using a dose modification strategy. This has formed the basis for the recommendations in the Summary of Product Characteristics (Table 18).

Table 18: Recommended dose modifications for VELCADE related neuropathic pain and/or peripheral sensory neuropathy.

Severity of peripheral neuropathy	Modification of dose and regimen
Grade 1 (paraesthesia and/or loss of reflexes) with no pain or loss of function	No action
Grade 1 with pain or Grade 2 (interfering with function but no activities of daily living)	Reduce to 1.0 mg/m^2
Grade 2 with pain or Grade 3 (interfering with activities of daily living)	Withhold VELCADE treatment until symptoms of toxicity have resolved. When toxicity resolves re-initiate VELCADE treatment and reduce dose to 0.7 mg/m^2 and change treatment schedule to once per week.
Grade 4 (permanent sensory loss that interferes with function)	Discontinue VELCADE

Ninety-one patients had ≥ Grade 2 peripheral neuropathy, and of these 37 had a dose modified according to the recommendations, 31 had VELCADE discontinued according to the recommendations, and the remaining 23 had no dose change. Of the 91 patients, the majority (64%) improved (9%) or had complete resolution (55%) of their symptoms (Table 19). Dose modification did not compromise efficacy.

Importantly, the rate of Grade ≥ 3 PN was lower than previously reported in Phase II studies, perhaps due to the dose modification guidelines.

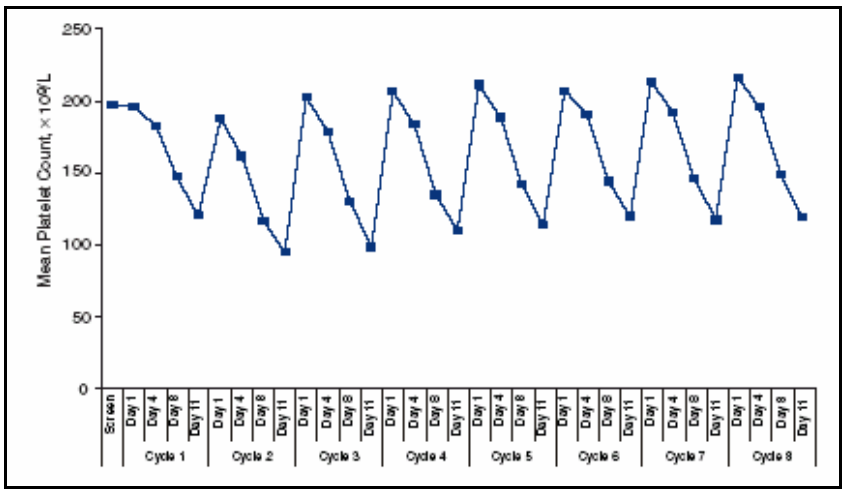
Table 19: Outcome and Time to Resolution of Treatment-Emergent Peripheral Neuropathy

Statistic	Outcome
Patients with ≥ Grade 2 Neuropathy	
N Improvement or resolution Median time to improvement or resolution	91 64% 110 days
Patients with a dose modification due to ≥ Grade 2 Neuropathy	
N Improvement or resolution Median time to improvement or resolution	37 70% 78 days
Patients with VELCADE discontinuation due to ≥ Grade 2 Neuropathy	
N Improvement or resolution Median time to improvement or resolution	31 61% 121 days
Patients without a dose change due to ≥ Grade 2 Neuropathy	
N Improvement or resolution Median time to improvement or resolution	23 52% 106 days

Thrombocytopenia

As seen in previous clinical studies (48), VELCADE was associated with a predictable, cyclic thrombocytopenia, with a general progressive decrease in platelet count during the dosing period and a return to baseline platelet count during the rest period of each treatment cycle (Figure 13).

Figure 13: The Cyclical Nature of VELCADE-associated Thrombocytopenia



In general, the lowest platelet count is predictable from the baseline count with the nadir being approximately 60% of the pre-treatment platelet count. Thrombocytopenia can be managed by altering the VELCADE dose, and the SmPC contains specific dose modifications. Platelet transfusions can be administered at the clinician's discretion.

Thrombocytopenia was reported in 35% of VELCADE patients and 11% of HDD patients, with 26% grade three and 4% grade four in severity for VELCADE patients. Only 2% patients discontinued due to thrombocytopenia.

Safety Summary

- The toxicity profile of both VELCADE and dexamethasone in the APEX trial were similar to that demonstrated in previous clinical trials.
- Adverse events to VELCADE were predominantly mild to moderate in severity.
- The most common toxicities included asthenic conditions, gastrointestinal disorders, haematological toxicities, and nervous system disorders
- Treatment-emergent peripheral neuropathy resolved or improved in 68% patients following dose modification
- Thrombocytopenia was observed in 35% of patients, and was predictable, cyclical and reversible.

2.9 Interpretation of clinical evidence (400 word maximum)

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

With a novel, targeted mechanism of action, VELCADE offers a new way of treating MM patients. The clinical trial evidence demonstrates that VELCADE is a highly effective treatment option that provides patients with extended survival.

Extended Survival

MM is currently an incurable and fatal disease and as such survival is the critical outcome for MM therapies. In the treatment of MM over the past decade, overall survival had not improved significantly. With the availability of VELCADE however, this became the first single-agent to demonstrate a significant survival advantage over a conventional chemotherapy in relapsed MM (8).

Furthermore, VELCADE produces consistent efficacy in patients exhibiting poor prognostic features usually associated with inferior outcomes, such as chromosome 13 deletion and elevated $\beta_2$microglobulin levels. These significant outcomes are challenging the traditional views of treating and managing MM.

The option of a new treatment and possibility of extending survival in a meaningful way can also have a significant beneficial impact on MM patients, and can translate into an optimistic outlook for their own future management.

Enhanced Response in Combination

Due to its novel mechanism of action, VELCADE has been shown to potentiate the effects of other anti-neoplastic therapies including dexamethasone. In UK clinical practice, clinicians frequently add dexamethasone to VELCADE treatment to enhance response. The clinical evidence demonstrates a clear synergy between VELCADE and dexamethasone, resulting in improved response rates. It is therefore not surprising that, in clinical practice, VELCADE is commonly used in combination with dexamethasone

Activity in Chemo-Resistant Relapsed MM

MM is an incurable disease. The aim of treatment is to reduce morbidity and to extend survival for as long as possible. A major problem is that all patients will eventually relapse following treatment. Following relapse, treatment options become increasingly limited, and there is an urgent unmet clinical need for new and effective therapeutic agents to be available. Following initial treatment with standard chemotherapy, patients frequently become refractory to further courses. VELCADE, because of its novel mechanism of action can, be effective in these patients.

Rapid and Robust Responses

First relapse MM treatment is rarely associated with complete remissions, and achieving robust responses at this stage has major implications on patient prognosis, outcomes, quality of life and second relapse treatment options.

VELCADE produced significantly more complete and partial responses than HDD as measured by the stringent EBMT criteria, with an overall response rate reaching 43%. Such response rates have been reported as unprecedented for a single agent MM therapy (8).

Response to VELCADE is rapid with the majority of patients responding before the 4th cycle of therapy. Furthermore, VELCADE responses are durable and are extended the higher the quality of response (8).

Both response and time to progression have been cited as two factors predictive of improved outcomes in front-line patients (35, 43, 44, 49). A response to VELCADE was associated with a longer time to progression than non-responders, and compared to HDD responders, further supporting the clinical impact of VELCADE.

Manageable Side Effect Profile

Toxicity is another factor that can impact a patient's quality of life. Importantly, the adverse events associated with VELCADE use are usually mild to moderate in severity and can be generally managed through dose modification strategies. Reducing the dose of VELCADE has been shown to diminish toxicities whilst retaining some meaningful clinical activity (3). Optimising the MM treatment pathway should focus on using effective agents whilst minimising potentially treatment limiting toxicities, and the SmPC for VELCADE gives specific guidance to achieve these outcomes.

63. Identify any factors that may influence the applicability of study results to patients in routine clinical practice; for example, issues relating to conduct of the trial versus 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 SPC?

The baseline characteristics of the 669 patients randomised in the APEX study are representative of MM patients who have received between one and three prior lines of therapy. The 51 UK patients enrolled in the study didn't differ significantly from the overall cohort.

The APEX trial used the stringent EBMT criteria to assess response to VELCADE. In everyday clinical practice, the EBMT response criteria is usually reserved for assessing response to stem cell transplantation. Responses to other therapies are generally assessed through monitoring percent reduction in paraprotein level. Using a less stringent response evaluation criteria, may lead to a perception of improvement in response rates observed in clinical practice.

3 Cost effectiveness

3.1 Published cost-effectiveness estimates

3.1.1 Identification and description of studies

64. Describe the strategies used to retrieve relevant cost-effectiveness studies from the published literature and from unpublished data held by the company. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided to enable the methods to be reproduced and the rationale for any inclusion and exclusion criteria used should be provided.

Specify:

65. the specific databases searched and service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- Health Economic Evaluation Database
- NHS Economic Evaluation Database (NHS EED)

A comprehensive, systematic literature search was carried out on the 7th of February 2006 to identify published economic studies that assessed the cost effectiveness of

VELCADE as a single agent in the treatment of multiple myeloma patients at first relapse. A summary of all databases searched is presented in Table 20 below.

Table 20: Databases Searched

Database searched	Date Span	Service Provider
Medline	1966 – week 4 Jan 06	OVID
Medline (in process)	Up to 7th Feb 06	OVID
EMBASE	1974 - 7th Feb 06	Data Star Web
Cochrane	Up to 7th Feb 06	Wiley Science
NHS EED	All Records	
Company Literature Management and Documentation (LMD) Database	Up to 7th Feb 06	Janssen Pharmaceutica
Conference proceedings searched		
ASH (American Society of Hematology)	2003-2005 (2006 conference not yet taken place)	ASH website (http://www.hematology.org/)
ISPOR (International Society of Pharmacoeconomics & Outcomes Research)	Up to 7th February 2006	ISPOR website (http://www.ispor.org/)

The complete search strategies used, including all the search terms: Text words (free text), Subject Index Headings (e.g. MeSH) and the relationship between the search terms (e.g. Boolean) are presented in Appendix 8. In total 83 references were identified (see table 21 below)

Table 21: Search Results

Database	References Identified
Medline	15
Medline in process	1
EMBASE	41
Cochrane	1
NHS EED	3
LMD database (company database)	14
ASH conferences	5
ISPOR conferences	3
TOTAL	83

All citations retrieved by the search were manually filtered using the inclusion and exclusion criteria shown below.

Studies that met the following criteria were included:

- The cost-effectiveness of VELCADE was considered
- The patients in whom cost-effectiveness was considered had multiple myeloma

Studies were excluded if they met the following criteria:

- Reviews, comments or letters (includes reviews of disease area, reviews of clinical studies, reviews of different types of treatment, comments on trials or drugs)
- Industry news, drug discovery, new developments (includes articles outlining early development of investigational drugs)
- Guidelines (i.e. guidelines on the use of different drugs for different treatments)
- Not related to the treatment of multiple myeloma
- Not cost-effectiveness studies

Data Abstraction Strategy

The abstracts of the 83 articles identified by the literature search were individually checked to see if they contained suitable cost effectiveness data, and to eliminate inappropriate papers.

The results from the data abstraction exercise reveal that four studies compared the cost effectiveness of VELCADE in patients with MM. Three of the studies were located from the database searches and the fourth as a result of reference checks on the paper by Haycox A et al (located in the EMBASE search). Unfortunately none of these studies related to the treatment of MM at first relapse and were therefore of limited value in terms of informing the current technology appraisal.

3.1.2 Description of identified studies

66. Please provide a brief overview of each study, stating the aims, methods, results and relevance to decision-making in England and Wales.

A summary of these studies is presented in Tables 22 and 23 below.

Table 22: Overview of Key Parameters Within Published Economic Studies

	Mehta J et al (50)	Bagust A et al (51)	Yoong K et al (52)	Grosso A et al (53)
Aims	To evaluate the cost-effectiveness of VELCADE in relapsed and refractory MM relative to best supportive care (BSC) and thalidomide.	To evaluate and compare the costs and health benefits of VELCADE to BSC as a third-line treatment for patients with relapsed and refractory MM	To conduct an economic analysis of VELCADE versus BSC in relapsed and refractory MM patients in Canada.	To critically review the clinical and economic benefits of Velcade in the treatment of relapsed and refractory MM patients.
Evaluation type	Cost per life year gained	Cost per life year gained Cost per QALY	Cost per life year gained Cost per QALY	Cost per death avoided
Modelling employed	Yes	Yes	Yes	No
Nature of Modelling	Decision analysis	Two part mathematical model	Kaplan-Meier analysis	N/A
Perspective	US third party payer	UK NHS	Canadian Provincial Ministry of Health	UK NHS perspective
Intervention/comparator	Three models developed: ▪ (full cohort model) VELCADE vs BSC ▪ (1st stratified model) VELCADE in patients who had previously received thalidomide versus BSC ▪ (2nd stratified model) VELCADE in patients who had <u>not</u> previously received thalidomide versus thalidomide	BSC	BSC	Dexamethasone
Population	Relapsed and refractory MM patients	Relapsed and Refractory MM patients	Relapsed and Refractory MM patients	Relapsed or chemo-resistant MM patients
Outcomes considered	Survival	Survival Health Utility	Survival Health Utility	Deaths
Timeframe	Estimated lifetime of patient	Estimated lifetime of patient	Estimated lifetime of the patient	8 months
Discounting	Unknown	Unknown	No	No
Cost year	2003	Not provided	2004	Not provided
Effectiveness (source)	-Richardson PG 2003 (4) -Delphi Panel	Richardson PG 2003 (4)	Richardson PG 2003 (4)	Richardson 2004 (8)
Costs (source)	Drug topics Red Book. Montvale, NJ.Thompson, June 2003 Office/clinic visits obtained from 2003 Physician Fee Schedule 2003 Hospital Outpatient Prospective	Not provided	Not stated by Canadian acquisition costs considered	Not provided

	payment system			
Quality of life/utility (data)	None	Sourced from SUMMIT trial (4). Values not listed	Sourced from SUMMIT trial (4). Values not listed	None

Table 23: Overview of Results of Published Economic Studies

	Mehta J et al (50)	Bagust A et al (51)	Yoong K et al (52)	Grosso A et al (53)
RESULTS				
Effectiveness	***Median overall survival*** Three models developed: ▪ (full cohort model) VELCADE 16 months vs BSC 2.5 months ▪ (1st stratified model) VELCADE in patients who had previously received thalidomide 15.7 months versus BSC 2.5 months ▪ (2nd stratified model) VELCADE in patients who had <u>not</u> previously received thalidomide 26 months versus thalidomide 8.6 months	VELCADE produced survival gains relative to BSC of 7.75 – 12.09 months. Utility values not provided	VELCADE mean survival = 1.51 years BSC mean survival = 0.68 years VELCADE QALY = 0.92 BSC QALY = 0.39	Absolute survival benefit of VELCADE vs dexamethasone was 3.29%
|Incremental Cost per life year gained	Full cohort model: $45,356 1stStratified model: $49,797 2nd Stratified model: $21,483	£17,161 - £33,,539	$45,399	
Incremental cost per QALY		£26,714 – £51,666	$70,852	
Cost per death avoided				£1,221,871 (cost per death avoided in an eight month period)
Sensitivity analyses	simple one-way analysis In general, the modified estimates used in the sensitivity analysis changed the ICER in both the full and stratified models. These changes did not alter the direction of the results. ICER results were most sensitive to the cost of VELCADE	None stated	Simple one-way analysis ICERS were not very sensitive to large changes in the cost and proportion of health resource use incurred. Changes to the Survival estimates led to ICERs of $37,380 to $58,288.	None stated
Clinical relevance to decision-making in England and Wales	Low relevance Included patients who were refractory to treatment and not at first relapse	Low relevance Included patients who were refractory to treatment and not at first relapse	Low relevance Included patients who were refractory to treatment and not at first relapse	Low relevance Actual drug usage was not considered as the data was not available

3.2 De novo economic evaluation(s)

3.2.1 Explanation of economic modelling approach

The results of the APEX trial confirm that VELCADE as a single agent in the treatment of first relapse MM patients is superior to conventional chemotherapy with HDD, resulting in significantly higher response rates, prolonged survival and delayed time to disease relapse (8). In assessing the cost-effectiveness of VELCADE, the APEX trial is key because it is the only randomised controlled trial conducted in this patient group.

3.2.2 Early termination of APEX

The Independent Data Monitoring Committee terminated the APEX trial prematurely after 8.3 months follow-up, when the interim analysis showed superior efficacy benefit with VELCADE compared to HDD. Although ethically and clinically unavoidable, the early termination of the APEX trial and the subsequent cross-over of patients from the HDD arm to VELCADE treatment presents a number of methodological challenges in terms of quantifying the incremental health outcomes and associated costs for use in economic evaluation.

Of primary importance for the economic model is the need to derive an accurate estimate of the expected lifetime survival gain with both VELCADE and HDD. The quantification of this survival gain directly from the APEX trial was not possible for two reasons:

The first is that the early termination of the APEX trial resulted in considerable censoring which meant that direct observation of the long-term survival differences between VELCADE and HDD is not possible.

The second is that patients within the HDD treatment arm were allowed to cross-over to receive VELCADE following early termination of the study. Within the APEX trial 60% of HDD patients crossed over to receive VELCADE. Therefore, it was necessary to identify sources of data from outside of the APEX trial to model the survival benefit of the comparator arm as well as using survival modelling techniques to estimate lifetime benefits and costs.

3.2.3 Relevance to Clinical Practice

The design, choice of comparator and selection of outcome measures in APEX were guided by the requirements of regulatory agencies such as the EMEA, FDA and MHRA. Whilst the APEX trial is internally valid, there are some elements of this regulatory trial design which impact on its external validity. In particular, some elements of the study design do not reflect the use of VELCADE in the UK. In this country, clinicians frequently treat all stages of MM with combination therapy. The rationale is that an effective combination of synergistic agents can increase response rates and have the potential to prolong survival relative to monotherapy. In UK clinical practice, VELCADE is routinely used in combination with dexamethasone. Commonly, dexamethasone is started at the same time as VELCADE, although some clinicians start treatment with VELCADE monotherapy and only add dexamethasone if patients fail to respond. Either way, this approach is used to enhance response to VELCADE. The synergistic relationship between dexamethasone and VELCADE, has been demonstrated in patients with relapsed and refractory disease (3, 4) and in treatment naïve patients (5). Clinical trials have

reported that adding dexamethasone to VELCADE in patients who achieved an inadequate response to VELCADE alone can boost responses from 50% to 62% in relapsed, refractory MM patients (3); and can achieve a 90% response rate in treatment-naïve patients (5).

The APEX trial also differs from current UK SmPC and from clinical practice because the protocol allowed patients who were not responding to VELCADE to continue on treatment for up to 11 cycles. The London Cancer Networks have developed a "VELCADE Consensus Statement" recommending that the number of cycles of VELCADE treatment should be based on level of response. For example if a patient has not responded to VELCADE by two cycles then adding in dexamethasone for a further two cycles is recommended. If after four cycles the patient is still not responding then it is recommended that treatment is stopped. Benefits of this approach include that patients are not unnecessarily exposed to cancer treatments and the associated adverse events and from an economic perspective acquisition costs are reduced and such an approach would be expected to result in a more efficient use of resources.

3.2.4 Measurement and Valuation of Health benefits

This economic analysis deviates slightly from the NICE reference case in that cost effectiveness is expressed in terms of cost per life year gained, rather than in QALYs. We have used life-years gained as opposed to QALYs for the following reasons:

- *MM is a rapidly progressive, debilitating and incurable cancer*. Given the high mortality rates associated with relapsed disease and the age of the affected population, increased survival is the single most important outcome for clinicians and patients.
- *Meaningful interpretation of the utility data from APEX is not possible*. The APEX trial did include the EQ5D questionnaire as a secondary outcome measure. However, the early termination at 8.3 months and subsequent cross-over of HDD patients to receive VELCADE hampered its interpretation. Furthermore, questionnaire completion was poor. At least two thirds of scheduled visit questionnaires prior to early termination were missing (Table 25). This high level of missing data and early termination of the trial means that meaningful interpretation of the EQ-5D results is not possible and the validity of this measure in a MM population remains uncertain.

Table 24: Missing Data Evaluation in APEX

Week Number	% Missing
Week 6	12.5%
Week 12	22.7%
Week 18	41.1%
Week 24	57.4%
Week 30	66.4%
Week 36	69.9%
Week 42	75.6%

A UK patient focus group involving seven MM patients was held in collaboration with the International Myeloma Foundation (IMF) to address the appropriateness of the EQ-5D. The main findings of this study confirm that the EQ-5D is unlikely to be an appropriate utility measure in this patient group.

The focus group confirmed that the EQ-5D lacks face validity and that psychological adaptation (as a result of coping strategies with the disease) compromises the applicability of this measure in this condition. These results are presented below.

Table 25: Patient responses to EQ5D Instrument

Participants found it difficult to remember what normal quality of life meant to them and thus their point of reference to describe their quality of life is one in which they are part of the MM patient treatment cycle.
There is a culture among the people who participated in the focus group that they are more robust and that there are many people with MM worse off than themselves. The consequence of this is a sustained optimism during remission that potentially impacts upon the sensitivity of EQ-5D.
Participants were very focussed on the next treatment step. It was like they knew where they were in the treatment cycle by the number and type of treatments that they had received. Continued survival equalled the number of treatments still available.

The focus group also identified two important domains which are not captured by the EQ-5D, but would be expected to have a considerable impact on utility. These domains are “the experience of being in hospital” and “living in fear of the future”.

Experience of being in hospital

This had a negative and extreme, even if relatively temporary impact on quality of life. A range of emotions were described by the participants in the focus group ranging from:

Feeling isolated and lonely. Often patients are admitted with infections, which require periods of isolation from each other.

Depression: feels like “a prison cell” because of not being allowed to leave the hospital room for days on end.

“Reality shock”: being exposed to other patients at more advanced stages of MM, which makes them, question what is ahead of them in their disease.

Living in fear of the future

Despite efforts to ‘normalise’ their lives the participants of the patient focus group, all lived in fear of their disease progressing. They were all aware of the importance of paraprotein levels for predicting future prognosis and all participants stated that leading up to their appointment with their physician that they grow more anxious about the results of the test. The focus group described the sense of relief felt when they got their results and they were reported as normal. Anxiety levels increase as the next blood test approaches. Overall, the fear of not knowing when the inevitable next relapse will come prevents them from making future plans and causes a feeling of vulnerability for the future.

In summary, the validity of the EQ-5D in MM is uncertain and this focus group suggests that further work is needed to evaluate utility in this population. This, together with a lack of data means that calculation of QALYs was not possible. Also, given the overriding importance of survival to this population, a focus on life-years gained is appropriate.

3.3 Overview of Decision Analytic Model

The model was designed to consider the impact on survival and cost-effectiveness of VELCADE for the treatment of MM patients after 1st relapse as i) a single agent compared with HDD, with or without stopping rules for non-responders, and ii) in combination with HDD.

3.3.1 Evaluation Design and Structure

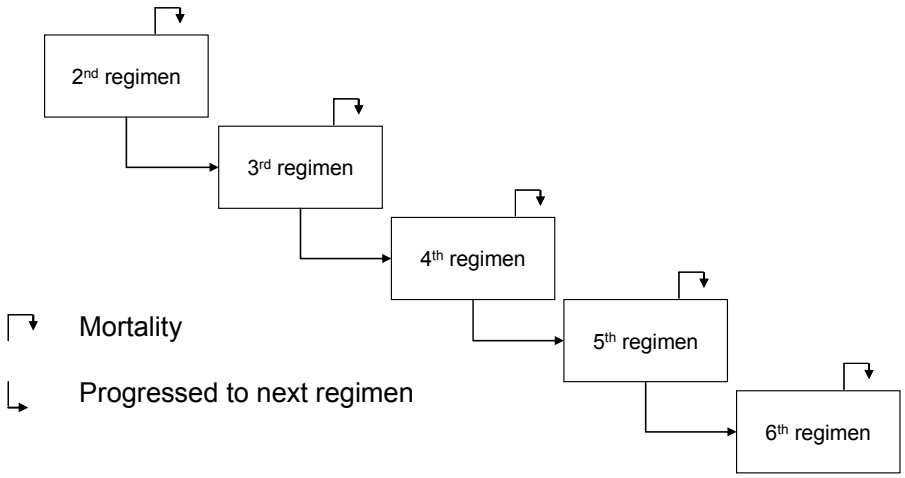
Patient Population

Patients included within the model were those who had experienced a 1st relapse of MM.

Model Framework

A semi-Markov model was developed, the structure of which is presented in Figure 14. It is assumed that all patients entering the model do so at first relapse (2nd regimen). Through subsequent cycles of the model, patients can remain on their current regimen, die or transition to subsequent treatments. The time horizon of the model is 15 years.

Figure 14: Semi-Markov Structure



3.4 Model Inputs

3.4.1 Modelling treatment effectiveness

Time to progression (TTP) and 1-year survival rates were taken from the APEX trial for patients who were receiving the treatment at 1st relapse at the start of the trial. These estimates are taken from the Richardson et al paper (8) which reports 8.3 months of follow-up within the assigned treatment arms.

The early termination, however does affect the ability to model long-term outcomes and mortality data with HDD. In an attempt to model lifetime survival following the

termination of APEX, a review of published epidemiological data was undertaken with the objective of identifying suitable data to use as the basis for modelling lifetime survival for both VELCADE and HDD (Appendix 10).

From this search one relevant peer-reviewed publication was identified. This observational study was conducted in 578 relapsed MM patients at the Mayo Clinic in the US (54). This study is discussed in section 3.4.2.

3.4.2 Summary of Mayo Observational Study Patient Population and Data (54)

The objective of the Mayo Observational Study was to observe the clinical course and outcomes of patients with MM who experience relapse following treatment. The study population consisted of patients diagnosed with MM who presented at the Mayo Clinic in Rochester, Minnesota, between January 1, 1985, and December 31, 1998. To ensure complete clinical and laboratory follow-up information the Mayo Clinic patient database was searched to identify patients who were seen at least six times per year, on average, over the course of their treatment and disease course. Five hundred seventy-eight patients, of a potential pool of 1027 patients, had complete treatment records and were included in the study. The median age of patients was 65 years (range, 26-92 years), and 228 patients (39%) were women. The median follow-up for those still alive (n=71) was 55 months (range, 0-202 months with only 4 patients having <1 year of follow-up).

As this was an observational study, patients were treated with a variety of regimens according to the standard of care for their particular disease stage and needs. No patients were treated with VELCADE as it was not available during this time period. However, 188 patients (32.5%) were treated at some point during the course of their follow-up with a combination of vincristine, adriamycin and dexamethasone (VAD), a regimen in which dexamethasone is believed to be the dominant agent (54). Of the 188 patients who ever received dexamethasone, 114 patients (60.6%) received it as their first regimen (i.e., prior to first relapse) and 74 patients (39.4%) received it after their first relapse.

The baseline patient characteristics of the APEX trial population and Mayo Observational Study were compared. In terms of patient demographics and disease characteristics the patient groups from both datasets were comparable. Available prognostic factors, including performance status and β_2-microglobulin levels, are well matched (Appendix 11).

The results of this analysis supported the use of the data from the Mayo Obervational Study for estimating longer-term survival within the economic model. The Mayo Observational Study reported an overall survival at 1 year of 72%, at 2 years 55%, and at 5 years 22%. The median overall survival for 578 patients in the study group was 28.4 months. At ten years from diagnosis, nearly all patients had died of either their disease or other causes.

3.4.3 HDD Survival Modelling Approach.

TTP and 1-year survival estimates for HDD were taken from the APEX trial. The following steps were taken to model the survival estimate for patients receiving HDD:

Step 1: Enter reported information on percent of patients who stayed on a regimen, switched to another regimen, or died. (Table 3 of Kumar et al (54))

Step 2: Construct a probability transition matrix from these data.

Step 3: Use the probability transition matrix to compute the percent of patients over time in each regimen.

Step 4: Check goodness of fit of this model with observed survival from time of diagnosis reported in the Mayo Observational Study.

Step 5: The1st relapse patients in the Mayo Observational study reflects treatment with a variety of therapies not just HDD. Therefore, the transition probabilities were adjusted through a single common hazard reduction so that the model predictions replicate the survival at 1 year in the APEX trial's HDD arm of patients who have relapsed after only one prior therapy. We use the hazard ratios directly from APEX trial to estimate the survival. This step is undertaken to ensure that the model is able to replicate the reported survival at 1 year in APEX by using the reported hazard ratios from the study.

A comprehensive description of each of these steps can be found in Appendix 12.

3.4.4 VELCADE Survival Modelling Approach

Hazard ratios for time to progression and overall survival with VELCADE were estimated from the APEX trial data for patients with 1st relapse. We used these ratios in the model as outlined in the steps below.

Step 1: Apply a probability of staying in regimen 2 based on the APEX trial's TTP hazard ratio of 0.56 (page 2492 of Richardson et al. (8)).

Step 2: Apply a probability of dying in regimen 2 based on the APEX trial's OS hazard ratio of 0.42 (page 2493 of Richardson et al. (8)).

Step 3: Compare the predicted 1-year survival from this model with the survival reported in the VELCADE arm of APEX for patients after 1st relapse (who had only one prior line of therapy).

A more detailed summary of the approach is presented in Appendix 13.

3.5 Resource identification, measurement and valuation

The analysis was undertaken from a UK NHS perspective. The number of doses for VELCADE and HDD are derived from analyses of the APEX trial (Appendix 14). Whilst the APEX trial attempted to collect resource use data from all patients participating in the trial, less than 15% of patients (51 patients) were enrolled from UK centres and it was not possible therefore to estimate the total direct management costs associated with VELCADE and HDD from these data. Bruce et al. studied the direct costs to the NHS of managing MM with and without prophylactic clondronate (55). This study was published in 1999 and is based on the RCT from the MRC VI myelomatosis trial. Data on resource use from the trial was supplemented by data from semi-structured interviews with 11 consultant haematologists who managed approximately 30% (n =207) of the patients in the trial. Tables 27 and 28 present the results of this study. This data provides a more relevant, UK-based source of management costs and was therefore used to estimate supplemental direct management costs in the model.

Table 26: Mean Values of Resource Use per Patient during the Standard Management of MM (Standard Deviation in Parentheses)

Resource use	Mean (SD)
Outpatient clinic, hours	82.40 (13.2)
Hospital ward, days	19.72 (6.75)
Hospice, days	1.85 (1.13)
Laboratory tests, tests	93.37 (31.14)
Blood transfusion, units	8.11 (3.21)
Skeletal survey, procedures	3.9 (0.34)

Table 27: Standard Management Costs by Resource Category (Standard Deviations in Parentheses) over the First 4 Years following Diagnosis

Resource Category	Cost of Standard Management	Proportion
Hospitalisation	£5,367 (1,836)	32%
Outpatient Visits	£4,722 (752)	28%
Procedures	£2,821 (266)	17%
Community Care	£954 (327)	6%
Laboratory Tests	£925 (117)	6%
Chemotherapy	£894 (379)	5%
Hospice Care	£611 (373)	4%
Other Drugs	£215 (79)	1%
Anti-emetics	£188 (181)	1%

In this study, the mean management costs for the first 4 years after diagnosis were equal to £16,697 (SD 2216). It was assumed that these costs were distributed evenly over 48 months (£348 per month), which we then inflated to 2006 costs to obtain an average monthly cost for managing myeloma of £443 (SD 59).

A limitation of using data from the Bruce cost analysis, is that we are not able to account for differences in adverse events between VELCADE and HDD. From the results of the APEX trial (See section 2.8), we know that the pattern of adverse events is similar although the incidence varies between the treatments. To account for these differences within the model, we have increased the monthly MM management costs for VELCADE by 25% compared with HDD to consider the differences in adverse event profiles between treatments based on the APEX trial. This is presented in Section 3.6.1.

3.6 Sensitivity Analysis

3.6.1 Simple One-way Sensitivity Analysis

Simple one-way sensitivity analyses were undertaken on variables. The variables we assessed included those that affect OS (hazard ratios, expected duration of treatment effect) and cost of the regimens (drug and administration costs and cost of

other care). As mentioned in Section 3.5, we increased the monthly MM costs for VELCADE by 25% (£553) compared with HDD (£443) to consider the potential influence of the higher percentage of patients who experienced diarrhoea, neutropenia, and thrombocytopenia in the APEX trial.

Ranges for 1-way sensitivity analyses were based on 5th and 95th percentiles of the variable distributions. The following table provide a summary of all inputs, ranges used in 1-way (and probabilistic) sensitivity analyses, and data sources.

Table 28: Summary of key input, ranges used in sensitivity analysis, and data sources

Parameters	VELCADE	HDD	Range*	Data source
Discount rate †	3.5%	3.5%	--	NICE
Time horizon, years †	15	15	--	Covers lifetime
Duration of treatment effect, years††	3	--	2 – 4	Richardson, ASH (9)
Hazard ratios				
Overall survival (OS)	0.42	--	± 0.05	APEX (8)
Time to progression (TTP)	0.56	--	± 0.05	APEX (8)
Cost of VELCADE				
Drug acquisition cost	£19,060	--	See footnote¶	APEX (8)
Administration cost	£1,975	£0		NHS OutPatient Mandatory Tariff 2005/6, APEX (8)
Cost of dexamethasone	£0	£82	± £8	APEX (8)
Cost of other care, per month				
Prior to progression	£443	£443	± £111	Bruce et al.,(55) APEX (8)
After progression	£443	£443	± £111	Bruce et al.,(55) APEX (8)

* Variables were simulated as normal distributions with 5th and 95th percentiles as presented.
† No range used for these parameters as they are policy variables set by NICE guidance.
¶ Unit costs are assumed not to vary, but the number of administration of VELCADE and HDD may vary, assumed ±5%.
†† based on median survival of the APEX trial having been updated to 29.8 months (9).

3.6.2 Probabilistic sensitivity analyses

In addition to one-way sensitivity analyses, a probabilistic sensitivity analysiss was undertaken using the variables in Table 29. Distributions were fitted to a number of variables including treatment effect (i.e., hazard ratios), duration of treatment effect, and costs of other myeloma care.

Hazard ratios typically are estimated as having lognormal distributions. Specially, let x represent the hazard ratio and y = ln(x) ~ Normal(μ,σ^2). For the OS hazard ratio, μ = -0.87 and σ = 0.06. For the TTP hazard ratio, μ = -0.58 and σ = 0.04.

Costs commonly have a skewed distribution, so lognormal distributions were used for all cost variables. Bruce et al. reported the SD for cost of other care was 13% (£59)

of the mean costs of £443. The unit costs of VELCADE and HDD are fixed, so would not be associated with a distribution. However, although compliance with treatment in APEX was high, the number of administrations may vary, to some extent. We have therefore varied the total costs of VELCADE and of HDD by ±5%.

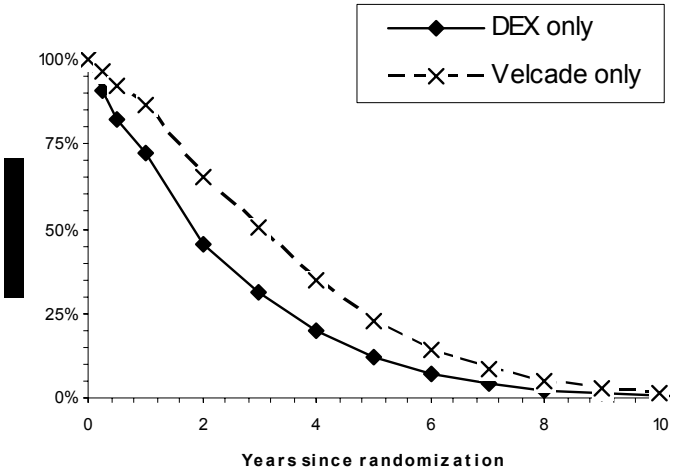
3.7 Results

All results presented within this section are discounted using the discount rate specified within NICE's reference case.

3.7.1 Survival results

The model shows a mean survival of 32.5 months with VELCADE compared to 22.6 months with HDD. The mean incremental survival difference is 9.9 months.

Figure 15: Comparison of Estimated Survival Difference between VELCADE and HDD



3.7.2 Treatment Cost Results

Table 30 and 31 present the cost of VELCADE and HDD treatment used in the economic analysis.

Table 29: Cost of VELCADE Treatment

	Estimated means
VELCADE	All Patients
Scheduled doses	26.2
Doses given	25.0
Proportion given	95.2%
Active treatment time	20.2
Drug cost per patient	£19,060
Admin cost per patient	£79.00
Total cost per patient	£21,035

Table 30: Cost of HDD Treatment

	Estimated True means
HDD	All Patients
Scheduled doses	37.5
Doses given	37.4
Proportion given	99.8%
Active treatment time	16.1
Drug cost per patient	£82
Admin cost per patient	£0
Total cost per patient	£82

VELCADE treatment cost £21,035 compared with £82 for HDD treatment. The mean management costs for the first 4 years after diagnosis were equal to £16,697 (SD 2216). It was assumed that these costs were distributed evenly over 48 months (£348 per month), which we then inflated to 2006 costs to obtain an average monthly cost for managing myeloma of £443 (SD 59).

As a consequence of longer survival, the cost of other care for myeloma is projected to be £4,374 higher for patients receiving VELCADE, £14,387, compared with HDD, £10,013. Thus, the total cost difference between VELCADE and HDD is £25,327.

3.7.3 Cost effectiveness results

The results of the cost effectiveness analysis show that the incremental cost per LYG of VELCADE as a single agent compared to HDD for patients at first relapse is £30,750 as shown in table 32.

Table 31: Cost-effectiveness Results

			Difference
Outcomes	Velcade	HDD	Velcade v HDD
Mean overall survival, months	35.7	24.5	11.2
Mean discounted overall survival	32.5	22.6	9.9
%Alive			
1 year	87%	72%	15%
2 years	65%	45%	20%
5 years	23%	12%	11%
Costs			
Velcade and/or HDD	£21,035	£82	£20,953
Other care	£14,387	£10,013	£4,374
Total	£35,421	£10,095	£25,327
Cost per discounted LYG			£30,750

3.7.4 Scenario analyses

Three further analyses are considered within the model:

(i) Limiting the number of cycles of VELCADE treatment in non-responding patients

(ii) Using the overall population of the APEX Trial

(iii) VELCADE and HDD combination Vs HDD only

3.7.4.1 Limiting the Number of cycles of VELCADE treatment in non-responding patients

As stated previously, the EBMT criteria was used to define response to treatment within the APEX trial (34). A summary of these criteria are presented in Table 32 below and are used to determine response within this analysis. Response has been defined within this analysis as a complete or partial response only.

Table 32: Summary of the EBMT Criteria (Adapted from reference (34))

	M Protein	Urinary light chain	PCs, marrow	Plasmacytoma	Skeletal Disease	Calcium
CR	None (IF neg)	None (IF neg)	<5%	None	Stable	Normal
PR	≥50% ↓	≥ 90% ↓□or <200 mg/24h	N/a	≥ 50% ↓ (size)	Stable	N/A
MR	≥25% ↓□	50-99 % ↓ but ≥ 200mg/24h	N/a	≥ 25% ↓ (size)	Stable	N/A
PD	>25% ↑ or min 5 g/L	>25% ↑ or ≥ 200mg/24h	>25% ↑□	New or ↑ size	New or ↑ size	↑□
Requires two determinations 6 weeks apart. Stable disease (SD): Not meeting criteria for MR or PD						

CR: Complete response; PR: partial response; MR: minimal response; PD: progressive disease; IF: immunofixation

In order to determine the optimal number of cycles for non-responding patients, a supplementary regression analyses was conducted. This analysis assessed the reduction in risk of progression in non-responding patients associated with continuing VELCADE treatment. The results of this analysis are presented in Table 34 below.

Table 33: Risk of progression as a function of number of cycles completed, by responder status

No. of cycles completed	Hazard ratio: VELCADE non-responder v HDD	P-value	Hazard ratio: VELCADE responder v HDD	P-value
2	0.81	0.11	0.24	0.0000
3	1.07	0.66	0.31	0.0000
4	1.15	0.47	0.34	0.0000
5	0.99	0.97	0.45	0.0002
6	1.26	0.41	0.49	0.0013

Hazard ratio of 1 means no difference in risk of progression between comparators. Hazard ratio > 1 means higher risk of progression with VELCADE and hazard ratio < 1 means lower risk of progression with VELCADE

It's evident from the results that no risk reduction was observed after 3 or more cycles. In other words, if patients do not respond within 3 cycles, they appear unlikely to benefit by receiving additional cycles of VELCADE.

Furthermore, 85.2% (115 patients) of the 135 patients who achieved a complete or partial response in APEX did so within 3 cycles. In patients who responded to VELCADE treatment we assumed that they would receive up to an additional five cycles (Maximum of eight cycles as per SmPC). The remaining 14.8% of patients achieved a response after 3 cycles. To account for the reduction that this may cause to the overall survival, we have estimated that the decline in OS would fall from 11.2 months to 9.4 months.

The results of this analysis shown in table 35 indicate that stopping VELCADE treatment for non-responders after 3 cycles decreases the mean aquistion costs of VELCADE by around £5,427 (£21,035 from Table 32 to £15,608 in Table 35). The ICER also falls to £27,926.

Table 34: Cost-effectiveness results

			Difference
Outcomes	Velcade	HDD	Velcade v HDD
Mean overall survival, months	34.0	24.5	9.4
Mean discounted overall survival	30.9	22.6	8.2
%Alive			
1 year	79%	72%	7%
2 years	61%	45%	16%
5 years	22%	12%	10%
Costs			
Velcade and/or HDD	£15,608	£82	£15,526
Other care	£13,659	£10,013	£3,646
Total	£29,266	£10,095	£19,172
Cost per discounted LYG			£27,926

3.7.4.2 Overall population of the APEX trial

In this analysis, we estimate the impact on survival and cost-effectiveness of VELCADE using all the patient data from the APEX trial. Within the APEX trial, 40% of patients started the trial at first relapse and the remaining 60% at second relapse and beyond.

The methods of economic modelling are the same as that described in section 3.4 and 3.5. The only changes made to the model are in terms of the hazard ratios for TTP (0.55) and one-year OS (0.57). These estimates are taken from the Richardson et al (8) paper which reports 8.3 months of follow-up within the assigned treatment arms and which is not affected by early termination of the study.

Table 36 presents the results of this analysis.

Table 35: Cost-effectiveness Results Based on APEX trial

			Difference
Outcomes	Velcade	HDD	Velcade v HDD
Mean overall survival, months	27.6	19.6	8.1
Mean discounted overall survival	25.5	18.2	7.3
%Alive			
1 year	80%	66%	14%
2 years	55%	35%	19%
5 years	14%	8%	6%
Costs			
Velcade and/or HDD	£21,035	£82	£20,953
Other care	£11,271	£8,059	£3,212
Total	£32,305	£8,141	£24,165
Cost per discounted LYG			£39,954

The results show that the cost per LYG is increased to £39,954.

3.7.4.3 Combination treatment with VELCADE plus HDD

In clinical practice, the combination of VELCADE and HDD is frequently used to treat patients at first relapse. Therefore, we undertook further analyses with the model to assess the cost-effectiveness of adding HDD to VELCADE at first relapse.

As discussed in (See Clinical Section, question 58), a number of published clinical studies have reported the synergistic relationship between VELCADE and HDD. For example, the CREST trial demonstrated that adding dexamethasone to VELCADE in patients who achieved an inadequate response to VELCADE alone can boost responses from 50% to 62% in relapsed, refractory MM patients (3).

Modelling Methods

In APEX the overall response rate for VELCADE as single agent from the APEX trial was 45% and the median duration of response (for patients who responded) was 8.1 months. The median time to progression for all patients was 7.0 months.

Adding HDD to VELCADE was found to increase the response rate to VELCADE by a factor of 1.24 (in relapsed refractory patients); hence, we estimate that the response rate for VELCADE+HDD is increased to 56% (1.24 x 45%). Based on this new estimate of response rate we were able to estimate the average monthly rate of progression for responders and non-responders was 0.081 and 0.102 and the average monthly rate of death after progression is 0.026. See Appendix 15 for a fuller explanation of the approach.

Table 37 below presents the results of these analyses.

Table 37: Cost-effectiveness Results of VELCADE+HDD

Outcomes	Velcade + HDD	HDD	Difference Velcade+HDD v HDD
Mean overall survival, months	37.0	24.5	12.5
Mean discounted overall survival	33.6	22.6	11.0
% Alive			
1 year	87%	72%	15%
2 years	68%	45%	22%
5 years	24%	12%	12%
Costs			
Velcade and/or HDD	£21,117	£82	£21,035
Other care	£14,876	£10,013	£4,863
Total	£35,992	£10,095	£25,898
Cost per discounted LYG			£28,281

The mean incremental OS therefore increases from 9.9 months to 11.0 months for VELCADE+HDD versus HDD. The incremental costs associated with VELCADE+HDD are increased marginally by £571 from £25,327 for VELCADE monotherapy in the basecase (Table 32) to £25, 898 in this analysis (Table 37). The resultant cost per LYG is £ 28,281. .

3.7.5 Results of Sensitivity Analysis

3.7.5.1 One-way sensitivity analysis

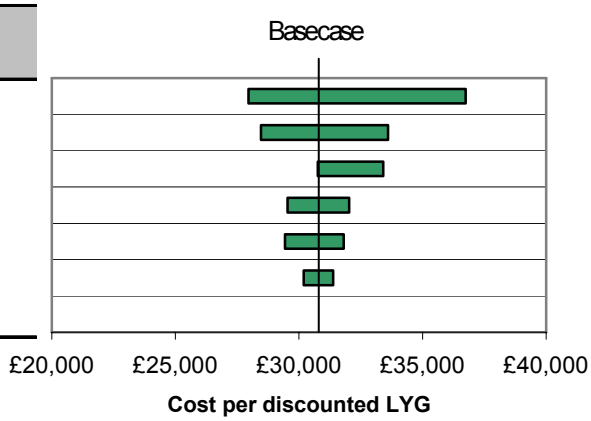
The following table shows the variables in the one-way sensitivity analyses, ranges assessed, resulting ICERs and the range of ICERs.

Table 36:

Variable	Basecase	Inputs		CE ratios		Range
		Left	Right	Left	Right	
Duration of treatment effect, years	3	4	2	£27,957	£36,747	£8,790
Hazard ratio - TTP	0.56	0.51	0.61	£28,464	£33,605	£5,141
Cost of other care - Velcade pre-progression	£443	£443	£554	£30,760	£33,406	£2,646
Cost of Velcade per course	£21,035	£20,033	£22,086	£29,534	£32,026	£2,493
Cost of other care - pre- and post-progression	£443	£354	£554	£29,430	£31,804	£2,374
Hazard ratio - OS	0.42	0.38	0.47	£30,200	£31,389	£1,189
Cost of HDD per course	£82	£86	£78	£30,745	£30,754	£9

Table 37:

Variable
Duration of treatment effect, years
Hazard ratio - TTP
Cost of other care - Velcade pre-progression
Cost of Velcade per course
Cost of other care - pre- and post-progression
Hazard ratio - OS
Cost of HDD per course



This (tornado) diagram illustrates the level of influence of each random variable across its range on the ICER, with the most influential variable on the top and least influential variable on the bottom. The most influential variable is the duration of treatment effect. We also found that increasing the cost of total management costs in the VELCADE arm only prior to progression by 25% (due to adverse events) over the cost of HDD increases the ICER to £33,406. In these sensitivity analyses, cost-effectiveness results remained reasonable closer to the base case ICER.

3.7.5.2 Probabilistic sensitivity analysis

The results of this analysis are presented in Figure 16 below.

Figure 16a: Probabilistic sensitivity analyses

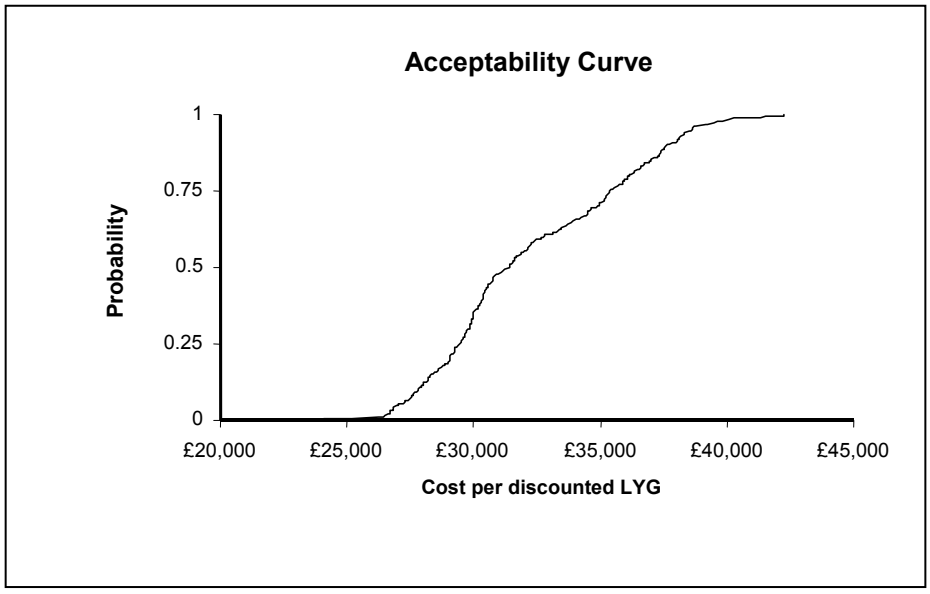
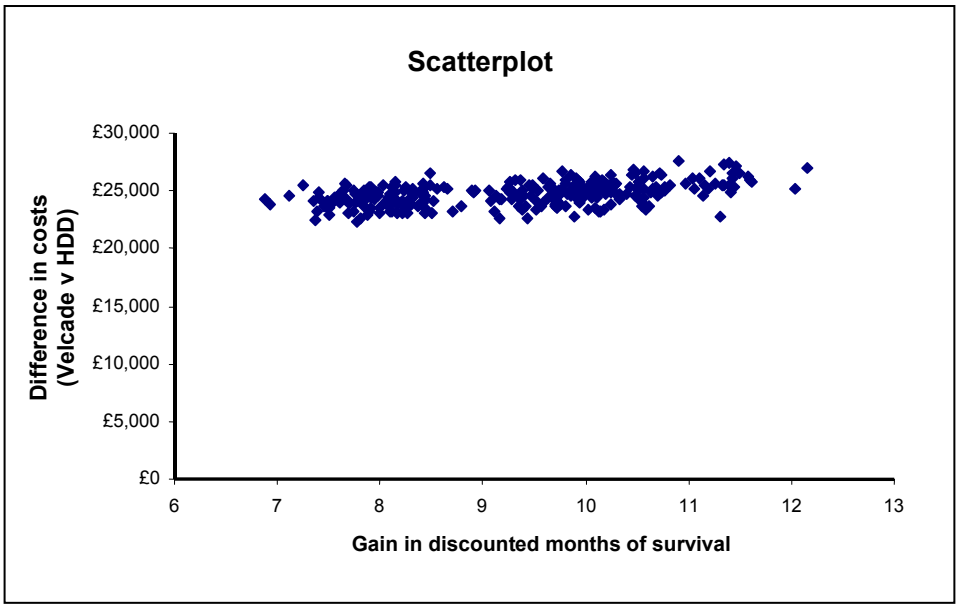


Figure 17a: CE Scatterplot



The result of the probabilistic sensitivity analysis shows that the 5th percentile is £26,855, and the 95th percentile is £38,564.

3.8 Discussion

The results of these economic analysis indicate that VELCADE increases mean OS by around 10 months compared with HDD in MM patients who have experienced their 1st relapse. This gain in OS is accompanied by an increased cost of £25,327, approximately 83% of which is associated with VELCADE treatment cost and the remainder associated with cost of additional myeloma care associated with prolongation of survival. The cost per LYG in the base-case is approximately £30,000.

The APEX trial included patients at second or subsequent relapse, as well as those at 1st relapse. When the model uses data for the full APEX patient population, (not just limiting the analysis to the patients at 1st relapse), VELCADE increased mean OS by over 7 months compared with HDD leading to cost per LYG of approximately £39K. Greater overall survival and a lower ICER are associated with its use in 1st relapse. Using VELCADE in later lines of treatment reduces survival benefits and results in a higher ICER.

Although the majority of patients crossed over after the premature termination of the study, there were a few patients in the HDD arm who had progressed before termination and crossed over to VELCADE earlier. The hazard ratios may in fact have been even lower if the trial had lasted longer and if relapse after HDD had involved treatment with other currently available therapies (and not just VELCADE). Second, the duration of treatment effect remains unknown at this point and may in fact extend beyond the input value of 3 years assumed in the model.

The modelling approach used in this submission was developed to investigate the impact of stopping rules and combination treatment with HDD on survival and cost-effectiveness. The results showed that implementation of a stopping rule for patients

who fail to respond reduced VELCADE acquisition costs by over £5,000. The cost per life-year gained was also lower than in the basecase, although the trade-off is some reduction in mean survival rates. Cost-effectiveness was optimal when VELCADE treatment was withdrawn in non-responders after 3 cycles. The analysis assumed that responders continued to receive VELCADE for up to 8 cycles as per SmPC. The analysis which examined combination treatment with VELCADE plus HDD revealed additional surivival benefits for patients at little additional cost compared to base case. Mean OS improved from 9.9 months to 11.0 months with an incremental cost increase (over the basecase) of £571.

The results of the 1-way sensitivity analysis showed that the ICER is most sensitive to the duration of VELCADE's treatment effect. Within the base case we assumed that this was limited to 3 years based on median survival of the APEX trial having been updated to 29.8 months and a survival benefit still persisting for the VELCADE (9). When this parameter was varied from 2-4 years the ICER ranged from £27 to 36K.

To supplement TTP data from the APEX trial, we used published epidemiological data to model long term survival in both treatment arms. The Mayo Observational Study was the critical piece of evidence for this analysis (54). This study was unique in following MM patients from diagnosis of MM to death. Although the study was conducted at Mayo Clinic in the USA, we compared the patient populations reported in Mayo Observational Study and APEX trial and found that the characteristics in the two populations were similar.

Although there was some resource use collected in the APEX trial, most of the data was from outside the UK. We therefore used published estimates of the costs of myeloma care relevant to the UK as this was felt to be a more accurate reflection of costs of routine management.

Another possible limitation of the model is that it does not include costs associated with differential rates of AEs in the base case analyses. The APEX trial reported higher numbers of patients experiencing thrombocytopenia and neutropenia in the VELCADE arm. However, using standard reporting methodology, these numbers were not adjusted for duration of exposure to the regimen in the base case. Sensitivity analysis show that if VELCADE costs are increased by 25% prior to progression to adjust for possible higher level of adverse events, the ICER increased to £33, 406.

In summary, across these analyses the cost per life-year gained for VELCADE compared to HDD was around £28,000 to £31,000. Sensitivity analyses revealed that the model was most sensitive to the duration of VELCADE treatment effect, time to progression and additional cost of treating the adverse events.

3.9 Implications for the NHS

These results show that across a broad range of scenarios, the cost-effectiveness of VELCADE versus HDD is around £28,000 - £31,000. Given the high mortality rates associated with relapsed MM and the age of the affected population, increasing survival is of paramount importance to clinicians and patients. VELCADE results in the greatest survival benefits and is more cost-effective when used at 1st relapse, rather than later in the treatment pathway. The model also confirms that combination with HDD adds over 1 month of survival for a very small additional cost.

Although a budget impact analysis is not requested under this new STA process, it is clear that the introduction of stopping rules will reduce drug budget expenditure on VELCADE, with average savings of over £5,000 per patient. These savings also contributed to a lower ICER compared to basecase.

4 References

1. Ubiquitin-Mediated Proteolysis. Advanced Information on the Nobel Prize in Chemistry 2004 [cited 2005 February 13]; Available from: http://nobelprize.org/chemistry/laureates/2004/chemadv04.pdf
2. Morgan GJ, Davies FE, Cavenagh J, Jackson GH. Position statement on the use of VELCADE in multiple myeloma. Available at www.bcshguidelines.com/pdf/Bortezomib_250705.pdf. Accessed 22nd December 2005. 2005.
3. Jagannath S, Barlogie B, Berenson J, Siegel D, Irwin D, Richardson PG, et al. A phase 2 study of two doses of bortezomib in relapsed or refractory myeloma. Br J Haematol. 2004 Oct;127(2):165-72.
4. Richardson PG, Barlogie B, Berenson J, Singhal S, Jagannath S, Irwin D, et al. A phase 2 study of bortezomib in relapsed, refractory myeloma. N Engl J Med. 2003 Jun 26;348(26):2609-17.
5. Jagannath S, Durie B, Wolf F, Camacho E, Irwin D, Lutzky M, et al. Bortezomib therapy alone and in combination with dexamethasone for patients with previously untreated multiple myeloma. Poster Presented at the 47th Annual Meeting of the American Society of Hematology 2005 10 - 13 December 2005 [cited 2006 20th January]; Available from: http://myeloma.org/pdfs/jagannath_Bortezomib.pdf
6. Medical Research Council. Myeloma IX trial: Protocol Summary. 2003. Available from: http://www.ukmf.org.uk/documents/myeloma9.pdf (Accessed 27th February 2006)
7. National Cancer Research Network. MRC Myeloma IX Myelomatosis therapy trial for patients of all ages. A randomised trial comparing second generation vs third generation bisphosphonates, induction chemotherapy regimens (CVAD vs CTD, and MP vs CTDa) and thalidomide maintenance vs no maintenance therapy. 2005. Available from: http://www.ncrn.org.uk/portfolio/data.asp?ID=1176 (Accessed 27th February 2006)
8. Richardson PG, Sonneveld P, Schuster MW, Irwin D, Stadtmauer EA, Facon T, et al. Bortezomib or high-dose dexamethasone for relapsed multiple myeloma. N Engl J Med. 2005 Jun 16;352(24):2487-98.
9. Richardson P, Sonneveld P, Schuster M, Irwin D, Stadtmauer EA, Facon T, et al. Bortezomib continues to demonstrate superior efficacy compared with high-dose dexamethasone in relapsed multiple myeloma: Updated results of the APEX trial. Blood. 2005;106(11):Abstract 2547.
10. Weber DM, Chen C, Niesvizky R, Wang M, Belch A, Stadtmauer E, et al. A multicentre, randomised, parallel group, double-blind, placebo-controlled study of lenalidomide plus dexamethasone versus dexamethasone alone in previously untreated subjects with multiple myeloma. Haematologica. April 2005;90(Supplement 1):155 (abstract P0.738).
11. Dimopoulos MA, Spencer A, Attal M, Prince M, Harousseau JL, Dmoszynska A, et al. Study of lenalidomide plus dexamethasone versus dexamethasone alone in relapsed or refractory multiple myeloma (MM): Results of a Phase 3 study (MM-010). Blood. 2005;106:Abstract 6.
12. Rajkumar SV, Blood E, Vesole D, Fonseca R, Greipp PR. Phase III clinical trial of thalidomide plus dexamethasone compared with dexamethasone alone in newly diagnosed multiple myeloma: a clinical trial coordinated by the Eastern Cooperative Oncology Group. J Clin Oncol. 2006 Jan 20;24(3):431-6.

13. Coleman MP, Rachet B, Woods LM, Mitry E, Riga M, Cooper N, et al. Trends and socioeconomic inequalities in cancer survival in England and Wales up to 2001. Br J Cancer. 2004 Apr 5;90(7):1367-73.
14. Multiple myeloma statistics for the UK. http://info.cancerresearchuk.org/cancerstats/types/multiplemyeloma/?a=5441: Cancer Research UK.
15. Zappasodi P, Corso A, Klersy C, Pica G, Mangiacavalli S, Varettoni M, et al. Changes in multiple myeloma epidemiology in the last thirty years: A single centre experience. Eur J Cancer. 2006 Feb;42(3):396-402.
16. Ries LAG, Eisner MP, Kosary CL, Hankey BF, Miller BA, Clegg L, et al. (Eds). SEER Cancer Statistics Review, 1975-2002, National Cancer Institute, Bethesda, MD, http://seer.cancer.gov/csr/1975_2002/; Based on November 2004 SEER data submission, posted to the SEER website 2005.
17. Karadag A, Oyajobi BO, Apperley JF, Russell RG, Croucher PI. Human myeloma cells promote the production of interleukin 6 by primary human osteoblasts. Br J Haematol. 2000 Feb;108(2):383-90.
18. Richardson PG, Hideshima T, Anderson KC. Bortezomib (PS-341): a novel, first-in-class proteasome inhibitor for the treatment of multiple myeloma and other cancers. Cancer Control. 2003 Sep-Oct;10(5):361-9.
19. Ropper AH, Gorson KC. Neuropathies associated with paraproteinemia. N Engl J Med. 1998 May 28;338(22):1601-7.
20. Pal PK. Clinical and electrophysiological studies in vincristine induced neuropathy. Electromyogr Clin Neurophysiol. 1999 Sep;39(6):323-30.
21. Dimopoulos MA, Eleutherakis-Papaiakovou V. Adverse effects of thalidomide administration in patients with neoplastic diseases. Am J Med. 2004 Oct 1;117(7):508-15.
22. San Miguel J, Richardson P, Sonneveld P, Schuster M, Irwin D, Stadtmauer EA, et al. Frequency, Characteristics and Reversibility of Peripheral Neuropathy (PN) in the APEX trial. Blood. 2005;106(11):Abstract 366.
23. Kyle RA, Gertz MA, Witzig TE, Lust JA, Lacy MQ, Dispenzieri A, et al. Review of 1027 patients with newly diagnosed multiple myeloma. Mayo Clin Proc. 2003 Jan;78(1):21-33.
24. Cavenagh JD, Croucher PI. Bone disease. In: Multiple myeloma, Richardson PG, Anderson KC (Eds). Chicago, Illinois: Remedica Publishing; 2004.
25. Smith A, Wisloff F, Samson D. Guidelines on the diagnosis and management of multiple myeloma. Br J Haematol. 2005;132:410 - 51.
26. Orlowski RZ, Stinchcombe TE, Mitchell BS, Shea TC, Baldwin AS, Stahl S, et al. Phase I trial of the proteasome inhibitor PS-341 in patients with refractory hematologic malignancies. J Clin Oncol. 2002 Nov 15;20(22):4420-7.
27. Cavenagh JD, Oakervee H. Thalidomide in multiple myeloma: current status and future prospects. Br J Haematol. 2003 Jan;120(1):18-26.
28. VELCADE Summary of Product Characteristics. Updated 19th October 2005.
29. Decadron Summary of Product Characteristics, October 2003.
30. EMEA\CPMP\269\04. CPMP Plenary Meeting Monthly Report; 2004 20-21 January.
31. FDA(US). FDA Approves Velcade for Multiple Myeloma Treatment. May 13 2003 [cited 2006 February 13]; Available from: http://www.fda.gov/bbs/topics/NEWS/2003/NEW00905.html
32. Data on file, Ortho Biotech UKI.
33. O'Brien PC, Fleming TR. A multiple testing procedure for clinical trials. Biometrics. 1979 Sep;35(3):549-56.
34. Blade J, Samson D, Reece D, Apperley J, Bjorkstrand B, Gahrton G, et al. Criteria for evaluating disease response and progression in patients with multiple myeloma treated by high-dose therapy and haemopoietic stem cell transplantation.

Myeloma Subcommittee of the EBMT. European Group for Blood and Marrow Transplant. Br J Haematol. 1998 Sep;102(5):1115-23.
35. Attal M, Harousseau JL, Stoppa AM, Sotto JJ, Fuzibet JG, Rossi JF, et al. A prospective, randomized trial of autologous bone marrow transplantation and chemotherapy in multiple myeloma. Intergroupe Francais du Myelome. N Engl J Med. 1996 Jul 11;335(2):91-7.
36. Lee SJ, Richardson PG, Sonneveld P, Schuster M, Irwin D, Massaro J, et al. Health-related quality of life associated with bortezomib compared with high-dose dexamethasone in relapsed multiple myeloma: Results from the APEX study. American Society of Clinical Oncology. New Orleans; 2005.
37. Alexanian R, Barlogie B, Dixon D. High-dose glucocorticoid treatment of resistant myeloma. Ann Intern Med. 1986 Jul;105(1):8-11.
38. Papandreou CN, Daliani DD, Nix D, Yang H, Madden T, Wang X, et al. Phase I trial of the proteasome inhibitor bortezomib in patients with advanced solid tumors with observations in androgen-independent prostate cancer. J Clin Oncol. 2004 Jun 1;22(11):2108-21.
39. Barlogie B, Smith L, Alexanian R. Effective treatment of advanced multiple myeloma refractory to alkylating agents. N Engl J Med. 1984 May 24;310(21):1353-6.
40. Friedenberg WR, Kyle RA, Knospe WH, Bennett JM, Tsiatis AA, Oken MM. High-dose dexamethasone for refractory or relapsing multiple myeloma. Am J Hematol. 1991 Mar;36(3):171-5.
41. Lazzarino M, Corso A, Barbarano L, Alessandrino EP, Cairoli R, Pinotti G, et al. DCEP (dexamethasone, cyclophosphamide, etoposide, and cisplatin) is an effective regimen for peripheral blood stem cell collection in multiple myeloma. Bone Marrow Transplant. 2001 Nov;28(9):835-9.
42. Dimopoulos MA, Zervas K, Kouvatseas G, Galani E, Grigoraki V, Kiamouris C, et al. Thalidomide and dexamethasone combination for refractory multiple myeloma. Ann Oncol. 2001 Jul;12(7):991-5.
43. Child JA, Morgan GJ, Davies FE, Owen RG, Bell SE, Hawkins K, et al. High dose chemotherapy with hematopoietic stem-cell rescue for multiple myeloma. N Engl J Med. 2003;348(19):1875 - 83.
44. Alvares CL, Davies FE, Horton C, G. P, Bhawana S, Zuha R, et al. Long-term outcomes of previously untreated myeloma patients: responses to induction chemotherapy and high-dose melphalan incorporated with a risk stratification model can help to direct the use of novel treatments. . British Journal of Haematology. 2005;129:607-14.
45. Richardson P, Sonneveld P, Schuster M, Irwin D, Stadtmauer EA, Facon T, et al. Safety and efficacy of bortezomib in high-risk and elderly patients with relapsed myeloma. ASCO Annual Congress; 2005.
46. Dubois D, Dhawan R, van de Velde H, Esseltine D, Gupta S, Viala M, et al. Descriptive and prognostic value of patient-reported outcomes: the bortezomib experience in relapsed and refractory multiple myeloma. J Clin Oncol. 2006 Feb 20;24(6):976-82.
47. Richardson PG, Briemberg H, Jagannath S, Barlogie B, Berenson J, Singhal S, et al. Characterisation and reversibility of peripheral neuropathy in patients with advanced multiple myeloma treated with bortezomib (VELCADE): The SUMMIT and CREST study group. American Society of Hematology. San Diego, California: Blood; 2004.
48. Lonial S, Waller EK, Richardson PG, Jagannath S, Orlowski RZ, Giver CR, et al. Risk factors and kinetics of thrombocytopenia associated with bortezomib for relapsed, refractory multiple myeloma. Blood. 2005;106(12):3777-84.
49. Durie BG, Jacobson J, Barlogie B, Crowley J. Magnitude of response with myeloma frontline therapy does not predict outcome: Importance of time to progression in Southwest Oncology Group chemotherapy trials. Journal of Clinical Oncology. 2004;22(10):1857 - 63.

50. Mehta J, Duff SB, Gupta S. Cost effectiveness of bortezomib in the treatment of advanced multiple myeloma. Manag Care Interface. 2004 Sep;17(9):52-61.
51. Bagust A, Haycox AR, Boland A, Chu P, Morgan GJ, Mujica Mota RE, et al. Economic evaluation of bortezomib (VELCADE) for relapsed and refractory multiple myeloma [oral presentation]. Blood. 2004;104:Abstract 268.
52. Yoong K, Bagust A, Haycox AR, Mujica Mota R, Dhawan R. Economic evaluation of bortezomib (VELCADE) for relapsed and refractory multiple myeloma. Presented at ISPOR 8th Annual European Congress; 2005 6 - 8 November; Florence, Italy; 2005. p. Abstract PCN11.
53. Grosso A, Urquhart R, Saini N. Novel drug for relapsed and chemo-resistant myeloma. Hospital Pharmacist. 2004;11(9):394-6.
54. Kumar SK, Therneau TM, Gertz MA, Lacy MQ, Dispenzieri A, Rajkumar SV, et al. Clinical course of patients with relapsed multiple myeloma. Mayo Clin Proc. 2004 Jul;79(7):867-74.
55. Bruce NJ, McCloskey EV, Kanis JA, Guest JF. Economic impact of using clodronate in the management of patients with multiple myeloma. Br J Haematol. 1999 Feb;104(2):358-64.