CARDAMON

Carfilzomib/Cyclophosphamide/**D**ex**a**methasone with **m**aintenance carfilzomib in untreated transplant-eligible patients with symptomatic MM to evaluate the benefit of upfr**on**t ASCT

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Please note: This trial protocol must not be applied to patients treated outside the Cardamon trial. UCL CTC can only ensure that approved trial investigators are provided with amendments to the protocol.

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1. PROTOCOL SUMMARY

1.1. Summary of Trial Design

Title:	Carfilzomib/Cyclophosphamide/Dexamethasone with maintenance carfilzomib in untreated transplant-eligible patients with symptomatic MM to evaluate the benefit of upfront ASCT
Short Title/acronym:	CARDAMON
EUDRACT no:	2014-000506-35
Sponsor name & reference:	UCL/12/0500
Funder name & reference:	Amgen Limited; 20159848
ISRCTN/Clinicaltrials.gov no:	NCT02315716
Design:	Randomised, multicentre, phase II trial
Overall aim:	**Primary** • To determine the efficacy (sCR and ≥VGPR) of the triple regimen Carfilzomib, Cyclophosphamide and Dexamethasone (CarCyDex) as induction in untreated patients with symptomatic MM who are candidates for ASCT • To evaluate the benefit (PFS at 2 years) of upfront ASCT in patients achieving at least a PR to induction with CarCyDex **Secondary** • To determine the efficacy (ORR: sCR, CR, VGPR, PR, PFS and OS) of an upfront protocol incorporating induction with CarCyDex, ASCT and then carfilzomib maintenance in patients with untreated symptomatic MM who are candidates for ASCT (ASCT arm) • To assess toxicity and tolerability of CarCyDex as induction and carfilzomib as maintenance therapy in untreated patients with symptomatic MM • To determine the efficacy of maintenance therapy in deepening disease response, assessed as conversion from PR or VGPR to

	CR/sCR, and from MRD-positive to MRD-negative on MPF in the ASCT and non-ASCT setting • To determine the efficacy (PFS) of an upfront protocol incorporating 8 cycles of CarCyDex followed by carfilzomib maintenance in patients with untreated symptomatic MM who are candidates for ASCT (non-ASCT arm) • To determine rate of MRD-negative disease following 4 cycles of induction with CarCyDex • To determine the increase in MRD-negative rate following ASCT versus consolidation with 4 further cycles of CarCyDex • To investigate the effects of CarCyDex treatment and of withholding ASCT on patient quality of life • To determine the benefit (PFS2) of withholding ASCT until first relapse in patients with untreated symptomatic MM who are candidates for ASCT
Primary endpoint:	• Major response rate (sCR, CR & VGPR) to 4 cycles of CarCyDex • Progression free survival at 2 years for both ASCT and non-ASCT (consolidation) arms
Secondary endpoints:	• Toxicity: AEs (including PN), dose reductions and delays, tolerability of the induction and maintenance regimens (treatment delays, discontinuation rates) • Disease response rate (sCR, CR, VGPR, PR) to CarCyDex induction • PFS in both ASCT and non-ASCT arms • PFS2 in both ASCT and non-ASCT arms

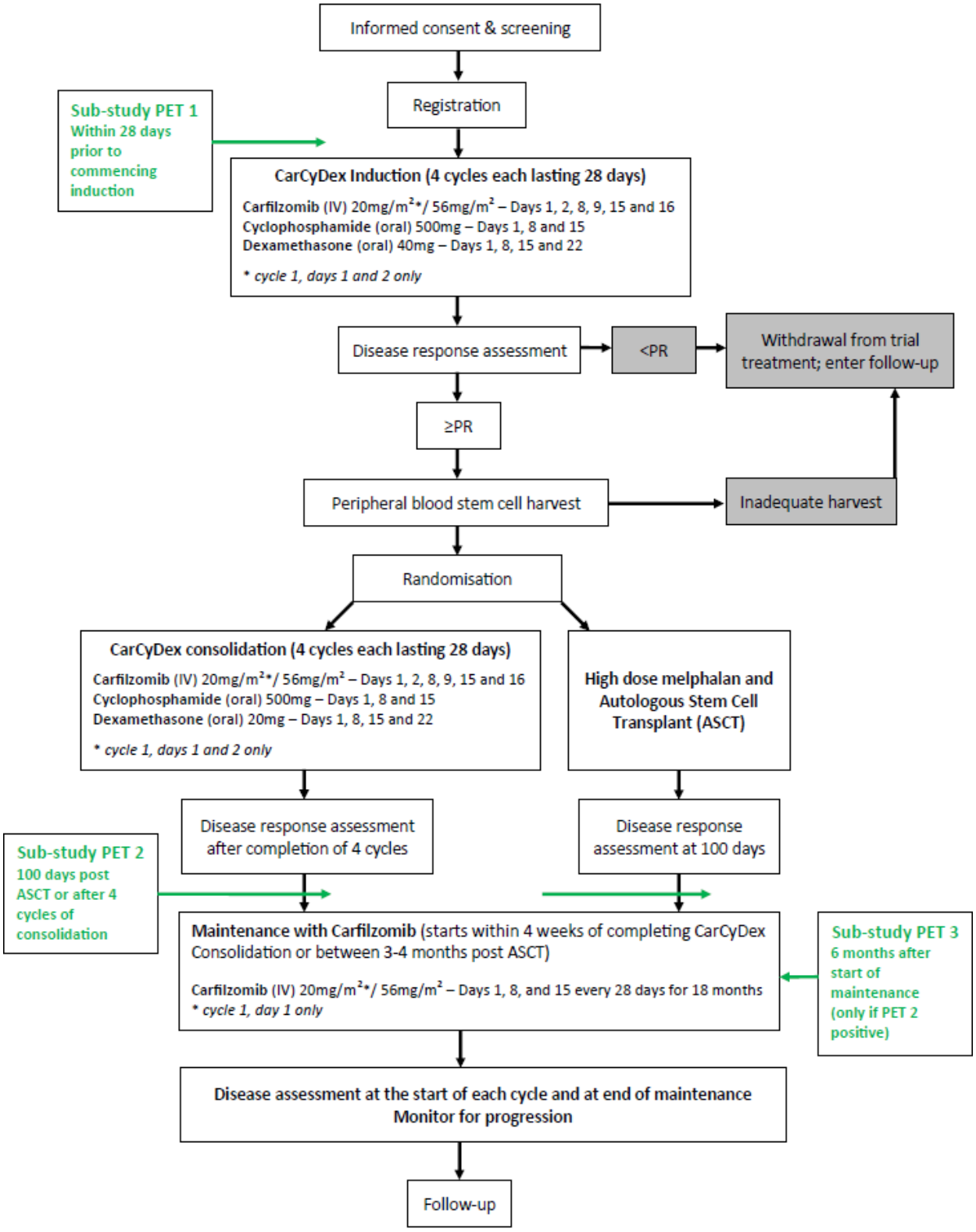
	• Improvement in disease response and conversion from MRD-positive to MRD-negative post ASCT and post Consolidation • Improvement of disease response and conversion from MRD-positive to MRD-negative following maintenance therapy • Quality of life in both ASCT and non-ASCT arms • Overall survival
Target accrual:	280 patients registered, 210 randomised. An interim review of disease response will take place once fifty-three patients have completed 4 cycles. If there are less than 22 responders (≥VGPR), the IDMC will decide whether the whole trial should continue as it is. Recruitment will not be paused for this analysis.
Inclusion & exclusion criteria:	**Inclusion criteria** *Demographic:* 1. Age ≥ 18 years 2. Life expectancy ≥ 3 months 3. Eastern Cooperative Oncology Group (ECOG) performance status 0–2 - see section 6.3.1 for exceptions *Laboratory* 4. Previously untreated patients with symptomatic MM (see Appendix 2) - see section 6.3.1 for exceptions. 5. Measurable disease as defined by one of the following: a. Secretory myeloma: • **Either** monoclonal protein in the serum (≥10 g/L) • **Or** monoclonal light chain in the urine (Bence Jones protein ≥200mg/24hours) • **Or** serum free light chain (SFLC, involved light chain ≥100mg/L provided the FLC ratio is abnormal) b. Non-secretory myeloma:

	• **Either** ≥30% clonal plasma cells in bone marrow (aspirate or trephine) • **Or** 10-30% clonal plasma cells in the marrow and >1 soft tissue or extra-osseous plasmacytoma ≥ 2 cm that is measurable for response assessment by CT or MRI 6. Suitable for high dose therapy and ASCT 7. Adequate hepatic function, with serum ALT ≤ 3.5 times the upper limit of normal and serum direct bilirubin ≤ 2 mg/dL (34 µmol/L) within 14 days prior to registration 8. Absolute neutrophil count (ANC) ≥ 1.0 × 10^9/L within 14 days prior to registration and subject has not received any growth factor support within 7 days of testing. ANC≥0.8x10^9/L allowed for patients with racial neutropenia 9. Haemoglobin ≥ 8 g/dL (80 g/L) within 14 days prior to registration (subjects may be receiving red blood cell (RBC) transfusions in accordance with institutional guidelines) 10. Platelet count ≥ 75 × 10^9/L (≥ 50 × 10^9/L if myeloma involvement in the bone marrow is > 50%) within 14 days prior to registration and subject has not received any platelet transfusions within 7 days prior to testing 11. Creatinine clearance (CrCl) ≥ 30 mL/minute within 14 days prior to registration, either measured or calculated using a standard formula (e.g. Cockcroft and Gault) *Ethical/Other* 12. Written informed consent in accordance with local and institutional guidelines 13. Females of childbearing potential (FCBP) must agree to ongoing pregnancy testing and to practice contraception 14. Male subjects must agree to practice contraception **Exclusion Criteria** 1. Pregnant or breast-feeding females

	2. Previous systemic treatment for myeloma, with the exception of steroids as detailed in section 6.3.1 3. Any major surgery within 21 days prior to registration which in the investigator's opinion would compromise trial treatment and/or the patient's ability to comply with trial visits. Surgery to relieve spinal cord compression or for treatment of bone fractures is permitted. 4. Acute active infection requiring treatment (systemic antibiotics, antivirals, or antifungals) within 7 days prior to planned start of treatment, unless otherwise agreed by the TMG 5. Known human immunodeficiency virus infection 6. Active hepatitis B or C infection (see appendix 4) 7. Unstable angina or myocardial infarction within 4 months prior to registration, NYHA Class III or IV heart failure, uncontrolled angina, history of severe coronary artery disease, severe uncontrolled ventricular arrhythmias, sick sinus syndrome, or electrocardiographic evidence of acute ischemia or Grade 3 conduction system abnormalities unless subject has a pacemaker 8. Uncontrolled hypertension or uncontrolled diabetes within 14 days prior to registration 9. Non-haematologic malignancy within the past 3 years (exceptions apply – see section 6.3.2) 10. Significant neuropathy (Grades 3–4, or Grade 2 with pain) within 14 days prior to registration 11. Known history of allergy to Captisol® (a cyclodextrin derivative used to solubilise carfilzomib) 12. Contraindication to any of the required concomitant drugs or supportive treatments, antiviral drugs, or intolerance to hydration due to preexisting pulmonary or cardiac impairment

	13. Subjects with pleural effusions requiring thoracentesis or ascites requiring paracentesis within 14 days prior to registration 14. Any other clinically significant medical disease or condition that, in the Investigator's opinion, may interfere with protocol adherence or a subject's ability to give informed consent
Planned number of sites:	25
Target country	UK
Treatment summary:	All patients will receive 4 cycles of induction chemotherapy comprising Carfilzomib, Cyclophosphamide and Dexamethasone (CarCyDex). Responding patients (i.e. response ≥PR) will be randomised to consolidation with a further 4 cycles of CarCyDex or high dose melphalan with autologous stem cell transplantation (ASCT). All randomised patients will receive maintenance carfilzomib for 18 months.
Anticipated duration of recruitment:	3 years
Duration of patient follow up:	For 10 years after the completion of induction treatment
Definition of end of trial:	10 years after the last patient completes induction treatment
Translational component:	Molecular classification of patients (FISH) to correlate with treatment outcomes. Targeted profiling of pathways (NFkappaB, Unfolded Protein Response (UPR)). MRD assays to evaluate disease response.
Other related research:	Radiological evaluation of disease response by PET-CT in a sub-group of up to 120 patients, to correlate with other response modalities and to explore prognostic value with respect to PFS and OS.

1.2. Trial Schema



2. INTRODUCTION

2.1. Background

Multiple myeloma (MM) is a plasma cell cancer with an incidence of approximately 5-6 per 100,000; in the UK, about 3,900 people were diagnosed with this cancer in 2008. The median age at diagnosis is 65-70 years, and less than 40% of people are diagnosed under the age of 65 years. MM remains incurable in the vast majority of sufferers, but recent advances in therapy have extended the survival from 2-3 years to 4-5 years on average[1]. The disease is chemosensitive in most newly diagnosed patients, and responds best to combination regimens incorporating chemotherapy and steroids. The overall aim of treatment therefore is to induce a period of disease stability or control (termed plateau phase) that, on currently approved protocols, lasts a median of 3 years, before disease relapse. When the disease relapses, patients who are fit enough are considered for salvage therapy. Patients who are fortunate to respond to salvage therapy will enter another plateau phase, usually of shorter duration than their first one. Subsequent disease relapses are characterised by lower response rates to re-treatment, and shorter periods of remission, with the eventual emergence of refractory disease and death.

Treatment strategies in newly diagnosed patients eligible for ASCT

Front line treatment for newly diagnosed patients who are young and fit enough includes induction therapy that is consolidated with high dose melphalan and autologous stem cell transplantation (ASCT), also termed high dose therapy (HDT). The benefit of HDT in this setting has been established by several randomised studies reviewed by Koreth et al[2]; most of which have demonstrated improvement in progression-free survival (PFS) for the patients allocated ASCT compared with those who received conventional chemotherapy only. In some studies this translated into improved overall survival (OS)[3,4]. Because of this, HDT is standard of care as part of frontline therapy in newly diagnosed patients who are young and fit enough. These studies were conducted using traditional VAD- or high dose dexamethasone-based regimens as induction chemotherapy, and the benefit of ASCT in this setting is attributed to an increased depth of response[3,5] as patients achieving a major response, defined as either a complete response (CR) or very good partial response (VGPR) have longer survival compared with patients in partial response (PR)[6]. For example, in most studies, the CR rate following induction therapy was 10% or less, but this increased to 20-40% following ASCT. In studies where the CR rate was similar between the chemotherapy and ACST arms, there was no difference in outcome[7].

Use of novel agents in frontline regimens in patients eligible for ASCT

The incorporation of proteasome inhibitors and immunomodulatory drugs (IMiDs) into frontline regimens has increased overall response (ORR) and CR/VGPR rates to induction therapy in newly diagnosed patients eligible for ASCT. Initial reports of feasibility and efficacy of combinations of thalidomide, bortezomib or lenalidomide with dexamethasone in this setting[8,9] led investigators to explore 3-drug regimens. The PAD regimen

(bortezomib, doxorubicin and dexamethasone) produced high response rates (ORR >90%, CR 29%) in a phase 2 study[10]. These results have recently been confirmed by the HOVON group, in a randomised controlled trial (RCT) comparing PAD with VAD as induction therapy prior to ASCT: ≥VGPR rate pre-ASCT of 27%, improving to 62% post-ASCT[11]. The IFM group reported that the combination of reduced dose bortezomib with thalidomide and dexamethasone (VTD) produced higher ≥VGPR rates compared to standard dose bortezomib with dexamethasone (50% vs 36%), and this was improved further post-ASCT, with maintenance of the superiority of the VTD arm[12]. The Italian GIMEMA group compared standard dose bortezomib in VTD with thalidomide and dexamethasone (TD) as induction therapy, reporting a significantly higher ≥VGPR rate of 62% vs 28%, which increased to 79% vs 58% post-ASCT[13]. This was associated with superior PFS (68% vs 56% at 3 years), although the impact of post-ASCT consolidation (with VTD in the test arm, and TD in the control arm) cannot be unpicked here. A similar comparison was conducted by the Spanish group, who also reported high response rates to VTD (59% ≥VGPR rate) pre-ASCT and further improvement post-ASCT[14]. Lenalidomide regimens have not been formally tested as induction prior to ASCT, however a retrospective analysis comparing phase 2 data on 3 regimens: lenalidomide and dexamethasone (RD), cyclophosphamide, lenalidomide and dexamethasone (CRD) and cyclophosphamide, bortezomib and dexamethasone (CyBorD) reported high ORR rates of 85-94%, and ≥VGPR rates of 47%, 47% and 67% respectively[15]. There was no significant difference in PFS or OS between the 3 regimens. Finally the triplet combination of lenalidomide, bortezomib and dexamethasone produces high response and major response rates (51-67% ≥VGPR[16]), whilst further addition of cyclophosphamide appears to increase toxicity without further improvement in efficacy[17].

Novel agents have also been employed in consolidation protocols, often incorporated into induction-ASCT regimens. Thus, the Italian RCT of VTD vs TD included consolidation with a similar regimen post-ASCT for each arm. An updated analysis of this study, using a landmark from the start of consolidation therapy showed that patients receiving consolidation with VTD had prolonged TTP and PFS compared with those receiving TD. These improved benefits correlated with a greater upgrading of response in the VTD arm (11% increase in CR rates) compared with the TD arm[18]. The HOVON study also reported an upgrading of response in the PAD arm, during maintenance with fortnightly single agent bortezomib (23% of patients), which is likely to contribute to the superior OS in that arm of the study. The use of lenalidomide as maintenance therapy post-ACST has produced the most impressive prolongation of PFS. The IFM study reported an improvement in PFS from 23 months in the placebo arm to 41 months in patients treated with low dose lenalidomide[19], while the CALGB study reported a PFS of 46 months in the lenalidomide arm compared to 27 months in the placebo arm[20].

Role of ASCT in context of major response to induction therapy

The substantial activity seen with the new drug regimens incorporating novel agents, at induction as well as in consolidation and maintenance protocols, prompts an urgent re-examination of the role (and timing) of ASCT in MM treatment[21], particularly as recent data indicate that patients who have already achieved a complete response (CR) following induction therapy obtain no further benefit from ASCT[22]. Thus, subjecting

patients who are in CR following induction therapy to upfront ASCT may expose them to unnecessary toxicity, as well as depriving them of the benefit of salvage ASCT at relapse. For such patients, the maximal benefit from, and hence optimal timing of, ASCT may be at relapse. The time has come to re-examine the benefits of upfront ASCT in the era of new agents[21].

The benefit of upfront ASCT was addressed many years ago in a sequential RCT in patients receiving traditional regimens[23]. In this study, where patients were assigned to early or late ASCT, the group receiving HDT only at relapse had similar OS compared with the group who received HDT upfront, despite a much shorter event-free survival (13 months vs. 38 months). More recently, the Mayo group have retrospectively analysed 290 patients who received initial therapy with thalidomide or lenalidomide and dexamethasone, and, following peripheral blood stem cell harvest (PBSCH), either received ACST on time (within 12 months of diagnosis, early SCT group) or did not (delayed SCT group)[17,24]. The delayed SCT group had deeper responses to initial therapy (32% ≥VGPR compared to 16% in early SCT group), and only 37% of them eventually received ASCT, for relapsed disease. Interestingly, time to progression from initiation of therapy was similar in the 2 groups (25.4 months in early SCT group, and 26 months in delayed SCT group), and there was no difference in OS between them. The overall response rate to SCT was also similar (92% in early SCT group vs 87% in late SCT group). Another retrospective study comparing different induction regimens also found no difference in PFS between patients who proceeded to ASCT compared with those who did not, but there was a benefit in terms of OS[15]. The only prospective study comparing ASCT with no ASCT that has reported is an Italian study that randomised patients, following induction with lenalidomide and dexamethasone (Rd), to consolidation with ACST or with MPR. Despite similar response rates (60% ≥VGPR) in the 2 arms post-consolidation, the PFS was significantly longer in the ASCT arm (NR vs 25.2 months in the non-ACST arm[25].

There are at least 2 prospective randomised studies that are currently addressing the benefit of upfront (or delayed) ASCT following induction with a novel agent containing regimen, the DFCI-IFM study, and the European Myeloma network study. In the UK, the NCRN single arm phase 2 PADIMAC study will estimate the PFS of patients who, after achieving a CR/VGPR to induction with PAD, receive no further therapy (no-ASCT). PADIMAC, which will also provide information on the impact of MRD status, will complete recruitment in Q2 2013. This current proposal is designed as a follow-on randomised phase 2 study to pursue this question, using recent insights provided by consolidation and maintenance protocols in order to optimise therapy in the non-ASCT arm, and exploiting the high anti-myeloma activity of carfilzomib-containing regimens (see Section 2.2). Thus, this study will address the research question: **Are patients who respond to a highly efficacious triplet regimen like CarCyDex disadvantaged by NOT proceeding to upfront ASCT?** This study will use a novel triplet combination incorporating carfilzomib (CarCyDex), and will randomise responding patients to receive either ASCT or a further 4 cycles of CarCyDex as consolidation (non-ASCT arm). All patients will receive a low dose maintenance regimen. Information on carfilzomib, and the rationale for the combination, is given below.

Rationale for use of PET-CT scanning for disease response assessment

Current techniques for assessing low levels of residual disease rely on biochemical assays for the monoclonal protein (serum electrophoresis, light chains), and on evaluation of randomly sampled bone marrow for presence of neoplastic plasma cells using multi-parameter flow cytometry[26]. Plain radiography has long been used in diagnostic assessment, given the high prevalence of osteolytic lesions in MM, but this is increasingly being superseded by the use of more sensitive cross-sectional techniques (MRI, CT-scanning)[27].

Functional imaging techniques have also recently been explored in the context of prognostication in newly diagnosed MM as well as in response assessment. The number and intensity of focal lesions at diagnosis, the presence of extramedullary disease and metabolic response on PET-CT following treatment have been shown to have prognostic value in newly diagnosed patients treated with ASCT and more recently also in patients ineligible for transplant, treated with novel agents and chemotherapy (Zamagni et al, 2015)[28-31]. High intensity of uptake on baseline PET appears to be associated with shorter PFS and OS, independent of stage and conventionally defined CR[31]. Nearly 1/3 of patients in a retrospective study involving 282 patients who achieved CR were reported to have a 'positive' PET scan which was associated with inferior PFS and OS. Persistent uptake also predicted for skeletal progression in the absence of otherwise identifiable signs of progressive disease[31]. In addition to providing a functional response measure, PET-CT assessment also affords an evaluation of spatial heterogeneity, both in terms of response to therapy, and underlying genetic signatures[32]. Preliminary results from the imaging sub-study, IMAGEN of the phase 3 IFM/DFCI trial that is comparing ASCT to chemotherapy consolidation in transplant eligible NDMM were presented at ASH 2015. The data indicate that achieving a metabolic response post-induction chemotherapy was associated with longer PFS, while a metabolic response prior to maintenance therapy was associated both with a longer PFS and OS[30]. We wish to confirm these findings in our study, and to investigate if the prognostic value of PET-CT response applies equally to the ASCT and the non-ASCT arms of the study.

2.2. Carfilzomib background

Carfilzomib (PR-171) is a tetrapeptide ketoepoxide-based inhibitor specific for the chymotrypsin-like active site of the 20S proteasome. The proteasome is a multicatalytic proteinase complex that is responsible for degradation of a wide variety of protein substrates within normal and transformed cells. Intracellular proteins targeted for degradation by the proteasome are first ubiquitinated via the ubiquitin conjugation system. Ubiquitinated proteins are cleaved within the proteasome by one or more of three separate threonine protease activities: a chymotrypsin-like activity, a trypsin-like activity, and a caspase-like activity. Carfilzomib is structurally and mechanistically distinct from the dipeptide boronic acid proteasome inhibitor bortezomib (Velcade®). In addition, when measured against a broad panel of proteases including metallo, aspartyl, and

serine proteases, carfilzomib demonstrated less reactivity against non-proteasomal proteases when compared to bortezomib[33,34].

Carfilzomib toxicology studies

In the initial Good Laboratory Practice (GLP)-compliant toxicity studies done by the drug maker, Onyx, carfilzomib was administered to rats and monkeys as two complete two-week cycles of once daily for five days (QdX5) with nine days rest[35]. Administration to rats at 12 mg/m^2, the severely toxic dose in 10% of animals (STD_{10}), caused > 90% proteasome inhibition in red blood cells one hour after dosing. Overall, stronger inhibition of the proteasome and longer duration of inhibition was tolerated with carfilzomib compared with bortezomib. Daily administration of bortezomib at anti-tumor doses is not tolerated in animals, and therefore daily bortezomib has not been given in the clinic. A dose-dependent decrease in proteasome activity was demonstrated in animals, and equivalent levels of proteasome inhibition were achieved with administration of carfilzomib as either an intravenous (IV) push or an IV infusion. The dose-limiting toxicities (DLTs) of carfilzomib in both the rat and monkey 28 day GLP toxicity studies included toxicity to the gastrointestinal tract, bone marrow, pulmonary, and cardiovascular systems. No behavioral or histopathological signs of neurotoxicity were observed, and carfilzomib does not cross the blood-brain barrier.

In 6-month rat and 9-month chronic toxicity studies, carfilzomib was administered on Days 1, 2, 8, 9, 15, and 16 of a 28-day cycle, mimicking the active anti-tumor regimen being used in ongoing Phase II studies in myeloma and solid tumors[35]. Tolerability was excellent, with no evidence of peripheral (or central) neurotoxicity, including neuropathology, observed, even at high doses. DLTs included effects on the gastrointestinal, renal, pulmonary, and cardiovascular systems and appeared related to Cmax effects. Of note, neutropenia was not observed; rather, transient neutrophilia was seen following acute dosing. Renal, cardiovascular and gastrointestinal toxicities were similar to those observed with bortezomib. Finally, cyclical thrombocytopenia, likely due to inhibition of platelet budding from megakaryocytes, was similar to that seen with bortezomib. Proteasome inhibition in the blood in excess of 90% was achievable at well-tolerated doses, which contrasts with the ~70% proteasome inhibition achievable with bortezomib at its maximum tolerated dose (MTD). In summary, these animal toxicity studies support the tolerability of carfilzomib in clinical studies, even on intensive dosing schedules and at doses achieving proteasome inhibition in excess of what can be achieved with bortezomib at its MTD on a less intensive schedule.

Clinical pharmacokinetics and pharmacodynamics

Following IV administration to patients, carfilzomib is rapidly cleared from the systemic circulation with a half-life < 1 hour and a clearance that is higher than hepatic blood flow. There is no systemic accumulation of carfilzomib after repeat doses. Exposure to carfilzomib increases dose-proportionally in the therapeutic dosage tested. No apparent effect of renal dysfunction on PK of carfilzomib has been noted to date. Carfilzomib is extensively metabolised to inactive products primarily via peptidase cleavage and

epoxide hydrolysis. Following administration of carfilzomib at doses ranging from 15 to 36 mg/m^2 to patients with haematological malignancies and solid tumors, inhibition of the CT-L activity of the proteasome in PBMCs averaged approximately 85%. Recovery of proteasome activity in PBMCs was not complete on Day 8 of the dosing cycle, suggesting a prolonged period of proteasome inhibition by carfilzomib between weeks of dosing. Near complete recovery of proteasome activity was observed in peripheral white blood cells between cycles.

Carfilzomib Preclinical Antitumor Activity

Continuous (72 hr) exposure to carfilzomib is associated with potent cytotoxic and pro-apoptotic activity across a broad panel of tumor-derived cell lines in culture[33,36]. Incubation of haematologic tumor cell lines with carfilzomib for as little as one hour leads to rapid inhibition of proteasome activity followed by accumulation of polyubiquitinated proteins and induction of apoptotic cell death. Carfilzomib has also been demonstrated to be cytotoxic in bortezomib-resistant tumor cell lines[33,36]. The anti-tumor efficacy of carfilzomib has been tested in immunocompromised mice implanted with a variety of tumor cell lines. In a human colorectal adenocarcinoma model HT-29, administration of carfilzomib on a twice-weekly Day 1, Day 2 schedule resulted in significant reduction in tumor size and was superior to a twice-weekly Day 1, Day 4 schedule using the same dose of carfilzomib, and a once-weekly dosing schedule using twice the dose level.

Phase 1 Experience with Carfilzomib as a Monotherapy

A Phase 1 clinical trial, PX-171-002, tested carfilzomib in subjects with relapsed/refractory haematologic malignancies[37]. During the dose escalation portion of the trial, 37 subjects received carfilzomib on Days 1, 2, 8, 9, 15, and 16 of a 28-day cycle. Subjects with MM, Non-Hodgkin's Lymphoma (NHL), Waldenström's Macroglobulinemia, and Hodgkin's Lymphoma (HL) were enrolled on the study.

No dose limiting toxicities (DLTs) were observed in the initial seven cohorts (doses ranged from 1.2 to 15 mg/m^2) of three subjects each. At the 20 mg/m^2 dose level, one of eight patients had a Grade 3 renal failure at Cycle 1, Day 2 which was considered possibly related to study drug and lasted for six days. The patient continued on study for the remainder of Cycle 1 before having disease progression. At the 27 mg/m^2 dose level, one of six subjects experienced a DLT during Cycle 1, consisting of severe hypoxia with pulmonary infiltrates following Day 2 of dosing. In subjects where the 27 mg/m^2 dose was efficacious, a "first dose effect" was seen that included a constellation of findings that appeared to be the clinical sequelae of rapid tumor lysis syndrome (TLS) and/or cytokine release. This effect was notable for fever, chills, and/or rigors occurring during the evening following the first day of infusion. On the second day, three of five subjects with multiple myeloma experienced an increase in creatinine to Grade 2 (including the subject with the DLT). This elevation was rapidly reversible and all three subjects were rechallenged with carfilzomib without recurrence of the events. Interestingly, all three subjects had a rapid decline in serum and/or urine M-protein levels; two subjects achieved a PR and the third subject achieved a minimal response (MR). There were no consistent changes in potassium, calcium, phosphorous, or uric acid levels although some

increases in LDH and other markers of tumor lysis were noted. Because of the possible TLS and reversible creatinine elevations, hydration and very-low dose dexamethasone prophylaxis were instituted in subsequent studies and have essentially eliminated clinically significant TLS/creatinine elevations and the other "first-dose" effects.

Haematologic toxicities were primarily mild or moderate. The thrombocytopenia reported with carfilzomib is cyclical and similar to that reported with bortezomib. The cause and kinetics of the thrombocytopenia following treatment are different from those of standard cytotoxic agents. To maximise the likely benefit of carfilzomib, subjects with thrombocytopenia should be supported as clinically indicated rather than having treatment reduced due to thrombocytopenia.

Of the 36 evaluable patients enrolled in PX-171-002, 20 had MM[38,39]. Four MM patients achieved a partial response (PR), one of two at the 15 mg/m^2 dose, one of six at the 20 mg/m^2 dose, and two of five at the 27 mg/m^2 dose. The responses have been rapid in onset, beginning in some subjects after 1-2 doses. The duration of response (DOR) ranged from 134 to 392 days. The minimal effective dose was 15 mg/m^2 wherein >80% proteasome inhibition in peripheral blood and mononuclear cells was observed one hour after dosing.

Phase 2 Experience with Carfilzomib as a monotherapy

Two Phase 2 clinical studies with carfilzomib in MM patients, PX-171-003-A0 (N=46) in relapsed and refractory MM and PX-171-004 (N=39) in relapsed MM have completed. In both studies, patients were dosed with 20 mg/m^2 on Days 1, 2, 8, 9, 15, and 16 on a 28 day schedule. In these studies there were four cases of suspected or documented TLS prior to institution of the prophylaxis guidelines. Since these guidelines were implemented, no further cases of TLS have been reported including in >350 additional patients with relapsed or refractory MM treated in ongoing Phase II studies. In both studies, the most common adverse events were fatigue, anaemia, thrombocytopenia (primarily cyclical), gastrointestinal, and dyspnoea. Almost all were Grades 1 or 2. There were reported cases of increases in serum creatinine that were primarily < Grade 2 and were transient, rapidly reversible, and non-cumulative. A very low rate of treatment-emergent peripheral neuropathy, 2.2% Grade 3/4, was observed in PX-171-003-A0 despite the fact that 78% of patients had Grade 1/2 neuropathy upon study entry[40]. The ORR in PX-171-003-A0 was 16% PR, 7% MR and 41% SD in these patients that entered the study with progressive disease and were refractory to their most recent therapy, often including bortezomib and/or an immunomodulatory drug (usually lenalidomide). The median time to progression on the PX-171-003-A0 study was 5.1 months with a DOR of 7.4 months (mean follow up of 7.6 months)[40].

A "stepped up" dosing schedule, referred to as 20/27 mg/m^2, has subsequently been incorporated into the PX-171-003 study (referred to as PX-171-003-A1) in order to maximise the clinical benefit of carfilzomib. Patients received 20 mg/m^2 for the first cycle and 27 mg/m^2 thereafter. The study completed enrollment of 266 patients by the end of 2009 and has formed the basis for an accelerated approval NDA filing this year[41]. This was a heavily pre-treated group, with a median of 5 prior lines of therapy, and the

majority (73%) were refractory to bortezomib. and 80% were refractory or intolerant to both bortezomib and lenalidomide. To date, this dosing schedule has been well tolerated[39]. No cases of TLS were observed and rates of BUN and creatinine elevation dropped sharply, with Grade 3/4 renal impairment dropping from 15% in A0 to 2.2% in A1, most likely due to hydration and very low dose dexamethasone. The other most common adverse events were similar to the A0 portion of the study. Treatment-emergent peripheral neuropathy remains low on this portion of the study (12.4%) with Grade 3 in only 3 patients, all of whom had pre-existing PN, and no Grade 4 event reported to date on PX-171-003-A1[41]. The most common treatment emergent AEs were fatigue (49%) and anaemia (46%). Rates of thrombocytopenia (G3/4 29%) and neutropenia (G3/4 11%) in the A1 study were similar to that seen in the pilot A0 study. In 257 response-evaluable patients, the ORR was 23.7%, median PFS was 3.7 months, DOR 7.8 months and OS 15.6 months. 31% of patients completed more than 6 cycles, and treatment discontinuations were mainly for progressive disease.

In PX-171-004, a first cohort of patients received 20 mg/m^2, while a second cohort had dose escalation up to 27 mg/m^2. Cohort 1 contained patients who were both bortezomib–exposed or bortezomib–naïve while cohort 2 only contained bortezomib naïve patients. Patients who were bortezomib-naïve (n=129) had a dose dependent response that increased from 42,4% in the 20 mg/m2 group to 52.2% in the 20/27 mg/m2 (stepped up dosing) group , while the bortezomib treated patients (N=33) had an ORR of 18% (3% CR, 3% VGPR and 12% PR)[42-44]. The median TTP was 8.3 months in cohort 1 bortezomib-naïve patients, while the TTP for cohort was not reached. Of note, disease control (PR + MR + SD) was achieved in ~65% of patients with progressive MM entering the study. Patients on these studies have been treated for >12 cycles with good tolerability and no cumulative toxicity (e.g., bone marrow, severe fatigue, or neuropathy) have not been observed.

Based on the results of PX-171-003 and -004, the FDA has granted accelerated approval for carfilzomib in patients who have received at least 2 prior therapies, including bortezomib and an IMiD in the United States.

More recent dose escalation studies of single agent Carfilzomib have reported results in abstract form at the annual ASH meetings. The PX-171-007 study established a MTD of 56mg/m^2 on a consecutive dosing schedule similar to the one above, with an overall response rate of 60%[45]. Similarly, this dosing schedule was also reported to be well tolerated and to produce a disease response of 58% in relapsed refractory patients[46]. The most commonly reported G 3/4 non-haematological AEs included hypertension (21%), lung infection (18%) and 35% of patients required a dose reduction. The CHAMPION study is investigating weekly carfilzomib (days 1, 8 and 15 of a 28-day cycle) with dexamethasone in a similar patient group, and reported an MTD of 70mg/m^2 [47].

Experience with Carfilzomib in Combination with Lenalidomide and Dexamethasone

PX-171-006 is a Phase 1b study in patients with relapsed multiple myeloma in which carfilzomib is administered in combination with lenalidomide (Revlimid®) and

dexamethasone. Carfilzomib was administered IV on Days 1, 2, 7, 8, 15, and 16; lenalidomide PO on Days 1 through 21, with dexamethasone 40 mg/day given on Days 1, 8, 15, and 22 in all cases. Enrolment has closed in this study, and no MTD was reached. The maximum per protocol doses of carfilzomib (27mg/m^2) with lenalidomide 25mg and low dose dexamethasone are being used[48]. The best ORR was 69% and the DOR was 18.8 months[49]. This regimen has been taken into Phase 3 in study PX-171-009 (ASPIRE), that has completed recruitment.

Dose Rationale

Preliminary data suggest that carfilzomib as a single agent can produce substantial response rates in myeloma subjects across a variety of dosing cohorts. Responses were seen over a wide therapeutic window, from 15 to 56 mg/m^2. Carfilzomib is rapidly cleared from plasma with an elimination half-life of < 60 minutes at the 20 mg/m^2 dose. Results of large, single arm studies at the 27 mg/m^2 dose indicate that this dose is very well tolerated with patients being treated for >10 cycles without cumulative toxicities. At a dose of 27mg/m^2, carfilzomib (bolus administration over 2-10') is well tolerated in MM patients overall and can be tolerated for >12 cycles in late stage MM patients with substantial comorbidities. A phase 1 dose escalation study (PX-171-007) of single agent carfilzomib in patients with solid tumours indicated that the dose of 36 mg/m^2 (bolus administration over 2-10 min) was well tolerated with only one DLT (fatigue) and an overall adverse event profile similar to that seen with the 27mg/m^2 carfilzomib experience with bolus dosing. Because of the long-term tolerability of carfilzomib, the Phase 1b portion of this study was re-opened, and a separate arm for multiple myeloma was added. In this Phase 1b/2 study, patients were treated with carfilzomib given as a 30-minute infusion, and using a stepped-up dosing regimen starting at 20/36 mg/m^2 (20 mg/m^2 given on Days 1 and 2 of cycle 1 only; followed by 36 mg/m^2 for all subsequent doses), escalating up to 20/45, 20/56 mg/m^2 and 20/70 mg/m^2. A total of 33 patients were enrolled and 20 were treated at the MTD of 20/56 mg/m^2. Median number of cycles received was 4, and 5 patients went onto receive ≥10 cycles, indicating the tolerability of carfilzomib at higher doses. The 20/56 mg/m^2 cohort had an ORR rate of 60%. The majority of the AEs in the 20/56 mg/m^2 cohort were G1-2 in severity with the exception of anaemia and thrombocytopenia. The most common AEs, irrespective of relationship to carfilzomib, in this cohort were dyspnoea (54%), fatigue (54%), nausea (54%), pyrexia (54%), anaemia (38%), chills (38%), hypertension (38%), and thrombocytopenia (38%). There was 1 report of G1 peripheral neuropathy (4%) in this cohort. Additionally, the most common ≥G3 AEs in this group were thrombocytopenia (38%), anaemia (21%), and hypertension (13%). Five patients (21%) treated at 20/56 mg/m^2 required dose reductions. Pharmacodynamic analysis demonstrated inhibition of proteasome chymotrypsin-like activity in peripheral blood mononuclear cells of >80% at 20 mg/m^2 and ≥95% at ≥56 mg/m^2. Carfilzomib at 56 mg/m^2 inhibited all 3 subunits of the immunoproteasome, resulting in ~78% inhibition in total activity.

Carfilzomib has been characterised in patients with CrCL < 15 mL/min or creatinine ≥ 2.5 mg/dL. In 3 Phase 2 studies (Studies PX-171-003, -004, and -005), the safety and efficacy of carfilzomib was studied in 179 patients (34%) with estimated baseline (i.e., pretreatment) glomerular filtration rates < 60 mL/min, and in 21 patients (4.0%) with

estimated baseline glomerular filtration rates < 30 mL/min, including 8 patients on haemodialysis. The pharmacokinetics of carfilzomib was not influenced by the degree of baseline renal impairment, including the patients on dialysis. Therefore, dosing adjustments of carfilzomib are unnecessary for patients with pre-existing renal insufficiency. Since dialysis clearance of carfilzomib concentrations has not been studied, the drug should be administered after the dialysis procedure.

Toxicity and adverse effects from clinical studies

The most frequently reported AEs (those occurring in ≥ 20% of patients) included fatigue, nausea, anaemia, dyspnoea, diarrhoea, thrombocytopenia, pyrexia, headache, cough, upper respiratory tract infection, vomiting, lymphopenia, peripheral oedema, increased blood creatinine, constipation, and back pain. All of these AEs were generally NCI-CTCAE Grades 1 and 2 in severity and the more severe AEs were reversible with symptomatic treatment, dose reduction, or withholding. The gastrointestinal side effects are generally mild and respond well to conventional measures. The haematologic effects seen are generally self-limiting and reversible. Although not prevalent, increases in creatinine have been reported and are predominantly Grade 1 or Grade 2 and reversible. It is not known if there is a clear association between renal failure and carfilzomib. Many cases of renal failure were confounded by documented or suspected TLS, sepsis/infection, light chain disease, and disease progression. One death in Study PX-171-004 in a patient with multiorgan failure due to TLS was considered to be carfilzomib-related. Guidelines for hydration and prophylactic allopurinol dosing were successfully instituted to mitigate the risks of TLS in clinical trials. Pretreatment included PO and IV hydration regimen and PO allopurinol 300 mg twice per day during the first cycle of carfilzomib with the option of continuing these measures in Cycle 2 in patients at risk for TLS. Peripheral neuropathy is a well-documented AE that occurs frequently in patients with MM either from the disease or as a consequence of treatment with bortezomib or thalidomide. In the carfilzomib clinical trials, the incidence and severity of PN have been low. The majority of the PN AEs has been Grade 1. There have been rare SAEs or study discontinuations due to PN.

Haematological toxicity: Carfilzomib is associated with thrombocytopenia. The thrombocytopenia pattern is cyclic with nadirs following the second dose each week and typically recovering prior to the initiation of the next treatment, similar to that observed with bortezomib. The severity of thrombocytopenia is related to the pretreatment platelet counts. Transfusions may be considered. The incidence of significant bleeding is < 5%. Platelet counts should be monitored at a minimum prior to each cycle of treatment and more frequently if baseline counts are > Grade 1. Severe neutropenia has been reported and may occur during treatment but is uncommon. Carfilzomib should be administered with caution to patients with ANC < 1.0 x 10^9/L and the drug should be held for ANC < 0.5 x 10^9/L. Febrile neutropenia is rare and carfilzomib should be held until the AE has resolved. In addition, patients with active infections or who are completing treatment for systemic infections should not receive carfilzomib until the infection has resolved.

Cardiac events: Acute development or exacerbation of congestive heart failure and new onset of decreased left ventricular function have been reported, including reports in

patients with no risk factors for decreased left ventricular ejection fraction. The incidence of heart failure events (acute pulmonary oedema, cardiac failure, congestive cardiac failure, cardiogenic shock, pulmonary oedema) is less than 8%. Patients with risk factors for or evidence of existing heart disease should be closely monitored throughout their treatment with carfilzomib. Carfilzomib should be withheld if CHF develops or appears to be exacerbated by treatment and may be resumed once the symptoms resolve. Consideration should be given to a reduction in dosage with gradual increase to full dose only if well tolerated. Ischemic heart disease and arrhythmias have also occurred. Dyspnoea may occur in association with cardiac disorders. Patients who experience dyspnoea should be evaluated for the presence of associated conditions and management should be tailored to the appropriate treatment for the underlying disorder.

Creatinine clearance: A phase II study to assess the influence of renal impairment on the pharmacokinetics of Carfilzomib has recently been reported[50]. A total of 50 patients were enrolled, of whom 12 had creatinine clearance > 80 mL/min; 12 had CrCl 50-79 mL/min; 10 participants had CrCl 30-49 mL/min; 8 participants had CrCl < 30 mL/min and 8 participants were on chronic dialysis. Adverse events in these participant groups were similar regardless of degree of renal dysfunction and included anaemia, fatigue, and diarrhoea as the most common adverse events observed. Serious AEs occurred in 33 patients (66%), the most common being pneumonia (8), ARF, CHF, dehydration and influenza (3 patients each). Carfilzomib PK was not significantly altered in renal failure, including patients on dialysis, while PD analysis confirmed prolonged and substantial proteasome inhibition that was similar to that documented in previous studies. Twelve of 47 response evaluable patients achieved a PR (ORR 25.5%), while in 36 response evaluable patients with renal impairment, ORR was 27.7%. The renal safety profile of carfilzomib was updated recently by Harvey et al[51] in 526 patients from four phase 2 studies (PX-171-003A0, PX-171-003A1, PX-171-004, and PX-171-005). This included 125 patients (23.8%) with moderate to severe renal failure (CrCL <50ml/min) and a further 39.4% with mild renal impairment (CrCl 50-80ml/min). Overall, only 68 (out of 515 with post-baseline creatinine values) patients (13%) had worsening of renal function. In 31 patients, this was transient, whilst in 37 patients, creatinine levels had not resolved as of last available values. Overall 174 patients (33.1%) of patients had renal AE's, the majority (78.2%) were grade 2 or less, and only 21 patients (4%) discontinued treatment due to a renal AE. Frequency and severity of AE's in PX-171-005 were similar between varying degrees of renal function, including patients on chronic haemodialysis. These data indicate that the incidence of treatment-emergent, renal-related AEs is low. Carfilzomib dose and schedule do not require adjustment in patients with renal impairment, including those on haemodialysis.

Recently, pooled safety data for single-agent carfilzomib (CFZ) in 526 patients with relapsed/refractory MM who took part in Phase 2 studies were presented at ASH 2011[52] Overall, CFZ had a favourable safety profile in these studies. The most frequently reported adverse events (AEs) occurring in ≥30% of patients included fatigue (55%), anaemia (47%), nausea (45%), thrombocytopenia (36%), dyspnoea (35%), diarrhoea (33%), and pyrexia (30%). The most common (≥10% of patients overall) ≥G3 AEs were thrombocytopenia (23%), anaemia (22%), lymphopenia (18%), pneumonia (11%), and neutropenia (10%). PN was reported infrequently (14% overall) across all studies.

Although 378 (72%) patients had baseline PN (≤G2), only 13% reported treatment-emergent symptoms during the study. PN was generally mild to moderate in severity (1.3% G3 PN with no G4 PN), and only 5 patients (1%) required dose modification or discontinuation due to PN. Renal AEs (mainly ≤G2) were reported in 174 (33%) patients, and CFZ was discontinued because of a renal AE in only 21 patients (4%). There were a total of 37 (7%) deaths on study, including within 30 days of the last dose of study drug. The primary cause of death was due to disease progression in 22/37 patients (4.2%); however, AEs, including in order of frequency, cardiac events, hepatic failure, and infection, contributed to 14 of these deaths.

Clinical experience of carfilzomib regimens in the frontline setting

A phase 1/2 study of carfilzomib (dosing from 20 mg/m^2 up to 36 mg/m^2) with lenalidomide and dexamethasone (CRD) in newly diagnosed patients with MM who were candidates for ASCT has recently been reported[53]. After 4 cycles of therapy, the overall response rate was 100% and ≥VGPR was 88% (n=53). Responses were rapid, with 94% response (≥PR) after one cycle. Haematologic toxicities were reversible and included (Grade 3/4): anaemia (18%), neutropenia (12%), and thrombocytopenia (10%). The most common non-haematologic toxicities (all grades) were hyperglycemia (76%), hypophosphatemia (61%), and infection (53%). Grade 3/4 non-haematologic AEs included hyperglycemia (24%), DVT/PE while on ASA prophylaxis (10%), infection (6%), and mood alteration (2%). PN was limited to G1/2 sensory (24%). A second study explored the combination of carfilzomib with thalidomide and dexamethasone in the same patient population[54,55], using carfilzomib dose of 20/27 mg/m^2 in a stepped-up dosing protocol, escalating up to 20/45 mg/m^2. Patients received 4 cycles, followed by ASCT and then consolidation with a further 4 cycles of the same regimen, with reduced dose thalidomide and dexamethasone. In 70 patients treated in cohorts 1 (20/27 mg/m^2) and 2 (20/36 mg/m^2), ORR after 4 cycles of induction was 96%. PBSCH was successfully achieved (60/60 patients) and HDM with ASCT was performed with complete haematological recovery (53/53). The regimen was well tolerated, with non-haematological toxicity of G3/4 of <5%. The addition of cyclophosphamide to CarThalDex in the CYCLONE study conducted by investigators at the Mayo clinics produced an ORR of 96%, with 18 of 24 evaluable patients achieving ≥VGPR[56,57]. Finally, the addition of carfilzomib to melphalan and prednisolone in the IFM study was studied in newly diagnosed, non-ASCT candidates. The MTD was established at 36mg/m^2 of Carfilzomib, administered on days 1, 2, 8, 9, 22, 23, 29 and 30 of 6-week cycles. In 35 evaluable patients, the ORR was 89%, with ≥VGPR rate of 43%. These regimens produce impressively high response and CR/VGPR rates, but the optimal combination for treatment of newly diagnosed transplant-eligible patients has yet to be established.

Rationale for this regimen and study design

The addition of a novel agent to the combination of cyclophosphamide and dexamethasone produces triplet regimens that are in general well tolerated and efficacious in both the upfront and relapsed setting. In the UK, this is the preferred combination and has formed the basis for the last national phase 3 studies (CTD in Myeloma IX, CTD vs CRD in Myeloma XI). The combination of carfilzomib with

cyclophosphamide and dexamethasone is novel and untested in the upfront setting in transplant-eligible patients with MM, however preliminary data from other triplet regimens incorporating carfilzomib and dexamethasone (with lenalidomide or with thalidomide) indicate high response rates with good tolerability (see above)[58,59]. Recently carfilzomib, cyclophosphamide and dexamethasone was reported to be well tolerated in the elderly newly diagnosed population of myeloma patients with a median age of 71 years, producing a response rate of 92% (67% VGPR) after 4 cycles[60]. Grade 3 /4 non-haematological AEs included infections (7%), cardiac (5%) renal (4%) and gastrointestinal (2%). PN (11%) was only G1 /2. The relatively lower budget impact (compared with IMiD combinations) of this regimen makes it attractive to study in the frontline setting. Recently, the maximal tolerated dose of Carfilzomib in this triplet regimen was reported at be 56mg/m^2, given as in IV infusion, in combination with cyclophosphamide and dexamethasone[61]. This study was in newly diagnosed patients eligible for ASCT, and stem cell collection was successful in all patients who underwent mobilisation. Overall response rate was 91%, and toxicities were as expected: drug related AE's occurring in >20% of patients were fatigue and thrombocytopenia. This regimen is also being studied in a phase 2 randomised trials (Myeloma UK MUK5) in patients suffering first relapse of their disease. Hence experience of this triplet regimen in the relapse setting is growing in the UK. Pending data on efficacy and tolerability, this regimen has the potential to be incorporated into the phase 3 setting in national myeloma studies in the UK. The rationale for evaluating the role of ASCT upfront in newly diagnosed MM patients has been described above.

The Carfilzomib dose of 56mg/m^2 in newly diagnosed patients is also supported by a recent report from the Dutch group who updated their dose escalation study results with Carfilzomib, Thalidomide and Dexamethasone to establish an MTD of 56mg/m^2 [54,62]. At this dose level, 4 cycles of induction resulted in a VGPR rate of 75% (n=20). Toxicities were as expected: gastrointestinal, thrombosis (related to the thalidomide) and infections. Finally the dose of 56mg/m^2 is supported by recent data from the relapsed setting[63,64].

The potential for extending disease control by the use of low dose single agent maintenance therapy is an important question in MM therapy today. We propose a schedule of 56mg/m^2 on days 1, 8 and 15; this dose is well tolerated in the single agent setting when given on consecutive day dosing at 6 doses every month (see above), and a higher dose of 70mg/m^2 has been established as the MTD when used on a weekly regimen with dexamethasone (CHAMPION study, see above). Thus we propose a phase 2 study of carfilzomib, cyclophosphamide and dexamethasone (CarCyDex), as induction therapy, followed by a randomisation (of responding patients) to ASCT or consolidation with further 4 cycles of CarCyDex, and then fixed period maintenance with single agent carfilzomib on an attenuated regimen for all patients.

3. TRIAL DESIGN

This phase II study has two stages. The first stage will confirm the efficacy of the triplet regimen, carfilzomib, cyclophosphamide and dexamethasone (CarCyDex), thus the primary outcome measure is objective response (CR+VGPR). In the second stage, patients achieving at least a partial response to the induction regimen will be randomised to either ASCT or further CarCyDex. This second stage will estimate the benefit of upfront ASCT, for those patients who respond (≥PR) to CarCyDex. Specifically, patients randomised to receive 4 further cycles of CarCyDex (no ASCT arm) will be compared with patients randomised to receive ASCT, for PFS at 2 years.

PET-CT sub-study

We propose to use PET-CT scanning for baseline evaluation, and as response assessment following induction and consolidation (chemotherapy and ASCT arms) in order to explore the prognostic value of a metabolic response on both disease free and overall survival. Additionally, for those patients who are not in complete metabolic response (CMR) post-ASCT/consolidation, we will repeat PET-CT scanning after 6 months of maintenance treatment. Thus, we will be able to compare the impact of PET-CT response between patients receiving high dose chemotherapy and ASCT versus those continuing on chemotherapy in a prospective clinical trial using quality assured PET-CT. We will also be able to evaluate the activity of maintenance therapy in terms of improving functional response / increasing CMR rate on PET-CT scanning after 6 months.

Up to 120 patients will be recruited to the PET-CT sub-study. Allowing for withdrawals from trial treatment before the end of consolidation/transplant, it is anticipated that 100 patients will have both a baseline PET-CT scan and a response PET-CT scan after consolidation/ASCT.

PET scanning

Patients will undergo a minimum of two PET-CT scans, with a third as directed by results of the second scan; the first scan will be at baseline within 28 days prior to starting chemotherapy, the second scan will take place at 100 days post-ASCT (ASCT arm) or after 4 cycles of consolidation with Carfilzomib, Cyclophosphamide and Dexamethasone [CarCyDex] (Consolidation arm). The third scan will only be for patients who are not in complete metabolic response (CMR) on their PET-CT scans at the post-ASCT/consolidation chemotherapy time point. This third scan will take place after 6 months of maintenance therapy. These time points will coincide with the bone marrow testing for minimal residual disease (MRD).

Whole body PET-CT scans will be performed in centres accredited by the UK PET Core Lab, based at St Thomas' Hospital, London [www.ncri-pet.org.uk/] with standardised methods for scanning preparation, acquisition and quality control, used successfully in previous multicentre national and international trials[65].

Detailed information relating to the PET procedures is given in the CARDAMON imaging manual and in Appendix 9 of the protocol.

3.1. **Objectives:**

Primary

- To determine the efficacy (sCR and ≥VGPR) of the triple regimen Carfilzomib, Cyclophosphamide and Dexamethasone (CarCyDex) as induction in untreated patients with symptomatic MM who are candidates for ASCT
- To evaluate the benefit (PFS at 2 years) of upfront ASCT in patients achieving at least a PR to induction with CarCyDex

Secondary

- To determine the efficacy (ORR: sCR, CR, VGPR, PR and median PFS) of an upfront protocol incorporating induction with CarCyDex, ASCT and then carfilzomib maintenance in patients with untreated symptomatic MM who are candidates for ASCT (ASCT arm)
- To assess toxicity and tolerability of CarCyDex as induction and carfilzomib as maintenance therapy in untreated patients with symptomatic MM
- To determine the efficacy of maintenance therapy in deepening disease response, assessed as conversion from PR or VGPR to CR/sCR, and from MRD-positive to MRD-negative on MPF in the ASCT and non-ASCT setting
- To determine the efficacy (ORR: sCR, CR, VGPR, PR and median PFS) of an upfront protocol incorporating 8 cycles of CarCyDex followed by carfilzomib maintenance in patients with untreated symptomatic MM who are candidates for ASCT (non-ASCT arm)
- To determine rate of MRD-negative disease following 4 cycles of induction with CarCyDex
- To determine the increase in MRD-negative rate following ASCT versus consolidation with 4 further cycles of CarCyDex
- To determine the benefit (PFS2) of withholding ASCT until first relapse in patients with untreated symptomatic MM who are candidates for ASCT
- To investigate the effects of CarCyDex treatment and of withholding ASCT on patient quality of life

Exploratory objectives of the PET sub-study

- To investigate the association between PET-CT parameters at baseline with other disease markers and with disease response (all response categories, PFS, OS)
- To investigate the association between CMR on PET-CT with IMWG response and with MRD-negative response by flow cytometry

- To compare the CMR rate in ASCT versus consolidation chemotherapy arms
- To investigate the effect of achieving a CMR on PFS, and on OS
- To investigate the activity of 6 months of maintenance Carfilzomib in terms of conversion of PET-positive disease to PET-negative disease (CMR)

3.2. Endpoints:

Primary

- Major response rate (sCR, CR+VGPR) to 4 cycles of CarCyDex
- Progression free survival at 2 years, taken from the date of randomisation, for both ASCT and non-ASCT (consolidation) arms

Secondary

- Toxicity: AEs (including peripheral neuropathy (PN)), dose reductions and delays, tolerability of the induction and maintenance regimens (treatment delays, discontinuation rates)
- Disease response rate (sCR, CR, VGPR, PR) to CarCyDex induction
- PFS in both ASCT and non-ASCT arms
- PFS2 defined as the time from initial randomisation to second progression or death from any cause
- Improvement in disease response and conversion from MRD-positive to MRD-negative post ASCT and post Consolidation
- Improvement of disease response and conversion from MRD-positive to MRD-negative following maintenance therapy
- Quality of life in both ASCT and non-ASCT arms
- Overall survival

PET-CT endpoints (exploratory) for patients participating in PET-CT sub study

- CMR rate after consolidation/ASCT
- CMR conversion rate after 6 months of maintenance in patients who are PET + after consolidation/ASCT
- PET response association with IMWG and MRD response
- PFS association with baseline PET-CT parameters and PET-CT response
- OS association with baseline PET-CT parameters and PET-CT response
- Disease response (as measured by PET-CT) association with baseline PET-CT parameters

3.3. Trial Activation

UCL CTC will ensure that all trial documentation has been reviewed and approved by all relevant bodies and that the following have been obtained prior to activating the trial:

- Research Ethics Committee approval
- Clinical Trial Authorisation from the Medicines and Healthcare products Regulatory Agency (MHRA)
- 'Adoption' into NIHR portfolio
- NHS permission
- Adequate funding for central coordination
- Confirmation of sponsorship
- Adequate insurance provision

Prior to commencement of the PET-sub-study:

- ARSAC approval

4. SELECTION OF SITES/SITE INVESTIGATORS

4.1. Site Selection

In this protocol trial 'site' refers to the hospital where trial-related activities are conducted.

Sites must be able to comply with:

- Trial treatment, imaging, clinical care, follow up schedules and all requirements of the trial protocol
- Requirements of the UK Policy Framework for Health and Social Care Research, issued by the Health Research Authority and the Medicines for Human Use (clinical trials) Regulations (SI 2004/1031), and all amendments
- Data collection requirements, including adherence to CRF submission timelines as per section 11.3
- Biological sample collection, processing and storage requirements
- Monitoring requirements, as outlined in the protocol (section 14 and Monitoring Plan)

Sites participating in the PET-CT sub-study must also ensure:

- Relevant license(s) in relation to medical radiation exposure is/are in place before they can enter patients into the sub-study, and that licenses are renewed as necessary during the trial.

Selection of Principal Investigator and other investigators at sites

Sites must appoint an appropriate Principal Investigator (PI), i.e. a health care professional authorised by the site to lead and coordinate the work of the trial on behalf of the site. Co-investigators must be trained and approved by the PI. All investigators must be medical doctors and have experience of treating myeloma. The PI is responsible for the conduct of the trial at their site and for ensuring that any amendments are implemented in a timely fashion. If a PI leaves/goes on a leave of absence, UCL CTC **must be informed promptly** and a new PI identified and appointed by the site.

Training requirements for site staff

All site staff must be appropriately qualified by education, training and experience to perform the trial related duties allocated to them, which must be recorded on the site delegation log. Evidence of study-specific training should be filed in the ISF for all staff who join the team after initiation.

CVs for all staff must be kept up-to-date, signed and dated and copies held in the Investigator Site File (ISF). A current, signed copy of the CV for the PI, with evidence of GCP training (or copy of GCP certificate) must be forwarded to UCL CTC upon request.

GCP training is required for all staff responsible for trial activities. The frequency of repeat training may be dictated by the requirements of their employing institution, or 2 yearly

where the institution has no policy, and more frequently when there have been updates to the legal or regulatory requirements for the conduct of clinical trials.

4.2. Site initiation and Activation

4.2.1 Site initiation

Before a site is activated, the UCL CTC trial team will arrange a site initiation with the site which the PI, the pharmacy lead and site research team must attend. The site will be trained in the day-to-day management of the trial and essential documentation required for the trial will be checked.

Site initiation will be performed for each site by either teleconference or an on-site visit at the site. Re-initiation of sites may be required where there has been a significant delay between initiation and enrolling the first patient, as per the trial monitoring plan.

4.2.2 Required documentation

The following documentation must be submitted by the site to UCL CTC prior to a site being activated by UCL CTC trial team:

- Trial specific Site Registration Form (identifying relevant local staff)
- Relevant institutional approvals
- A completed site delegation log that is initialled and dated by the PI
- Signed and dated copy of the PI's current CV (with documented, up to date, GCP training, or a copy of GCP training certificate)
- Trial specific prescription & labels
- A signed Clinical Trial Site Agreement (CTSA) between the Sponsor and the relevant institution (usually a NHS Trust)

The following are required for sites participating in the PET sub-study only and must be in place before they can enter patients into the sub-study:

- Relevant license(s) relation to medical radiation exposure
- PET accreditation by the UK PET Core Lab

Site activation letter

Once the UCL CTC trial team has received all required documentation and the site has been initiated, a site activation letter will be issued to the PI, at which point the site may start to approach patients.

Once the site has been activated by UCL CTC, the PI is responsible for ensuring:

- adherence to the most recent version of the protocol;
- all relevant site staff are trained in the protocol requirements;
- appropriate recruitment and medical care of patients in the trial;
- timely completion and return of CRFs (including assessment of all adverse events);

- prompt notification and assessment of all serious adverse events, urgent events, pregnancies and lactational exposures;
- that the site has facilities to provide **24 hour medical advice** for trial patients.

5. INFORMED CONSENT

Sites are responsible for assessing a patient's capacity to give informed consent.

Sites must ensure that all patients have been given the current approved version of the patient information sheet, are fully informed about the trial and have confirmed their willingness to take part in the trial by signing the current approved consent form.

Sites must assess a patient's ability to understand verbal and written information in English and whether or not an interpreter would be required to ensure fully informed consent. If a patient requires an interpreter and none is available, the patient should not be considered for the trial.

The PI, or, where delegated by the PI, other appropriately trained site staff, are required to provide a full explanation of the trial and all relevant treatment options to each patient prior to trial entry. During these discussions, the current approved patient information sheet for the trial should be discussed with the patient.

A **minimum of twenty four (24) hours** should be allowed for the patient to consider and discuss participation in the trial. However, in order to prevent unnecessary return visits patients may consent on the same day as being given the information sheet, provided the member of staff taking consent is satisfied that the patient understands the trial and implications. A member of the research team at the hospital must then phone the patient in the following days to confirm that they are still willing to participate in the trial.

Written informed consent on the current approved version of the consent form for the trial must be obtained before any trial-specific procedures are conducted. The discussion and consent process must be documented in the patient notes.

Sites participating in the PET sub-study will use an additional Patient Information Sheet and Consent Form for the purposes of consenting patients to the sub-study. Participation in the sub-study is optional, and if a patient declines to take part in the sub-study, they can still be entered into the main trial.

Site staff are responsible for:

- checking that the current approved version of the patient information sheet and consent form are used;
- checking that information on the consent form(s) is complete and legible;
- checking that the patient has completed/initialled all relevant sections and signed and dated the form;
- checking that an appropriate member of staff has countersigned and dated the consent form to confirm that they provided information to the patient;
- checking that an appropriate member of staff has made dated entries in the patient's medical notes relating to the informed consent process (i.e. information given, consent signed etc.);
- giving the patient a copy of their signed consent form, patient information sheet, patient diary and patient contact card;

- following registration: adding the patient trial number to all copies of the consent form, which should be filed in the patient's medical notes and investigator site file

The right of the patient to refuse to participate in the trial without giving reasons must be respected. All patients are free to withdraw at any time. Also refer to section 15 (Withdrawal of Patients).

6. SELECTION OF PATIENTS

6.1. Pre-registration Evaluation (screening tests)

The following assessments or procedures are required to evaluate the suitability of patients for registration to the trial:

Assessments to be done within 14 days prior to registration:

- Haematology including full blood count and differential
- Biochemistry including renal function tests, creatinine clearance (as per local biochemistry protocols), liver function tests, calcium, phosphate and urate
- Pregnancy test in women of child bearing potential (urine or blood permitted)
- ECOG performance status
- ECG

Assessments to be done within 6 weeks prior to registration:

- Medical history including prior medications, treatments, surgical procedures and history of hypertension
- Physical examination
- Echocardiogram (or alternatively, MUGA with evidence of adequate left ventricular ejection fraction)
- Serum β2 microglobulin
- Disease staging (ISS)
- LDH
- Serum electrophoresis with paraprotein quantification
- Urinary electrophoresis
- 24-hr urinary Bence Jones Protein estimation (result required for registration if the patient has no measurable disease by paraprotein or serum free light chains)
- Serum Free light chains (Freelite)
- Immunoglobulins*

Assessments to be done within 3 months prior to registration:

- Virology:
    - HIV
    - Hepatitis B surface antigen (HBsAg), surface antibody (HBsAb), core antibody (HBcAb) (required) HBV DNA (if indicated)
    - Hepatitis C
- Bone marrow plasmacytosis (bone marrow aspirate and trephine)**
- Whole body imaging as per local site policy (e.g. CT, PET-CT or MRI. Skeletal survey should be performed only if other imaging options are unsuitable or if patient declines)**
- Cytogenetics/FISH***

* Results do not need to be available for registration

** Results do not need to be available for registration if diagnosis of multiple myeloma already confirmed by IMWG criteria (Appendix 2)

***Suggested list of FISH tests: IgH translocations: t(4;14), t(11;14), t(14;16), t(14:20) 17p del, 1p del, 1q gain, 13q del. An anonymised copy of the local cytogenetics report should be faxed / emailed to UCL

CTC with the registration form, or if results still pending at time of study registration, posted to UCL CTC as soon as available. Cytogenetics results must be sent to UCL CTC prior to randomisation. Sites not able to perform cytogenetics/FISH at baseline need to send an extra 4-8ml of bone marrow aspirate to the UCL Cancer Institute laboratory in addition to the 4-6mls baseline sample for Nf-kappaB pathway assay (see Appendix 8 for details)

Other results to be provided (test can be performed any time prior to registration, but where performed on more than one occasion, the most recent result should be provided):

- Immunofixation of serum **and** urine

If any results fall outside the timeframes above, they **must** be repeated prior to registration.

For patients who consent to the PET sub-study, within 28 days prior to starting chemotherapy:

- PET-CT scan from vertex to toes. Images are to be anonymised and sent to the UK PET Core Lab for central review.

N.B. baseline PET-CT can be performed after study registration, but must be prior to starting trial treatment. If performed prior to study registration, images should not be sent to the core lab until the patient has been registered.

Baseline quality of life

Baseline quality of life questionnaires (EQ5D, QLQ-C30 and QLQ-MY24) should be completed by the patient within 14 days prior to registration. If this is not possible, they may be completed at any time up to cycle 1 day 1 of treatment.

The following research samples must be taken and sent to the central once preliminary registration has been completed:

- Bone marrow aspirate for genomic and pathway tests to be sent to the Myeloma laboratory, UCL Cancer Institute *
- Peripheral blood sample for genomic and pathway tests to be sent to the Myeloma laboratory, UCL Cancer Institute *
- Bone marrow aspirate for Minimal Residual Disease to be sent to the HMDS *

* See Appendix 8 for full details for preparation and shipping of samples

Any non-routine procedures/investigations must not be performed prior to informed consent being taken.

In order to avoid unnecessarily repeating bone marrow biopsies for the trial research samples, it is recommended that the patient's disease is diagnosed based on their peripheral blood and radiology results. Patients should be consented, and provisionally registered into the trial prior to bone marrow investigations (see section 7.1 "Preliminary registration"). In rare circumstances where the patient is found to be ineligible for the Cardamon trial after preliminary registration, sites should inform UCL CTC who will request that all samples are destroyed by the trial laboratories.

6.2. Screening Log

A screening log must be maintained by the site and kept in the Investigator Site File. This must record each patient screened for the trial and the reasons why they were not registered in the trial if this is the case. The log must be sent to UCL CTC when requested, with patient identifiers removed prior to sending.

6.3. Patient Eligibility for registration

There will be no exception to the eligibility requirements at the time of registration. Queries in relation to the eligibility criteria must be addressed prior to registration. Patients are eligible for the trial if all the inclusion criteria are met and none of the exclusion criteria applies.

Patients' eligibility must be confirmed by an investigator who is suitably qualified and who has been allocated this duty, as documented on the site staff delegation log, prior to registering the patient. Confirmation of eligibility must be documented in the patient's notes and on the Full Registration CRF.

6.3.1 Inclusion criteria

- Previously untreated patients with symptomatic MM (see appendix 2) eligible for stem cell transplantation, with the exception of the following treatments:
    - local radiotherapy to relieve bone pain and/or spinal cord compression
    - bisphosphonates
    - corticosteroids within the last 3 months. Within 14 days prior to study entry, the maximum permitted dose is 160mg (i.e. 4 days of Dexamethasone at 40mg, or equivalent), unless otherwise agreed by the TMG.
- Suitable for high dose therapy and ASCT
- Age ≥ 18 years
- Life expectancy ≥ 3 months
- Eastern Cooperative Oncology Group (ECOG) performance status 0–2), except:
    - ECOG >2 is permissible if resulting from complications related to myeloma (i.e. due to spinal cord compression). Please check with UCL CTC if unsure as to whether this exception may be applicable.
- Measurable disease as defined by one of the following:
    - Secretory myeloma:
        - **Either** monoclonal protein in the serum (≥10 g/L)
        - **Or** monoclonal light chain in the urine (Bence Jones protein ≥200mg/24hours)
        - **Or** serum free light chain (SFLC, involved light chain ≥100mg/L provided the FLC ratio is abnormal)
    - Non-secretory myeloma:

- **Either** ≥30% clonal plasma cells in bone marrow (aspirate or trephine)
- **Or** 10-30% clonal plasma cells in the marrow and >1 soft tissue or extra-osseous plasmacytoma ≥ 2 cm that is measurable for response assessment by CT or MRI

- Adequate hepatic function, with serum ALT ≤ 3.5 times the upper limit of normal and serum direct bilirubin ≤ 2 mg/dL (34 µmol/L) within 14 days prior to registration
- Absolute neutrophil count (ANC) ≥ 1.0 × 10^9/L within 14 days prior to registration and subject has not received any growth factor support within 7 days of testing. ANC≥0.8x10^9/L allowed for patients with racial neutropenia.
- Haemoglobin ≥ 8 g/dL (80 g/L) within 14 days prior to registration (subjects may be receiving red blood cell (RBC) transfusions in accordance with institutional guidelines)
- Platelet count ≥ 75 × 10^9/L (≥ 50 × 10^9/L if myeloma involvement in the bone marrow is > 50%) within 14 days prior to registration and subject has not received any platelet transfusions within 7 days prior to testing
- Creatinine clearance (CrCl) ≥ 30 mL/minute within 14 days prior to registration, either measured or calculated using a standard formula (e.g. Cockcroft and Gault)
- Written informed consent
- Females of childbearing potential (FCBP) must agree to ongoing pregnancy testing and to practice contraception
- Male subjects must agree to practice contraception

6.3.2 Exclusion criteria

- Pregnant or breast-feeding females (lactating women may participate if breastfeeding ceases for the duration of trial treatment and until 12 months after last treatment)
- Previous systemic chemotherapy for myeloma, with the exception of steroids, as detailed above (see section 6.3.1)
- Any major surgery within 21 days prior to registration which in the investigator's opinion would compromise trial treatment and/or the patient's ability to comply with trial visits. Surgery to relieve spinal cord compression or for treatment of bone fractures is permitted
- Acute active infection requiring treatment (systemic antibiotics, antivirals, or antifungals) 7 days prior to planned start of treatment, unless otherwise agreed by the TMG
- Known human immunodeficiency virus (HIV) infection
- Active hepatitis B or C infection (refer to appendix 4)

- Unstable angina or myocardial infarction within 4 months prior to registration, NYHA Class III or IV heart failure, uncontrolled angina, history of severe coronary artery disease, severe uncontrolled ventricular arrhythmias, sick sinus syndrome, or electrocardiographic evidence of acute ischemia or Grade 3 conduction system abnormalities unless subject has a pacemaker
- Uncontrolled hypertension or uncontrolled diabetes within 14 days prior to registration
- Non-haematologic malignancy within the past 3 years with the exception of a) adequately treated basal cell carcinoma, squamous cell skin cancer, or thyroid cancer; b) carcinoma in situ of the cervix or breast; c) prostate cancer of Gleason Grade 6 or less with stable prostate-specific antigen levels; or d) cancer considered cured by surgical resection or unlikely to impact survival during the duration of the study, such as localised transitional cell carcinoma of the bladder or benign tumors of the adrenal or pancreas
- Significant neuropathy (Grades 3–4, or Grade 2 with pain) within 14 days prior to registration
- Known history of allergy to Captisol® (a cyclodextrin derivative used to solubilise carfilzomib)
- Contraindication to any of the required concomitant drugs or supportive treatments, including hypersensitivity to all anticoagulation and antiplatelet options, antiviral drugs, or intolerance to hydration due to preexisting pulmonary, cardiac or renal impairment
- Patients with pleural effusions requiring thoracentesis or ascites requiring paracentesis within 14 days prior to registration
- Any other clinically significant medical disease or condition that, in the Investigator's opinion, may interfere with protocol adherence or a subject's ability to give informed consent

6.4. Pregnancy and birth control

Definition of women of childbearing potential (WOCBP) and fertile men:

A woman of childbearing potential (WOCBP) is a sexually mature woman (i.e. any female who has experienced menstrual bleeding) who has not:

- undergone a hysterectomy or bilateral oophorectomy/salpingectomy
- been postmenopausal for 12 consecutive months (i.e. who has not had menses at any time in the preceding 12 consecutive months without an alternative medical cause)
- had premature ovarian failure confirmed by a specialist gynaecologist
- XY genotype, Turner syndrome, uterine agenesis

A man is considered fertile after puberty unless permanently sterile by bilateral orchidectomy.

Risk of Exposure to trial treatment during pregnancy

The risk of exposure to trial treatment has been evaluated using the safety information available in the Investigator Brochure for carfilzomib and Summary of Product Characteristics for cyclophosphamide, dexamethasone and melphalan. Overall the trial treatment has been assessed as having a high risk of teratogenicity/fetotoxicity and genotoxicity.

Females of childbearing potential should be advised to avoid becoming pregnant while being treated with carfilzomib. Given that carfilzomib was clastogenic in the in vitro chromosomal aberration test in peripheral blood lymphocytes, as a precaution, females of childbearing potential and/or their male partners should use highly effective contraception methods or abstain from sexual activity (if in line with the preferred lifestyle of the patient) during and for 30 days after treatment with carfilzomib. If pregnancy occurs during this time, patients should be apprised of the potential hazard to the foetus.

It is not known if carfilzomib will reduce the efficacy of oral contraceptives. Due to an increased risk of venous thrombosis associated with carfilzomib, subjects currently using a hormonal method of contraception associated with a risk of thrombosis should use an alternative method of highly effective contraception.

Based on its mechanism of action and findings in animals, carfilzomib may cause fetal harm when administered to a pregnant woman. Carfilzomib caused embryo-fetal toxicity in pregnant rabbits at doses that were lower than the recommended dose.

Cyclophosphamide is genotoxic and mutagenic, both in somatic and in male and female germ cells. Therefore, women should not become pregnant and men should not father a child during therapy with cyclophosphamide. Both women and men should wait at least 6 to 12 months after stopping cyclophosphamide before attempting to conceive or father a child.

Animal data indicate that exposure of oocytes during follicular development may result in a decreased rate of implantations and viable pregnancies, and in an increased risk of malformations. This effect should be considered in case of intended fertilization or pregnancy after discontinuation of cyclophosphamide therapy. The exact duration of follicular development in humans is not known, but may be longer than 12 months. Sexually active women and men should use effective methods of contraception during these periods of time.

The ability of corticosteroids to cross the placenta varies between individual drugs, however, dexamethasone readily crosses the placenta.

Administration of corticosteroids to pregnant animals can cause abnormalities of foetal development including cleft palate, intra-uterine growth retardation and effects on brain growth and development. There is no evidence that corticosteroids result in an increased incidence of congenital abnormalities, such as cleft palate/lip in man. However, when administered for prolonged periods or repeatedly during pregnancy, corticosteroids may increase the risk of intra-uterine growth retardation. Hypoadrenalism may, in theory,

occur in the neonate following prenatal exposure to corticosteroids but usually resolves spontaneously following birth and is rarely clinically important. As with all drugs, corticosteroids should only be prescribed when the benefits to the mother and child outweigh the risks. When corticosteroids are essential however, patients with normal pregnancies may be treated as though they were in the nongravid state.

The manufacturers of melphalan state that it is possible that this drug could cause congenital defects. No formal pregnancy risk window is stated, but the manufacturers warn that melphalan should not be given during pregnancy, and women should not breastfeed while taking melphalan.

Based on the information above, the pregnancy risk window for this trial is from start of treatment until 12 months post trial treatment.

Pregnancy testing

All female participants who are WOCBP must undergo a pregnancy test as part of trial screening, and within 14 days prior to starting treatment. Pregnancy testing must be maintained monthly on day 1 of each cycle until the last treatment cycle, and at the end of treatment. Testing should be done in line with local practice (i.e. serum or urine).

Contraception advice

Requirements for female patients

All female participants who are WOCBP must consent to use one of the following methods of highly effective contraception from full study registration until 12 months post last trial treatment administration. Methods with low user dependency are preferable, particularly where introduced as a result of participation in the trial.

- progestogen-only hormonal contraception associated with inhibition of ovulation:
  - oral (e.g. desogestrel)[1]
  - injectable
  - implantable[2]
- intrauterine device (IUD)[2]
- intrauterine hormone-releasing system (IUS)[2]
- bilateral tubal occlusion[2]
- vasectomised partner[2,3]
- sexual abstinence[4]

1. Hormonal contraception may be susceptible to interaction with the IMP/NIMP, which may reduce the efficacy of the contraception method. Combined contraceptives are not recommended due to the increased risk of thromboembolic events.

2. Contraception methods that are considered to have low user dependency.

3. Vasectomised partner is a highly effective birth control method provided that partner is the sole sexual partner of the WOCBP trial participant and that the vasectomised partner has received medical assessment of the surgical success.

4. Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.

Requirements for male patients with female partners who are pregnant or WOCBP:

Due to the risk of genotoxicity and/or risk to the foetus from exposure to seminal fluid:

- Male patients (including male patients who have had vasectomies) must consent to use condoms with female partners who are WOCBP or partners who are pregnant, from full study registration until 12 months post last trial treatment administration.
- Male patients must also advise their female partners who are WOCBP regarding contraceptive requirements as listed for female patients who are WOCBP.

Requirements for all male patients:

Males must not donate sperm for at least 12 months after the last dose of trial treatment.

For female and male patients:

The method(s) of contraception used must be stated in the patient medical notes. The medical notes of male participants should include a statement that the female partner has been informed about contraception advice.

Action to be taken in the event of pregnancy

Female patients:

If a female patient becomes pregnant

- prior to initiating treatment, the patient will not receive trial treatment unless they elect to have a termination (please note, in such instances, termination must be the patient's own choice)
- during treatment, the patient will be withdrawn from further treatment and, if they consent to pregnancy monitoring, followed up until pregnancy outcome
- after the end of the treatment, but during the pregnancy at-risk window (12 months post treatment), the patient will be followed up until pregnancy outcome if they consent to pregnancy monitoring.

Male patients:

If a female partner of a male patient becomes pregnant between the patient's informed consent and 12 months after the end of treatment, the male participant can continue with the study if they agree to use condoms in line with the protocol. Their partner will be followed up if they have given consent to pregnancy monitoring.

Notification to UCL CTC – see section 12.6 (Pregnancy and Lactational Exposure).

Long term infertility

The effect on human fertility is unknown for carfilzomib, however, cyclophosphamide has been shown to interfere with oogenesis and spermatogenesis. It may cause sterility in

both sexes. Cyclophosphamide-induced sterility may be irreversible in some patients. Investigators should discuss these risks with patients, as appropriate, prior to consent and trial registration.

It is recommended that men wanting to father children should preserve unexposed sperm prior to commencing chemotherapy.

Lactation

Mothers should be advised against breast-feeding while receiving trial treatment and for one year afterwards. If the patient is not willing to give up breastfeeding, they will be deemed ineligible for trial (see section 6.3 above).

Notification to UCL CTC – see section 12.6 (Pregnancy and Lactational Exposure).

7. REGISTRATION PROCEDURES

7.1. Preliminary Registration

The purpose of preliminary registration is to allow patients likely to be eligible for the trial but where final confirmation of eligibility based on their bone marrow biopsy is pending, to be allocated a trial number for use when sending baseline tissue samples to the UCL Cancer Institute and HMDS (see appendix 8 for details). This will facilitate the sample tracking process and potentially avoid the need for repeat bone marrow biopsies.

In order to undertake preliminary registration, the following criteria must be met:

- The patient must have given written informed consent for the trial
- The site investigator must have confirmed the patient is potentially eligible based on their peripheral blood and radiology results
- The patient's bone marrow biopsy must have been scheduled.

The site must then complete the preliminary registration form and send it to the UCL CTC via fax or email, before sending samples to the central laboratories.

Registration/Randomisation fax number:	020 7679 9861
Registration/Randomisation email address:	ctc.cardamon@ucl.ac.uk
UCL CTC Office hours:	09:00 to 17:00 Monday to Friday (UK time)
Telephone number for enquiries:	020 7679 9860

N.B. If the site is unable to fax, pre-registration forms may be sent by email. If emailing forms, two copies of the original must be taken and patient identifiable information (e.g. NHS number, day and month of birth) must be redacted on one copy before it is emailed to ctc.cardamon@ucl.ac.uk. The identifiable information must be provided to UCL CTC via telephone so that UCL CTC can transcribe this information onto the form. The second photocopy must be posted to UCT CTC, and the original kept in the patient file at site.

Once UCL CTC has confirmed that the patient has been consented appropriately and is provisionally eligible for the trial, they will assign a unique trial number for the patient and email confirmation of the trial number to the main contact for the site.

This trial number will remain the patient's unique trial identifier throughout the trial, and should be used for all samples sent during the trial.

The patient must **under no circumstances start any trial treatment** until the patient has completed the full registration process (see section 7.2) and the UCL CTC have confirmed that the patient may start trial treatment.

Preliminary registration is not mandatory, but is strongly advised. If eligibility has already been confirmed based on a clinical bone marrow biopsy performed prior to trial consent, the site may proceed straight to use of the full registration form. In these instances, patients will need to have a repeat biopsy to obtain the required research samples.

If, after being allocated a trial number, a patient is found to be ineligible for the trial, and will not be proceeding to full registration, the site must inform the UCL CTC, quoting

the patient's unique trial number and date of sample dispatch. The UCL CTC will then contact all trial laboratories to request destruction of the patient's samples and will email the site to confirm destruction.

7.2. Full Registration

Full patient registration will be undertaken centrally at UCL CTC, and must be performed prior to commencement of any trial treatment.

Following pre-treatment evaluations (as detailed in section 6.1), confirmation of eligibility and consent of a patient at a site, the registration form must be fully completed and then faxed or emailed to UCL CTC. The faxed/emailed registration form will be used to confirm patient eligibility at UCL CTC.

N.B. If the site is unable to fax, registration forms may be sent by email. If emailing forms, two copies of the original must be taken and patient identifiable information (e.g. NHS number, day and month of birth) must be redacted on one copy before it is emailed. The identifiable information must be provided to UCL CTC via telephone so that UCL CTC can transcribe this information onto the form. The second photocopy must be posted to UCT CTC, and the original kept in the patient file at site.

UCL CTC will e-mail confirmation of the patient's inclusion in the trial, and that the patient may commence trial treatment, to the main contact and pharmacy.

Once a patient is fully registered onto the trial they must be provided with the following:

- A copy of their signed consent form and patient information sheet
- A patient contact card. Site on-call contact details for 24 hour medical care must be added to this card and patients advised to carry this with them at all times while participating in the trial

An anonymised copy of the patient's baseline cytogenetics results must be sent to UCL CTC either with the registration CRF or, if results are pending, as soon as possible after registration.

After registration, samples of the diagnostic bone marrow trephine (paraffin-embedded tumour block or 15 unstained slides) must be sent to the central laboratory (Department of Research Pathology, UCL; see appendix 8 for details). Sites may wish to send trephine blocks for their patients in batches; these should be sent at least once every 3 months.

7.3. Randomisation

Patient randomisation will be undertaken centrally at UCL CTC following the completion of 4 cycles of induction chemotherapy and peripheral blood stem cell harvest for all patients that achieve a partial response or better. Patients will not be eligible for randomisation if they cannot continue carfilzomib due to toxicity.

Patients will be randomised 1:1 using minimisation, stratified by:

- Site
- Depth of response (a response of VGPR or better against PR)

- ISS stage (stage I against stages II and III; see appendix 5)
- Genetic risk (high risk against standard and low risk). High risk is defined as any ONE of the following findings on FISH analysis of selected CD138+ cells:
    - IgH translocation t(4;14), t(14;16) or t(14;20)
    - Deletion 17p (if present in ≥50% of cells)
    - 1p deletion and /or 1q gain

  Patients with failed cytogenetics/FISH samples will be stratified as "Failed".

Randomisation must be performed prior to the initiation of further trial treatment.

The 'PBSCH, Post-PBSCH and Randomisation CRF' must be fully completed, and signed by the local PI then faxed or emailed to UCL CTC. The faxed form will be used to confirm eligibility prior to randomisation at UCL CTC.

Once eligibility has been confirmed and the patient has been randomised, UCL CTC will e-mail confirmation of the treatment allocation to the main contact and pharmacy.

7.4. **Initial Trial Drug Supply**

Refer to Summary of Drug Arrangements (SoDA) for details of initial supply of carfilzomib for the trial.

The initial supply of carfilzomib to a site will be triggered upon activation of the site, and will be delivered to pharmacy at site in accordance with the Summary of Drug Arrangements.

Cyclophosphamide and dexamethasone are to be supplied from hospital commercial stock as detailed in the Summary of Drug Arrangements.

8. TRIAL TREATMENT

8.1. Investigational Medicinal Products

For the purpose of this protocol, the IMPs are:

- Carfilzomib (during induction, consolidation and maintenance)
- Cyclophosphamide (during induction and consolidation)
- Dexamethasone (during induction and consolidation).

For the purpose of this protocol, melphalan is a non-investigational medicinal product (NIMP). Dexamethasone is regarded as a NIMP during maintenance.

Carfilzomib

Description

Carfilzomib is a synthetic small molecule peptide bearing the chemical name (2S)-N-((S)-1-((S)-4-methyl-1-((R)-2-methyloxiran-2-yl)-1-oxopentan-2-ylcarbamoyl)-2-phenylethyl)-2-((S)-2-(2-morpholinoacetamido)-4-phenylbutanamido)-4-methylpentanamide. The molecular formula is $C_{40}H_{57}N_5O_7$ and the molecular weight is 719.91. It specifically functions as an inhibitor of the chymotrypsin-like activity of the 20S proteasome which leads to the accumulation of protein substrates within the cell and induction of apoptosis.

Carfilzomib is licensed in the EU in combination with lenalidomide and dexamethasone to treat adults with multiple myeloma who have received at least one prior therapy. It is licensed in the US (as Kyprolis®) for the treatment of patients with multiple myeloma who have received at least two prior therapies, including bortezomib and an immunomodulatory agent, and have demonstrated disease progression on or within 60 days of completion of the last therapy.

Supply

Carfilzomib will be manufactured in Greenville, NC, USA by Pantheon Manufacturing Services LLC and supplied for the trial by Amgen Ltd (US). It will be labelled and distributed to UK sites by Amgen Ltd (US) or their delegated distributor who will perform the final QP release.

Formulation

Carfilzomib for Injection will be provided as a lyophilised powder which, when reconstituted, contains 2 mg/mL isotonic solution of carfilzomib Free Base in 10 mM sodium citrate buffer (pH 3.5) containing 10% (w/v) sulfobutylether-β-cyclodextrin (SBE-β-CD, Captisol®).

Storage

Lyophilised Carfilzomib for Injection must be stored at 2–8ºC under the conditions outlined in the Summary of Drug Arrangements, in a securely locked area to which access is limited to appropriate study personnel.

Drug Preparation and Administration.

- Please refer to the Summary of Drug Arrangements for guidance on reconstitution. Please note the following: Carfilzomib is to be dose-capped at 2.2m^2 BSA.

  The dose of carfilzomib may be rounded to the nearest ml.

  Dose banding is permitted for all IV IMPs as per national guidelines (dose capped at maximum 2.2m^2BSA).
- **IV hydration** will be given immediately prior to carfilzomib during Cycle 1. This will consist of 250 to 500 mL normal saline or other appropriate IV fluid to be administered as per local policies. If lactate dehydrogenase (LDH) or uric acid is elevated (and/or in subjects considered still at risk for TLS) at Cycle 2 Day 1, then the recommended IV hydration should be given additionally before each dose in Cycle 2. The goal of the hydration program is to maintain robust urine output (e.g. ≥ 2 L/day). Subjects should be monitored regularly during this period for evidence of fluid overload.
- If the subject has a dedicated line for carfilzomib administration, the line must be flushed with a minimum of 20 mL of normal saline prior to and after drug administration.
- Carfilzomib will be given as an IV infusion over 30 minutes. The dose will be administered at a facility capable of managing hypersensitivity reactions. Subjects will remain at the clinic under observation for at least 1 hour following each dose of carfilzomib in Cycle 1, after which it can be dropped unless clinically necessary. During these observation times, **post dose IV hydration** (up to 500 mL normal saline or other appropriate IV fluid formulation) may be given at the discretion of the treating clinician. Subjects should be monitored periodically during this period for evidence of fluid overload. Further details of pre- and post-dose hydration, and for management of TLS, are given under Section 8.4.
- In cycle 1, it is recommended that subjects are weighed at least once each week, e.g. on days 1, 8 and 15 prior to treatment on those days. A weight gain of >5% of body weight may indicate fluid overload, and appropriate measures (e.g. omitting IV hydration, or even administering a small dose of a diuretic) should be taken.
- In those subjects considered at risk for TLS additional oral hydration may be considered at the local Investigator's discretion. Subjects should be monitored for evidence of fluid overload.

Cyclophosphamide

Cyclophosphamide is a standard treatment for multiple myeloma and cyclophosphamide tablets and powder for solution for injection or infusion will be supplied from pharmacy stock (at sites' own cost).
Dose banding is permitted for all IV IMPs as per national guidelines.

Dexamethasone

Dexamethasone is a standard treatment for multiple myeloma and dexamethasone tablets and solution for injection or infusion will be supplied from pharmacy stock (at sites' own cost).

Dose banding is permitted for all IV IMPs as per national guidelines.

8.2. Treatment summary

8.2.1. Induction treatment

All patients will receive 4 cycles of carfilzomib, cyclophosphamide and dexamethasone (CarCyDex) as follows.

Carfilzomib	IV	20mg/m^2*/56mg/m^2	Days 1, 2, 8, 9, 15 and 16
Cyclophosphamide	Oral**	500mg	Days 1, 8 and 15
Dexamethasone	Oral**	40 mg	Days 1, 8, 15 and 22

* cycle 1, days 1 and 2 only
**Patients who are unable to swallow tablets due to complications of disease may receive cyclophosphamide as an IV infusion or injection at a dose of 375mg. Dexamethasone tablets may be dissolved, or given as an IV infusion or injection at a dose of 40mg if required. Dose banding is permitted for all IV IMPs as per national guidelines. Tablets should be commenced as soon as the patient is able to swallow.

This cycle is repeated every 28 days. Response should be assessed at the start of each cycle, and in the absence of disease progression or intolerance, participants should receive 4 cycles of treatment. Start of cycle/within cycle during induction treatment can be delayed by up to 2 weeks. In exceptional cases where the delay is longer than this, please contact the UCL CTC.

Schedule of treatment for induction (4 x 28 day cycles)

Day	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Car	X*	X*						X	X					
Cy	X							X						
Dex	X							X						

Day	15	16	17	18	19	20	21	22	23	24	25	26	27	28
Car	X	X												
Cy	X													
Dex	X							X						

Car: carfilzomib 20mg/m^2 (c1 d1/d2) or 56mg/m^2 (all subsequent doses) by IV infusion over 30 minutes
Cy: cyclophosphamide 500 mg po (or 375mg IV if patient is unable to swallow tablets)
Dex: dexamethasone 40 mg po (or 40 mg IV if patient is unable to swallow tablets). Additional dexamethasone at 4mg po/IV prior to carfilzomib doses during cycle 1.
See section 8.3 (Dose modifications) for details of dose adjustments to be made due to adverse events.

Supportive care for patients receiving induction carfilzomib: These are as described for carfilzomib under section 8.4. Note in particular the section on monitoring, prophylaxis and treatment of TMA.

At the beginning of each cycle, patients must be given a diary card to record the number of oral dexamethasone and cyclophosphamide taken at home and any adverse events they experience. The diary should be collected at the end of each cycle, along with any unused tablets, reviewed and filed as source data.

At the end of 4 cycles, patients will be assessed for disease response using blood and urine tests as appropriate. Note that bone marrow assessment will take place after stem cell harvesting (see below).

Patients who fail to achieve a PR or better should be withdrawn from trial treatment. The Treatment Summary CRF must be completed and submitted to UCL CTC promptly. The recommended second line treatment is bortezomib, thalidomide, and dexamethasone (VTD), however, the patient's treatment is at the discretion of the treating investigator. See section 9.7 for details of the follow up schedule for these patients.

8.2.2 PBSC Mobilisation and PBSC Harvest

All patients achieving at least a PR (see appendix 3) will undergo peripheral blood stem cell harvest (PBSCH).

- Mobilisation should be at least 4 weeks from the end of induction therapy. The optimum time from the end of induction therapy to mobilization is 4-6 weeks, and

should be performed within a maximum of 12 weeks. Delays beyond this should be discussed with the Chief Investigator

- Premobilisation investigations shall be performed according to local policy
- A suggested mobilization regimen is Cyclophosphamide (1.5-3.0 gm/m^2), followed by daily G-CSF until day of harvest
- During mobilization, local supportive care protocols should be followed
- PBSC harvest should be performed using local protocols
- It is suggested that at least 2 x 10^6 CD34+ cells/kg be harvested
- Timing of the PBSC harvest should be coordinated by estimating the peripheral blood CD34+ cell count, detected by flow cytometry. The PBSC harvest product should be analysed for the CD34+ cell content, by flow cytometry. These estimations should be evaluated using the ISHAGE protocol[66]. If lower numbers are used this should be done based on local experience with their technology and numbers

8.2.3 Inadequate PBSC harvest

Patients failing to mobilise adequate numbers of PBSC (≥2x10^6 CD34+ cells/kg), may undergo a second mobilisation strategy, according to local protocols. Second mobilisation should aim to be completed within 6 weeks of the first mobilisation. In the event of patients failing to mobilise adequate numbers of PBSC at a second mobilisation, the patient will be withdrawn from trial treatment, and future management will be at the local investigator's discretion. The Treatment Summary CRF must be completed and submitted to UCL CTC promptly. See section 9.7 for details of the follow up schedule for these patients.

Bone marrow aspirate and trephine samples should be obtained prior to the second mobilisation in order to assess disease, even if the patient is subsequently taken off study.

8.2.4 Post-PBSCH response assessment

All patients will undergo full disease response assessment including local bone marrow aspirate and trephine to assess plasma cell infiltration after PBSCH and before starting consolidation or ASCT.

The following research sample must be taken up to 14 days after PBSCH and sent to the central laboratory:

- Bone marrow aspirate for Minimal Residual Disease (MRD) testing, to be sent to the HMDS

Following successful PBSCH, eligible patients will be randomised to ASCT or consolidation (see section 7.3 for details).

8.2.5 High dose melphalan and ASCT

Pre-ASCT investigations should follow local policy, and transplant conditioning should also follow local protocols. Patient should proceed to transplant as soon as possible after

randomisation, and high dose melphalan should be given no more than 4 weeks after randomisation. Disease response will be fully assessed at 100 days post-ASCT. The Day 100 Post-ASCT CRF must be completed and submitted at the time of the day 100 post-ASCT visit.

The following research samples must be taken 100 days post ASCT (+/- 14 days) and sent to the central laboratories:

- Bone marrow aspirate for Minimal Residual Disease (MRD) testing to be sent to HMDS
- Bone marrow aspirate for genomic pathway analysis (Nf-kappaB and UPR) to be sent to the Myeloma laboratory, UCL Cancer Institute
- Peripheral blood sample for genomic tests to be sent to the Myeloma laboratory, UCL Cancer Institute

See appendix 8 for further details

For patients participating in the PET-CT sub-study, a PET-CT must also be performed between d100-d128 post ASCT (must be performed prior to starting maintenance). Images must be sent to the PET core laboratory for central review within 2 weeks of receipt.

A simplified result of the central review will be provided to the site (CMR or not CMR); as this is an exploratory investigation, the central review result must not be used to inform the local investigator's post-transplant response assessment, nor should it be used to guide treatment decisions.

8.2.6 Consolidation with 4 cycles of CarCyDex

Participants randomised to consolidation will receive 4 further cycles of CarCyDex

Carfilzomib	IV	20mg/m^2*/56 mg/m^2	Days 1, 2, 8, 9, 15 and 16
Cyclophosphamide	Oral**	500mg	Days 1, 8 and 15
Dexamethasone	Oral**	20 mg	Days 1, 8, 15 and 22

* cycle 1, days 1 and 2 only

** Patients who are unable to swallow tablets due to complications of disease may receive cyclophosphamide as an IV infusion or injection at a dose of 375mg. Dexamethasone tablets may be dissolved, or given as an IV infusion or injection at a dose of 20mg if required. Dose banding is permitted for all IV IMPs as per national guidelines. Tablets should be commenced as soon as the patient is able to swallow.

Consolidation treatment should commence within 2 weeks of randomisation wherever possible, and no more than 4 weeks post randomisation. From cycle 2, start of cycle/within cycle can be delayed by up to two weeks. In exceptional cases where the delay is longer than this, please contact the UCL CTC.

Schedule of treatment for Consolidation (non-ASCT arm only, 4 x 28 day cycles)

Day	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Car	X*	X*						X	X					
Cy	X							X						
Dex	X							X						

Day	15	16	17	18	19	20	21	22	23	24	25	26	27	28
Car	X	X												
Cy	X													
Dex	X							X						

Car: carfilzomib 20mg/m^2 (c1 d1/d2) or 56mg/m^2 (all subsequent doses) by IV infusion over 30 minutes
Cy: cyclophosphamide 500 mg po (or 375mg IV infusion or injection if required)
Dex: dexamethasone 20 mg po (or 20mg IV infusion or injection if required). Additional dexamethasone at 4mg po/IV prior to carfilzomib doses during cycle 1.
See section 8.3 (Dose modifications) for details of dose adjustments to be made due to adverse events.

Supportive care for patients receiving consolidation carfilzomib: These are as described for carfilzomib under section 8.4. Note in particular the section on monitoring, prophylaxis and treatment of TMA.

At the beginning of each cycle, patients must be given a diary card to record the number of oral dexamethasone and cyclophosphamide taken at home. The diary should be collected at the end of each cycle, along with any unused tablets, reviewed and filed as source data.

Response should be assessed at the start of each cycle, and full disease assessment will be done at the end of the 4 cycles of consolidation. The Post-Consolidation CRF must be completed and submitted at the end of Consolidation.

The following research samples must be taken and sent to central laboratories within 28 days of completing 4 cycles of consolidation, and prior to starting maintenance:

- Bone marrow aspirate for Minimal Residual Disease (MRD) testing to be sent to HMDS
- Bone marrow aspirate for genomic pathway analysis (Nf-kappaB and UPR) to be sent to the Myeloma laboratory, UCL Cancer Institute
- Peripheral blood sample for genomic tests to be sent to the Myeloma laboratory, UCL Cancer Institute

For patients participating in the PET-CT sub-study, a PET-CT must also be performed within 14-28 days of completing Consolidation and prior to starting Maintenance. Images must be sent to the PET Core Lab for central review.

A simplified result of the central review will be provided to the site (CMR or not CMR); as this is an exploratory investigation, the central review result must not be used to inform the local investigator's post-consolidation response assessment, nor should it be used to guide treatment decisions.

8.2.7 Maintenance with carfilzomib

Maintenance therapy should commence within 4 weeks of completing consolidation (Consolidation arm patients), or between 3 and 4 months post ASCT (for ASCT arm patients). If for logistical reasons this is not possible, please contact the UCL CTC for advice.

All participants who do not have progressive disease at this point will receive Carfilzomib 56mg/m^2 on days 1, 8 and 15 every 28 days, **except for cycle one day 1, when they will receive 20mg/m^2*. Each dose of carfilzomib will be administered with dexamethasone 10mg (IV or PO). Start of cycle/within cycle during maintenance treatment can be delayed by up to 4 weeks. In exceptional cases where the delay is longer than this, please contact the UCL CTC.

The carfilzomib step up dosing in this phase is to reduce the risk of reactions and AEs (see below), especially if patients have had a break from carfilzomib therapy. In addition to the dose of pre-med Dexamethasone, described above, an additional dose of dexamethasone 10mg PO will be given the day after dosing throughout maintenance, with dose reductions for toxicity as in section 8.3.3. If the clinician is considering reducing the dose of Dexamethasone for reasons other than steroid induced toxicity this must be discussed and agreed with the TMG and the patient must be counselled that if side-effects due to carfilzomib occur, the dose may need to be increased.

Maintenance will continue for 18 months or until disease progression, withdrawal for toxicity or other reason. Disease assessment will take place at the start of every cycle (i.e. on day 1 of the cycle). Patients will be monitored for progression.

There is no plan currently to provide carfilzomib to patients outside the trial.

Schedule of treatment for Maintenance - 28 day cycles for 18 months or until disease progression

Day	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Car	X*							X						
$Dex_{IV/PO}$	X							X						
Dex_{PO}		X							X					

Day	15	16	17	18	19	20	21	22	23	24	25	26	27	28
Car	X													
$Dex_{IV/PO}$	X													
Dex_{PO}		X												

Car: carfilzomib 20mg/m^2 (c1 d1) or 56mg/m^2 (all subsequent doses) by IV infusion over 30 minutes
$Dex_{IV/PO}$: dexamethasone 10 mg (IV or PO as pre-medication for carfilzomib)
Dex_{PO}: dexamethasone 10mg (PO)

See section 8.3 (Dose modifications) for details of dose adjustments to be made due to adverse events.

Supportive care for patients receiving maintenance carfilzomib: These are as described for carfilzomib under section 8.4. Note in particular the section on monitoring, prophylaxis and treatment of TMA.

The following research sample must be taken and sent to the central laboratory 6 months post start of maintenance * (+/- 14 days; for logistical reasons where this is not possible, please contact UCL CTC for further guidance):

- Bone marrow aspirate for Minimal Residual Disease (MRD) testing to be sent to HMDS

*The sample should be taken even if patient is no longer on maintenance at 6 months.

For patients participating in the sub-study who remained PET positive after consolidation/ASCT, a PET-CT must also be performed within 28 days after completing six cycles (6 months) of maintenance. Images must be sent to the PET Core Lab for central review.

A simplified result of the central review will be provided to the site (CMR or not CMR); as this is an exploratory investigation, the central review result must not be used to inform the local investigator's post-consolidation response assessment, nor should it be used to guide treatment decisions.

8.3. Dose Modifications

Dose modifications are listed separately below for each IMP in the study. Sites should ensure that they check modification for **all** IMPs as certain toxicities may require modifications of the dose of more than 1 IMP.

8.3.1 Carfilzomib Dose Reductions / Adjustments

If more than 2 doses are missed in any one cycle due to toxicities or for other reasons, please consider making up the missed doses before the start of the next cycle. In cases of uncertainty, please contact UCL CTC.

Dose reduction guidelines for carfilzomib:

Current dosing level	Dose reduction
56 mg/m^2	Modify to 36 mg/m^2
36 mg/m^2	Modify to 27 mg/m^2
27 mg/m^2	Modify to 20 mg/m^2
20 mg/m^2	Modify to 15 mg/m^2

Dose Reduction for Haematologic Toxicities

Patients will have a FBC prior to each dose of carfilzomib during treatment (i.e. days 1, 8, 15, (and days 2, 9 and 16 if clinically indicated) during induction and consolidation, days 1, 8 and 15 during maintenance).

The tables below provide dose reduction guidelines for the following:

- Grade 3 thrombocytopenia with active bleeding
- Grade 4 thrombocytopenia
- Grade 4 neutropenia

Grade 4 anaemia and Grade 3 thrombocytopenia (without active bleeding) do not require the carfilzomib dose to be withheld. However, participants should receive supportive measures in accordance with institutional guidelines.

Thrombocytopenia

Thrombocytopenia	**Thrombocytopenia with active bleeding**	**Recommended Action Carfilzomib**
When platelets		
Fall to < 25 × 10^9/L	Fall to <50 – 25 x 10^9/L	Interrupt carfilzomib, follow FBC weekly
Return to ≥ 25 × 10^9/L	Return to ≥ 50 x 10^9/L	Resume at full dose
Subsequently drop to < 25 × 10^9/L	Subsequently drop to <50 – 25 x 10^9/L	Interrupt carfilzomib, follow FBC weekly
Return to ≥ 25 × 10^9/L	Return to ≥ 50 x 10^9/L	Resume at 1 dose decrement

Neutropenia

When ANC	**Recommended Action Carfilzomib**
Falls to < 0.5 × 10^9/L	Interrupt carfilzomib, add growth factor, follow FBC weekly
Returns to > 1.0 × 10^9/L (if neutropenia was the only toxicity noted)	Resume at full dose
Returns to > 1.0 × 10^9/L (if other toxicity noted)	Resume at 1 dose decrement
Subsequently drops to < 0.5 × 10^9/L	Interrupt carfilzomib
Returns to > 1.0 × 10^9/L	Resume at 1 dose decrement

Dose Reduction for Non-Haematologic Toxicities

Dose modification guidelines for carfilzomib related, non-haematologic toxicities, are listed in the table below.

If the participant tolerates a reduced dose for two cycles, consider dose escalating to the dose prior to reduction. If toxicity continues or recurs, a 2nd carfilzomib dose reduction may be permitted at the discretion of the Investigator. No more than three dose reductions will be permitted in an individual participant on study. If toxicity continues or recurs after three dose reductions, all trial treatment should be discontinued.

For all other non-haematologic toxicities assessed as carfilzomib-related ≥ Grade 3, consider withholding carfilzomib until resolution to ≤ Grade 1 or baseline, and consider restarting at one dose level reduction. Patient should be monitored and treated as per local clinician discretion.

For non-haematologic events ≥ Grade 3 not treatment-related, please monitor and treat as per clinical discretion.

Non-haematologic toxicity	**Grade**	**Recommended Action Carfilzomib**
Acute Kidney Injury	Grade 3 or 4	Stop carfilzomib or reduce dose as appropriate. Consider restarting carfilzomib at 1 dose level reduction as clinically appropriate.
Cardiac Disorders e.g. : • Congestive cardiac failure • Pulmonary edema • Ejection fraction decreased • Myocardial ischemia • Myocardial infarction • Supraventricular tachycardia	Grade 3 or 4	Stop carfilzomib until recovery from cardiac disorder. Consider restarting carfilzomib at 1 dose level reduction as clinically appropriate.
Dyspnea	Grade 3 or 4	Stop carfilzomib until recovery from dyspnea or return to baseline. Consider restarting carfilzomib at 1 dose level reduction as clinically appropriate.
Hepatic Toxicity	Grade 3 or 4	Stop carfilzomib or reduce dose as appropriate. Consider restarting carfilzomib at 1 dose level reduction as clinically appropriate.
Hypertension	Grade 3 or 4*(see footnote)	Stop carfilzomib until well controlled (grade 2 or less). Consider restarting carfilzomib at 1 dose level reduction as clinically appropriate.
Hypertensive crisis	Grade 4	Stop carfilzomib until resolved or returned to baseline. Consider whether to restart carfilzomib as clinically appropriate.
Posterior Reversible Encephalopathy Syndrome (PRES)	Grade 3 or 4	Stop carfilzomib if PRES is suspected and discontinue carfilzomib if PRES is confirmed. If diagnosis of PRES is excluded, carfilzomib can be restarted at the initial dose if clinically appropriate.

Pulmonary Hypertension	Grade 3 or 4	Stop carfilzomib until pulmonary hypertension has resolved or returned to baseline. Consider whether to restart carfilzomib as clinically appropriate.
Pulmonary Toxicity e.g. : • Acute respiratory distress syndrome • Acute respiratory failure • Acute diffuse infiltrative pulmonary disease i.e. pneumonitis and interstitial lung disease	Grade 3 or 4	Stop carfilzomib until pulmonary toxicity has resolved or returned to baseline. Consider whether to restart carfilzomib as clinically appropriate.
Thrombotic Microangiopathy (including thrombotic thrombocytopenic purpura and hemolytic uremic syndrome)	Grade 3 or 4	If the diagnosis is suspected, stop carfilzomib and manage as per the guidance in section 8.4. If TMA is confirmed, permanently discontinue carfilzomib. If the diagnosis is excluded, carfilzomib can be restarted at the decision of the PI.
Tumour Lysis Syndrome	Grade 3 or 4	Stop carfilzomib until tumour lysis syndrome has resolved. Consider restarting carfilzomib at 1 dose level reduction as clinically appropriate.
Venous Thrombosis (including deep vein thrombosis and pulmonary embolism)	Grade 3 or 4	Consider holding treatment until established on anti-coagulation
Allergic reaction/hypersensitivity	Grade 2 or 3 Grade 4	Hold until ≤ Grade 1, reinstitute at full dose Discontinue carfilzomib
Infection	Grade 3 or 4	Hold carfilzomib until infection has resolved and anti-infective treatment has been completed. In the absence of neutropenia, restart at full dose. If neutropenic, follow neutropenic instructions above.
Herpes zoster or simplex	Any grade	Hold carfilzomib until lesions are dry. Consider reinstituting at full dose
Neuropathy	Grade 2 or 3 Grade 4	Continue to dose. If neuropathy persists for more than two weeks hold carfilzomib until resolved to ≤ Gr 2 without pain. Then restart at 1 dose decrement. Discontinue carfilzomib

*if the treating clinician considers the grade 3 hypertension as sporadic, not medically significant, or has additional supporting information, carfilzomib treatment should continue without being held/reduced.

Hypertension

All patients should be routinely evaluated for hypertension and treated appropriately. It is important that the hypertension is well controlled before the patient receives carfilzomib. It may be necessary to administer an additional dose of anti-hypertensive medication on the day of carfilzomib treatment. In case of uncertainty, please contact the TMG for advice, via UCL CTC, and consider an extra "step-up" in the induction cycle 1 dosing, so using 20mg/m^2 on days 1, 2, then 36 mg/m^2 days 8, 9 and finally up to 56mg/m^2 on days 15, 16 and thereafter.

Day	1	2	8	9	15	16
20 mg/m^2	X	X				
36 mg/m^2			X	X		
56 mg/m^2					X	X

Changes in Body Surface Area

Patients should be weighed at the start of each cycle, and dose re-adjusted if the difference between their current weight and the weight used to calculate their dose for the previous cycle is >20%.

Participants with a Body Surface Area (BSA) of greater than 2.2m^2 will receive a capped dose based upon 2.2m^2 BSA.

8.3.2 Cyclophosphamide Dose Reductions / Adjustments

Please refer to the most recent SPC for cyclophosphamide for dose modification guidelines. The dose of cyclophosphamide may be modified for a participant as per the dosing table below.

Current dosing level (oral)	**Dose reduction**
500mg	Modify to 400mg
400mg	Modify to 300mg
300mg	Modify to 200mg
200mg	No further reduction, discontinue dosing permanently

Current dosing level (IV)	**Dose reduction**
375mg	Modify to 300mg
300mg	Modify to 225mg
225mg	Modify to 150mg
150mg	No further reduction, discontinue dosing permanently

8.3.3 Dexamethasone Dose Reductions / Adjustments

Please refer to the most recent SPC for dexamethasone for dose modification guidelines. The dose of dexamethasone may be modified for a participant as per the dosing table below during any cycle of induction or consolidation.

Current dosing level (oral or IV)	**Dose reduction**
40mg	Modify to 20mg
20mg	Modify to 10mg
10mg	Modify to 4mg
4mg	No further reduction, discontinue dosing permanently

During maintenance each dose of carfilzomib should be administered with dexamethasone 10mg (IV or PO) as prophylactic pre-medication. In addition to the dose of pre-med dexamethasone, described above, dexamethasone 10mg (PO) will be given on the day after carfilzomib throughout maintenance. In cases of toxicity, please consider dose reducing pre/post-med dexamethasone as outlined below:

Current dosing level	**Dose reduction**
10mg	Modify to 8mg
8mg	Modify to 6mg
6mg	Please contact UCL CTC for doses below 6mg or if considering complete omission of dexamethasone

If Grade 3 or 4 corticosteroid toxicity occurs (i.e. toxicity requiring temporary dexamethasone cessation or life threatening), or if a patient experiences grade ≤2 corticosteroid toxicity that either the patient or their treating clinician considers to be unacceptable, dexamethasone should be given at a reduced dose for the rest of the cycle and all subsequent cycles. If Grade 3 or 4 corticosteroid toxicity persists at the reduced dose, dexamethasone should be omitted from all future dosing in the study. Following resolution of any toxicity, dexamethasone may be re-escalated to full dose at PI discretion.

If the clinician is considering reducing the dose of dexamethasone during maintenance for reasons other than steroid induced toxicity, this must be discussed and agreed with the UCL CTC and the patient must be counselled that if side-effects due to carfilzomib occur, the dose may need to be increased. If the clinician is considering increasing the dose of dexamethasone beyond 10mg during maintenance, please contact the UCL CTC.

8.4. Supportive Care

Safety Considerations

Based upon the experience in the Phase 1 and 2 clinical studies with carfilzomib, the following observations are noted:

- A "first dose effect" has been seen, which is notable for fever, chills, rigors, and/or dyspnoea occurring during the evening following the first day of infusion and an increase in creatinine on Day 2, which may be the clinical sequelae of rapid tumour lysis and/or cytokine release.
- Should a "first dose" effect occur at any point during Cycle 1 or 2, treatment with high dose glucocorticoids (e.g. IV methylprednisolone 50–100 mg) is recommended. In addition, intravenous fluids, vasopressors, oxygen, bronchodilators, and paracetamol should be available for immediate use and instituted, as medically indicated.
- Dexamethasone 4 mg po/IV should be administered prior to all carfilzomib doses during the 1st cycle of induction and consolidation, and prior to any doses that represent a dose-escalation. During every cycle of maintenance, a higher dose of dexamethasone (10mg) should be given on the day of dosing and the day after dosing.
- Acyclovir or similar should be given to all participants with a history of herpes simplex or zoster, per institutional prophylaxis guidelines, unless contraindicated.
- CrCl changes are mostly transient, reversible, and non-cumulative. All participants should be well hydrated. Clinically significant electrolyte abnormalities should be corrected prior to dosing with carfilzomib. Renal function must be monitored closely during treatment with carfilzomib. Serum chemistry values, including creatinine, must be obtained and reviewed prior to each dose of carfilzomib during Cycles 1 and 2.
- Participants with active or suspected infection of any kind that required systemic treatment should not be dosed with carfilzomib until the infection has resolved and if being treated with anti-infective, the course of antibiotics has been

completed.

- Thrombocytopenia has been transient and typically resolves during the week between treatments. For platelet counts <25 x 10^9/L, carfilzomib dosing must be held. If platelet counts do not recover, the dose of carfilzomib may be reduced or held according to the Dose Reductions / Adjustments rules outlined in Section 8.3.1.
- Participants should have anaemia corrected in accordance with local guidelines.
- Carfilzomib treatment can cause nausea, vomiting, diarrhoea, or constipation sometimes requiring the use of antiemetics or antidiarrhoeals. Fluid and electrolyte replacement should be administered to prevent dehydration.
- The plasma sodium can be low in patients with myeloma because the positively charged paraprotein lowers the anion gap, thus lowering the sodium. Pseudohyponatraemia can also occur due to the increased plasma viscosity related to the paraprotein. Both are reasons for the finding of a low sodium level in patients with active disease, and are unlikely to be related to IMP when the paraprotein is over 10g/L.

Guidelines for Monitoring, Prophylaxis and Treatment of Tumour Lysis Syndrome (TLS), which may be associated with multi-organ failure, has been observed in treatment Cycles 1 and 2 in some participants with MM who have been treated with carfilzomib.

The following safety measures are mandatory for all participants. In addition, MM participants with high tumour burden (e.g., Durie-Salmon or ISS Stage II/III) or rapidly increasing M-protein or light chains or compromised renal function (CrCl < 50 mL/min) should be considered to be at particularly high risk.

Concomitant medication

- TLS should be managed according to local guidelines in all participants. It is recommended that allopurinol be prescribed unless contra-indicated (e.g. allergy) to all participants at 300mg (with appropriate dose reduction for renal impairment) po daily, from Cycle 1 Day -1 or earlier until day +17 of cycle 1. For participants at high risk of TLS (see above), the dose may be escalated to 300mg po bd for days -1 to +4 of cycle 1, then reduced to 300mg od until day +17. Allopurinol dose should be adjusted according to the package insert. Participants who do not tolerate allopurinol should be discussed with the Chief Investigator. In some circumstances (e.g. participants are exceptionally high risk of TLS), rasburicase may be used at the investigator's discretion.

Oral hydration

- All participants must be well hydrated (i.e., volume replete). Begin oral hydration equal to approximately 30 mL/kg/day (~6–8 cups of liquid per day), starting 48 hours prior to the planned first dose of carfilzomib. Compliance must be reviewed with the participant and documented by the site personnel prior to initiating treatment with carfilzomib; treatment is to be delayed or withheld if oral hydration is not deemed to be satisfactory.

Intravenous Fluids

- 250–500 mL of IV normal saline (or other appropriate IV fluid formulation) is

recommended to be given before each carfilzomib dose during Cycle 1 (see Section 8.1). Post dose IV hydration may also be given, at the discretion of the treating clinical team. The goal of the hydration program is to maintain robust urine output, (e.g., ≥ 2 L/day). Participants should be monitored periodically during this period for evidence of fluid overload, in which case furosemide or other appropriate diuretic should be administered.

- In participants considered to be still at risk for TLS at completion of Cycle 1, hydration should be continued into Cycle 2, if clinically indicated. Participants in whom this program of oral and IV fluid hydration is contraindicated, e.g., due to pre-existing pulmonary, cardiac, or renal impairment, will not be eligible to participate in the trial.
- IV hydration pre- or post- carfilzomib dosing is unlikely to be required during consolidation.
- IV hydration pre- or post- carfilzomib dosing can be given in maintenance at the discretion of the local PI.

Laboratory Monitoring

Results of laboratory studies must be reviewed and deemed acceptable prior to administering the carfilzomib dose. See section 9 (Assessments) for further details. Participants with laboratory abnormalities consistent with lysis of tumour cells (e.g., serum creatinine ≥ 50% increase, LDH ≥ 2-fold increase, uric acid ≥ 50% increase, phosphate ≥ 50% increase, potassium ≥ 30% increase, calcium ≥ 20% decrease) prior to dosing should not receive the scheduled dose. Participants with such abnormalities should be re-evaluated again within the next 24 hours (or sooner, if clinically indicated) and then periodically as clinically indicated.

Clinical Monitoring

Inform participants receiving CarCyDex of signs and symptoms that may be indicative of TLS, such as fevers, chills/rigors, dyspnoea, nausea, vomiting, muscle tetany, weakness, or cramping, seizures, and decreased urine output. Advise participants to report such symptoms immediately and seek medical attention.

Management of Tumour Lysis Syndrome

If TLS occurs, cardiac rhythm, fluid, and serial laboratory monitoring should be instituted. Correct electrolyte abnormalities, monitor renal function and fluid balance, and administer therapeutic and supportive care, including dialysis, as clinically indicated.

All cases of TLS must be reported to the UCL CTC as a Serious Adverse Event (SAE) through the normal process within 24 hours of the clinical site becoming aware of the event.

Guidelines for Monitoring, Prophylaxis and Treatment of Thrombotic Microangiopathy (TMA)

Cases of TMA are reported in subjects receiving Carfilzomib, and indeed also with Bortezomib. The incidence is low and TMA occurs sporadically, is more common during

cycles 1-4 of induction treatment, but is also reported during consolidation and maintenance. It is seen in triplet combination regimens, in doublets with dexamethasone, as well as in single agent dosing in maintenance, and at doses ranging from 20mg/m^2 to 56 mg/m^2. Typically, patients present with nausea, with or without vomiting, extreme fatigue, dark urine, diarrhoea, fever and occasionally signs of infection. Laboratory tests confirm acute kidney injury, and features of a MAHA with low haptoglobin, schistocytes on the blood film, high LDH, anaemia, and often profound thrombocytopenia. ADAMTS13 levels, coagulation tests and complement levels are within the normal range. Renal biopsies, when performed, have all confirmed the diagnosis of TMA. Signs and symptoms to look out for are nausea, vomiting, fever and dark urine, in addition to the above.

Clinical Monitoring

Inform participants of signs and symptoms that may be indicative of TMA, such as nausea, fevers, vomiting, diarrhoea, dark urine, and low urine output. Advise participants to report such symptoms immediately and seek medical attention. Participants experiencing nausea in the 24-48 hours following a dose of carfilzomib should attend for repeat blood tests to exclude TMA.

Patients may require close monitoring with telephone contact. Patients should receive the first and second dose (Cycle 1 day 1 and day 2) of carfilzomib at 20mg/m^2 during induction and consolidation. Patients should receive the first dose (Cycle 1 day 1) of carfilzomib at 20mg/m^2 during maintenance. After the initial lower doses escalate to the protocol dose of 56mg/m^2. All patients should be checked for good blood pressure control, although this does not necessarily protect against the syndrome.

Management of Thrombotic Microangiopathy

Most cases of TMA present like haemolytic uraemic syndrome (HUS)/thrombotic thrombocytopenic purpura (TTP). ADAMTS13 levels should be assessed at the earliest opportunity but are usually normal in proteasome inhibitor based TMA. Patients with a history of hypertension may be more susceptible, despite good control of their blood pressure. If TMA occurs, supportive care and serial laboratory monitoring should be instituted. Given that the underlying mechanism in drug-induced TMA is unknown, the benefit of treatment with plasma exchange is unclear. Correct electrolyte abnormalities, monitor renal function and fluid balance, treat infections, and institute renal support, including dialysis, as clinically indicated. The natural history of most cases is spontaneous resolution with return of renal function to baseline, however, this can take several months. If TMA is confirmed, carfilzomib should be discontinued.

Poorly controlled hypertension

Blood pressure should be monitored as clinically indicated. Patients with a history of hypertension, or who have diastolic BP>80mmHg, and/or systolic BP>140mmHg on one or more occasions in the 7 days prior to commencing study medication, should have further ambulatory monitoring, and, if uncontrolled hypertension is confirmed, they should be started on anti-hypertensive medication, or have their antihypertensive medication reviewed **before** starting carfilzomib. Blood pressure should be monitored

regularly throughout trial treatment, and anti-hypertensive treatment initiated or altered in line with NICE guidelines.

Concomitant Medications

Concomitant medication is defined as any prescription or over-the-counter preparation including vitamins and supplements.

Required Concomitant Medications

Dexamethasone 4 mg po/IV will be administered prior to all carfilzomib doses during the first cycle of induction and consolidation, and prior to any doses that represent a dose escalation. If treatment-related fever, rigors, chills, and/or dyspnoea are observed post any dose of carfilzomib after dexamethasone has been discontinued, dexamethasone (4 mg po/IV) should be re-started and administered prior to subsequent doses. Should symptoms recur, the dose may be increased to 8 mg po/IV.

During maintenance, patients will receive 10mg Dexamethasone on the day of carfilzomib, and 10mg Dexamethasone the day after (see above for details). This is a safety measure that has been introduced to minimise incidence and risks of side effects, and to increase tolerability of the maintenance regimen.

Optional and Allowed Concomitant Medications

Approved bisphosphonates and erythropoietic agents are allowed. Participants may receive anti-emetic and laxative medication as per institutional guidelines. Colony-stimulating factors may be used if neutropenia occurs but should not be given prophylactically.

Participants should receive anti-varicella (anti-herpes) agent prophylaxis (e.g. acyclovir, famiciclovir) in accordance with institutional guidelines. It is also recommended that participants should receive antibiotic prophylaxis (e.g. ciprofloxacin, co-amoxiclav) for the first 2 treatment induction cycles.

For all haematological toxicities, the use of growth factors and blood products according to local guidelines is permitted. Participants may receive RBC or platelet transfusions, if clinically indicated, per institutional guidelines. Participants who require repeated platelet transfusion support should be discussed with the Chief Investigator. Participants may receive supportive care with erythropoietin or darbepoetin, in accordance with institutional guidelines.

All transfusions and/or blood product related procedures must be recorded on the appropriate case report form (CRF).

8.5. Contraindications

Concurrent therapy with an approved or investigative anticancer therapeutic with activity against multiple myeloma is not allowed. Other investigative agents (e.g., antibiotics or antiemetics) should not be used during the study.

8.6. Management of overdoses, trial treatment error, misuse, abuse or occupational exposure

Overdose
Administration of a quantity of a trial treatment, either per administration or cumulatively, which is in excess of the protocol specified dose. The dose can be evaluated as an overdose by either the trial team at site or the Sponsor upon review.

Overdoses should be reported on an incident report (see section 13.1). Any adverse events resulting from an overdose should be reported as an SAE (see section 12.2.2 for reporting procedures).

Trial Treatment Error
Any unintentional error in prescribing, dispensing, or administration of a trial treatment while in the control of a healthcare professional or consumer. The error can be identified by either the trial team at site or by the Sponsor on review.

Trial treatment errors should be reported on an incident report (see section 13.1). Any adverse events resulting from a medication error should be reported as an SAE (see section 12.2.2 for reporting procedures).

Misuse
Situations where the trial treatment is intentionally and inappropriately used in a way that is not in accordance with the protocol.

Any instances of intentional misuse should be reported on an incident report (see section 13.1). Any adverse events resulting from misuse should be reported as an SAE (see section 12.2.2 for reporting procedures).

Abuse
The persistent or sporadic, intentional, excessive use of a trial treatment, which is accompanied by harmful physical or psychological effects.

Any instances of abuse should be reported on an incident report (see section 13.1). Any adverse events resulting from abuse should be reported as an SAE (see section 12.2.2 for reporting procedures).

Occupational exposure
Exposure to a trial treatment as a result of one's professional or non-professional occupation. Occupational exposure should be reported on an incident report (see section 13.1).

8.7. Pharmacy Responsibilities

All pharmacy aspects of the trial at participating sites are the responsibility of the PI, who may delegate this responsibility to the local pharmacist or other appropriately qualified personnel, who will be the Pharmacy Lead. The delegation of duties must be recorded on the site staff delegation log.

Carfilzomib supplied for the Cardamon trial is for Cardamon patients only and must not be used outside the context of this protocol.

Temperature Excursions

All temperature excursions outside the storage conditions specified in the IB for carfilzomib and the Summary of Drug Arrangements must be reported to UCL CTC as per the 'Pharmacy Procedure for Reporting Temperature Excursions' (see Pharmacy Site File)

Upon identifying an excursion:

- all affected trial stock must be quarantined IMMEDIATELY
- the trial specific 'Notification of Temperature Excursion' form must be completed and e-mailed to ctc.excursions@ucl.ac.uk or faxed to 020 7679 9861.

Please note that UCL CTC must be informed immediately if a patient has been administered drug affected by a temperature excursion.

Drug accountability

Amgen Ltd and the Investigator will maintain records of each shipment of investigational product. The records will document shipment dates, method of shipment, batch numbers, and quantity of vials contained in the shipment. Upon receipt of the investigational product, the designated recipient at the study site will inspect the shipment, verify the number and condition of the vials, and prepare an inventory or drug accountability record.

Drug accountability records must be readily available for inspection by regulatory authorities, and by representatives of Amgen for Carfilzomib only.

Empty and partially used vials should be accounted for and destroyed at the study site in accordance with the internal standard operating procedures. Drug destruction records must be readily available for inspection by representatives of Amgen and by regulatory authorities.

Only sites that cannot destroy unused drug on-site will be required to return their unused supply of investigational product.

As dexamethasone and cyclophosphamide tablets can be given to the patient to take at home, all returned tablets should be counted and destroyed as per local practice and destruction recorded on the accountability logs.

The Pharmacy Lead must ensure that appropriate records are maintained. These records must include accountability for each drug including receipt, dispensing, returned medication and destruction of returned/unused medication. Template accountability forms will be supplied, however, sites may be permitted to use their own drug accountability records providing the same information is captured, as a minimum. Such in-house records must be submitted to UCL CTC for review and authorisation for use prior to patient enrolment.

Copies of completed drug accountability logs must be submitted to UCL CTC for all trial patients at the end of treatment or upon request. Also refer to section 14.2 (Central Monitoring).

Please refer to summary of drug arrangements for more details on supply, ordering (if applicable), labelling, storage, preparation and handling, and destruction of each IMP.

8.8. Clinical Management after Treatment Discontinuation

Patients who stop treatment early will have subsequent treatment at the discretion of the treating clinician. Those patients that have not progressed should continue to have their trial assessments at the relevant time points (refer to section 9) unless they have expressly requested to discontinue all trial activity. Patients who have progressed should be followed up for survival purposes only.

Also refer to section 15 (Withdrawal of Patients) for further details regarding treatment discontinuation, patient withdrawal from trial treatment and withdrawal of consent to data collection.

8.9. Drug Provision after the End of the Trial

At present there is no provision for those trial patients who have completed treatment to continue with Carfilzomib maintenance regimen.

9. ASSESSMENTS

9.1. Assessments during induction

Patients will be seen in clinic every 4 weeks, prior to the start of the next cycle of treatment.

Patients must be reminded to bring their diary and remaining medication, including packaging (even if empty), with them to every hospital visit. Any adverse events recorded in the diary should be discussed with the patient. All events should be reported in line with section 12. The previous cycle's diary should be collected and retained with the patients CRF as source data.

Diaries must be reconciled with returned medication to ensure consistency. Any discrepancies should be discussed with the patient.

Patients who do not respond to induction therapy (less than PR) will be treated at the discretion of the treating clinician and followed up in line with section 9.7 of the protocol.

All tests at the end of induction should be performed within 14 days after day 28 of the fourth cycle of CarCyDex.

Patients must have a FBC and biochemistry tests prior to days 1, 8, & 15 of each cycle. These are to be repeated on days 2, 9 & 16 if clinically indicated. Results of laboratory studies must be reviewed and deemed acceptable prior to administering the carfilzomib dose. The validity period for FBC is 48 hours, and for biochemistry it is 72 hours.

Disease response assessment must be based on blood and / or urine tests performed at the start of each cycle (day 1, ± 7 days), this must be assessed by the PI or delegated investigator (see appendix 3). Disease response for each cycle must be assessed according to the paraprotein/BJP/SFLC results of tests performed at the beginning of the following cycle. For example, response to cycle 1 would be assessed at the start of cycle 2, and documented on the cycle 2 CRF.

Disease response assessment is not applicable at the beginning of cycle 1, however paraprotein, serum free light chains and urinary Bence Jones Protein levels must be recorded if available.

At the end of induction, disease response assessment must be performed within 14 days after the last treatment (cycle 4, day 28), and prior to PBSCH. This should be reported on the End of Induction CRF.

Assessments	**Day 1 of each cycle**	**Days 2, 9 & 16**	**Day 8 & 15**	**End of induction (within 14 days of cycle 4, D28)**
FBC and differential	X[e]	X [e]	X[e]	X
Biochemistry: renal & liver function tests, calcium, phosphate, urate	X[f]		X[f]	X
Blood pressure	X	X	X	
Creatinine clearance	X			X
Pregnancy test for WOCBP	X			
Immunoglobulins	X			X
Serum electrophoresis	X[a, b]			X[b,]
24-hr urinary BJP	X[a, b]			X[b,]
Serum Free light chains	X[a, i]			X[b]
Serum and urine immunofixation	X[a, h]			X[h]
Echo and ECG[j]				X
Whole body imaging as per local site policy (CT, PET-CT or MRI)[g]				X[d]
Disease response assessment	X[c]			X
Adverse event recording for the previous cycle	X[c]			X

a. No need to repeat pre-registration assessments if done within 14 days prior to day 1 cycle 1
b. If used as a measure of disease and/or to confirm CR (see Appendix 3).
c. Not cycle 1
d. Only if clinically indicated or if soft tissue plasmacytomas present at registration
e. FBC and differential may be performed up to 48 hours prior to visit
f. Biochemistry may be performed up to 72 hours prior to visit
g. Skeletal survey can be performed only if other imaging options are unsuitable or if patient declines
h. In responding patients, to confirm CR only
i. If used as a measure of disease and/or to confirm sCR (see Appendix 3).
j. MUGA scans with evidence of adequate left ventricular ejection fraction may also be used

9.2. Assessments after PBSCH

Patients who respond to induction therapy (≥PR) will proceed to PBSCH. The assessments below must be performed after PBSCH. These assessments, including bone marrow, should be performed within 2 weeks after PBSCH (for logistical reasons where this is not possible, please contact UCL CTC for further guidance), and before starting consolidation or ASCT:

Assessments	Within 14 days after PBSCH
FBC and differential	X
Biochemistry: renal & liver function tests, calcium, phosphate, urate	X
Immunoglobulins	X
Serum electrophoresis	X[a]
24-hr urinary BJP	X[a]
Serum free light chains	X[a, d]
Serum and urine immunofixation	X[b]
Bone marrow aspirate and trephine for response assessment	X
Bone marrow aspirate for minimal residual disease	X[c]
Disease response assessment	X
Adverse event recording	X
Quality of life	X

a. Only if used as a measure of disease
b. Only to confirm CR (see Appendix 3)
c. Research sample to be sent to central lab (HMDS; see appendix 8 for details)
d. If used as a measure of disease and/or to confirm sCR (see Appendix 3)

Patients with PD at this point will be taken off study and treated according to local protocols at the discretion of their treating physician. The patient will be followed up in accordance with section 9.7 of the protocol.

All other patients will be randomised to receive either 4 further cycles of CarCyDex (Consolidation arm) or to proceed to high dose melphalan and ACST (ASCT arm).

9.3. Assessments during consolidation therapy (Consolidation arm)

Patients will be seen in clinic every 4 weeks, prior to the next cycle of CarCyDex.

Patients must be reminded to bring their diary and remaining medication, including packaging (even if empty), with them to every hospital visit. Any adverse events recorded by a patient must be transferred into the patient's notes and trial CRFs. The previous cycle's diary should be collected and retained with the patients CRF as source data. Diaries must be reconciled with accountability logs and with returned medication to ensure consistency.

Patients must have a FBC and biochemistry prior to days 1, 8, & 15 of each cycle and repeated on days 2, 9 & 16 if clinically indicated. Results of laboratory studies must be reviewed and deemed acceptable prior to administering the carfilzomib dose. The validity period for FBC is 48 hours and for biochemistry it is 72 hours.

Disease response assessment must be based on blood and urine tests performed at the start of each cycle (day 1, ± 7 days), this must be assessed by the PI or delegated investigator. Disease response for each cycle must be assessed according to the paraprotein/BJP/SFLC results of tests performed at the beginning of the following cycle. For example, response to consolidation cycle 1 would be assessed at the start of consolidation cycle 2, and documented on the consolidation cycle 2 CRF.

A full response assessment will be carried out at the end of consolidation therapy, and will be reported on the Post-Consolidation CRF. All end of consolidation assessments (see table below for details) must be performed within 14 days of completing the last cycle (cycle 4, day 28) of consolidation, with the exception of the PET-CT scan for PET-CT sub-study patients, which is to be performed 14-28 days after completing consolidation and sent to the UK PET core lab for central review. All end of consolidation investigations must be completed prior to starting maintenance.

Assessments	**Day 1 of each cycle**	**Days 2, 9 & 16**	**Day 8 & 15**	**End of consolidation (within 14 days after day 28 of cycle 4 unless otherwise stated)**
FBC and differential	X[g]	X[f, g]	X[g]	X
Biochemistry: renal & liver function tests, calcium, phosphate, urate	X[h]		X[h]	X
Blood pressure	X	X	X	
Pregnancy test for WOCBP	X			
Immunoglobulins	X			X
Serum electrophoresis	X[a]			X[a]
24-hr urinary BJP	X[a]			X[a]
Creatinine clearance	X[f]			X
Serum free light chains	X[a]			X[a]
Serum and urine immunofixation	X[c]			X[c]
Local bone marrow plasmacytosis (aspirate & trephine)				X
Bone marrow aspirate for genomic and pathway tests				X[d]
Blood sample for genomic and pathway tests				X[d]
Bone marrow aspirate for minimal residual disease				X[e]
Disease response assessment	X			X
Adverse event recording for the previous cycle	X[b]			X
Quality of life				X
PET-CT scan (PET sub-study only)				X[i]
Whole body imaging as per local site policy (CT, PET-CT or MRI)				X[j]

a. Only if used as a measure of disease, or to confirm CR (see Appendix 3)
b. Not cycle 1

c. Only to confirm CR
d. Sample to be sent to central lab (UCL Cancer Institute; see appendix 8)
e. Sample to be sent to central lab (HMDS; see appendix 8)
f. Only as clinically indicated
g. FBC and differential may be performed up to 48 hours prior to visit
h. Biochemistry may be performed up to 72 hours prior to visit
i. Only for patients taking part in PET-CT sub-study. To be performed within 14-28 days post consolidation and prior to starting maintenance
j. If clinically indicated or for response assessment if persistent soft tissue plasmacytomas present

9.4. Assessments at 100 days post ASCT (ASCT arm)

The following assessments must be performed at day 100 post-ASCT (or within 14 days thereafter):

Assessments	Day 100 post ASCT
FBC and differential	X
Biochemistry: renal & liver function tests, calcium, phosphate, urate	X
Immunoglobulins	X
Serum electrophoresis	X[a]
24-hr urinary BJP	X[a]
Creatinine Clearance	X
Serum free light chains	X[a]
Serum and urine immunofixation	X[b]
Bone marrow aspirate and trephine for response assessment	X
Bone marrow aspirate for genomic and pathway tests	X[c]
Blood sample for genomic and pathway tests	X[c]
Bone marrow aspirate for minimal residual disease	X[d]
Disease response assessment	X
Adverse event recording for the previous cycle	X
Quality of life	X
PET-CT scan (PET sub-study patients)	X[e]
Whole body imaging as per local site policy (CT, PET-CT or MRI)	X[f]

a. Only if used as a measure of disease or to confirm CR
b. Only to confirm CR
c. Research sample to be sent to central lab (UCL Cancer Institute; see appendix 8)
d. Research sample to be sent to central lab (HMDS; see appendix 8)
e. Only for sites taking part in the PET-CT sub-study. To be performed 100-128 days post ASCT, and prior to starting maintenance. Images to be sent to PET core lab for central review.
f. If clinically indicated or for response assessment if persistent soft tissue plasmacytomas present.

9.5. Assessments during maintenance (all patients)

Patients who do not have progressive disease following consolidation or ASCT, will enter the carfilzomib maintenance phase of the study. Patients will be seen every 4 weeks; the

following assessments must be performed on day 1, or within 7 days prior to day 1 (unless otherwise stated).

Patients must have a FBC and biochemistry on days 1, 8 & 15. Results of laboratory studies must be reviewed and deemed acceptable prior to administering the carfilzomib dose. The validity period for FBC is 48 hours and 72 hours for biochemistry.

Disease response assessment must be based on blood and urine tests performed at the start of each cycle (day 1, ± 7 days), this must be assessed by the PI or delegated investigator. Disease response for each cycle must be assessed according to the paraprotein/BJP/SFLC results of tests performed at the beginning of the following cycle. For example, response to cycle 1 would be assessed on at the start of cycle 2 and documented on the cycle 2 CRF. Response will be assessed by comparing against the highest disease burden reading pre-treatment.

A full response assessment will be carried out at the end of maintenance therapy, and will be reported on the End of Maintenance CRF. All end of maintenance assessments (see table below for details) must be performed within 14 days of day 28 of the last cycle of maintenance.

Assessments	**Day 1 of each cycle**	**Days 8 & 15**	**After 6 months of maintenance**	**End of maintenance (within 14 days after day 28 of the last maintenance treatment)**
FBC and differential	X[a]	X[a]		
Biochemistry: renal & liver function tests, calcium, phosphate, urate	X[b]	X[b]		
Monitoring for signs or symptoms of TMA	X	X		
Blood pressure	X	X		
Pregnancy test for WOCBP	X			X
Immunoglobulins	X			
Serum electrophoresis	X[c]			
24-hr urinary BJP	X[c]			
Serum free light chains	X[c]			
Serum and urine immunofixation	X[g]			
Bone marrow aspirate and trephine for response assessment			X	X[g]
Bone marrow aspirate (Minimal Residual Disease)			X[e]	
Cytogenetics/FISH				
Disease response assessment	X		X	X
Adverse event recording for the previous cycle	X[d]			X
Quality of life			X	
PET-CT scan			X[f]	
Whole body imaging as per local site policy (CT, PET-CT or MRI)				X[h]

a. FBC and differential may be performed up to 48 hours prior to visit
b. Biochemistry may be performed up to 72 hours prior to visit
c. Only if used as a measure of disease or to confirm CR
d. Not required pre cycle 1
e. Sample to be sent to central lab (HMDS; see appendix 8)
f. Only for sites taking part in PET-CT sub-study and if patient was not in CMR at 100 days post-ASCT or after 4 cycles of consolidation. To be performed 6 months after start of maintenance (+ 28 days). Images to be sent to PET core lab for central review.
g. Only required to confirm CR
h. If clinically indicated or for response assessment if persistent soft tissue plasmacytomas present.

9.6. Assessments at Relapse/Progression

Assessment of disease progression will be based on the results of local analyses, which should include a FBC, biochemistry and FISH at a minimum. Imaging may be performed according to local policy. Progression will be categorised using the Modified IMWG Uniform Response Criteria (see Appendix 3).

A blood sample and a bone marrow sample must be sent to the central laboratory (Myeloma laboratory, UCL Cancer Institute) at relapse, before start of salvage therapy. See section 9.7.

Minimum requirement for assessments at relapse/progression:

Assessments	**At relapse**
FBC and differential	X
Biochemistry: renal & liver function tests, calcium, phosphate, urate	X
Serum electrophoresis	X
24-hr urinary BJP	X
Serum free light chains	X
Disease response assessment	X
Local bone marrow aspirate & trephine biopsy	X
Cytogenetics/FISH	X
Bone marrow aspirate for genomic and pathway tests	X[a]
Blood sample for genomic and pathway tests	X[a]

a. Sample to be sent to central lab (UCL Cancer Institute; see appendix 8)

A progression form should also be completed at the time of second disease progression (investigations at second progression to be performed as per local policies).

9.7. Follow Up For Patients Withdrawn from Trial Treatment

i) Patients without disease progression

Patients who discontinue study treatment for any reason other than progression/inadequate response/inadequate bone marrow harvest (see section 15), should be followed up 3 monthly for 12 months post last trial treatment. Investigations,

including disease status assessments should be performed as per local policies. Additionally, women of childbearing potential should have a pregnancy test 1 month after last trial treatment. After 12 months, patients should enter long term follow up as detailed in section 9.9.

Patients who discontinue treatment during the first 6 months of maintenance should still have a bone marrow sample taken and sent to the central laboratory (Myeloma laboratory, UCL Cancer Institute) at 6 months from the start of maintenance.

If the patient relapses during follow up, a 1st Progression-Relapse CRF must be completed and sent to UCL CTC, and a blood sample and a bone marrow sample should be taken to be sent to the central laboratory (Myeloma laboratory, UCL Cancer Institute), before start of salvage therapy (see section 9.6 for more information). A 2nd Progression-Relapse CRF should also be completed at the time of second disease progression (investigations at second progression to be performed as per local policies).

If patients have withdrawn consent for further data collection as part of the trial (see section 15.2) this follow up data will not be collected.

ii) Patients with disease progression/inadequate response/inadequate stem cell harvest

Patients who progress at any point during the study treatment, achieve <PR after induction treatment, or have an inadequate stem cell harvest should continue to be followed up for survival and subsequent treatment information (including subsequent relapses as defined by IMWG criteria) at 6 monthly intervals from the date of progression (see section 9.9). Investigations, including disease status assessments should be performed as per local policies. Additionally, women of childbearing potential should have a pregnancy test 1 month after last trial treatment.

If a patient relapses, either during trial treatment or during follow up, a 1st Progression-Relapse CRF must be completed and sent to UCL CTC, and a blood sample and a bone marrow sample should be taken to be sent to the central laboratory (Myeloma laboratory, UCL Cancer Institute) before start of salvage therapy (see section 9.6 for more information). A 2nd Progression-Relapse CRF should also be completed at the time of second disease progression (investigations at second progression to be performed as per local policies).

9.8. Follow up for who complete all trial treatment

See section 9.5 for details of end of maintenance investigations, to be completed 4 weeks after completion of treatment. This includes a pregnancy test for women of childbearing potential. Thereafter, patients who complete all trial treatment (induction, consolidation/ASCT and maintenance) should be followed up 3 monthly for 12 months post last trial treatment. Investigations, including disease status assessments should be performed as per local policies. After 12 months, patients should enter long term follow up as detailed in section 9.9.

If patients relapse during follow up, a 1st Progression-Relapse CRF must be completed and sent to UCL CTC, and a blood sample and a bone marrow sample should be taken and sent to the central laboratory (Myeloma laboratory, UCL Cancer Institute) before start of salvage therapy (see section 9.6 for more information). A 2nd Progression-Relapse CRF should also be completed at the time of second disease progression (investigations at second progression to be performed as per local policies).

9.9. **Long term follow up**

All patients, except those who withdraw consent, should enter long term follow up. This may be done by correspondence with the local centre, or for local patients, according to routine clinical practice, at 6 monthly intervals. Patients will be monitored for survival and progression and information on subsequent treatment. Follow up will continue for 10 years following completion of their induction treatment. During long term follow up, no additional assessments or samples will be taken on patients over and above that of routine care, though additional tests will be done on the bone marrow sample taken at relapse (as per section 10 and Appendix 8).

The appropriate progression CRF should be submitted as soon as possible for patients who relapse, regardless of the time until the next follow up visit and whether the patient has previously relapsed.

All efforts should be made to contact the patient's GP to assess their condition, if a patient fails to attend a clinic or cannot be followed up at site.

Patients in the trial will be tracked through the Health & Social Care Information Centre if necessary.

10. TRANSLATIONAL RESEARCH/EXPLORATORY BIOLOGICAL STUDIES

All patients will have an aliquot of their bone marrow sample taken for translational studies directly associated with the trial (see below) and at specific time points during the study. Patients will also have an extra blood sample taken at the time of their screening tests, and at specific time points during the study. In addition, patients will be asked if they would allow any surplus material at UCL remaining after the trial-associated tests have been done, to be stored by UCL for future analysis. These samples will be tested for genetic and biomarkers in relation to myeloma. Patients will be asked to sign a separate consent to allow surplus material to be stored. All future analyses on stored material will be subject to Ethics approval.

Assessment of tumour genetics and pathway activation
Bone marrow samples will be taken at baseline, after consolidation or post-ASCT, and at the time of disease relapse. Blood samples will be taken at the same time-points, that is, at baseline, after consolidation or post-ASCT, and at the time of disease relapse. Blood and bone marrow samples are to be sent to the Myeloma Laboratory at UCL Cancer Institute for processing (see appendix 8). Both bone marrow and blood samples will be taken into EDTA and sent by overnight post, or by courier (depending on the sample) to the UCL Cancer Institute. A laboratory agreement will be in place for this work.

Peripheral blood mononuclear cells will be obtained from the blood sample by centrifugation, and plasma will be stored for analysis of cell free DNA. Myeloma cells will be obtained from the bone marrow sample using immuno-magnetic bead selection. Pellets will be stored for RNA and DNA extraction, and protein lysates for immunoblotting. All material will be stored in the Myeloma Laboratory, Cancer Institute, and assays and tests will be carried out according to GCP standards.

RNA will be analysed for pathway activation (NFkappaB, ER stress, immune activation and suppressive pathways, T cell receptor, protein processing function), and immune profiles and results correlated with disease response. Where sufficient material is obtained, RNA will also be sequenced to obtain more precise information on gene expression.

DNA will be subjected to whole exome sequencing, or, where there is insufficient material, for directed sequencing of selected genes and genomic loci. Results correlated with patient clinical features and outcomes. DNA obtained from the blood samples will be used as the normal control for each patient, in order to identify tumour-specific genomic changes. Blood samples will also be used to extract cell free, or myeloma tumour DNA for sequencing. This is in case the bone marrow samples are of insufficient quality or quantity for testing.

Protein lysates will be probed for target proteins, including proteasome sub-units and results correlated with disease response.

Assessment of myeloma cell phenotype on bone marrow trephine sections
Bone marrow trephine sections will be analysed for myeloma cell phenotype, including CD20, CD56 and CD28 as well as D-type cyclin, and for immune cell subsets. This analysis will be carried out by the group of Dr Manuel Rodriguez-Justo in the Research Department of Pathology, Room 220, 21 University Street, Rockefeller Building, UCL WC1E 6DE.

Assessment of Minimal residual disease (MRD) by multiparameter flow cytometry (MFC)
MRD data analysis will be performed by HMDS on bone marrow aspirate samples (FC028 for CD138+ cell selection and MH02 for DNA extraction). Any DNA extracted will be stored until the end of the trial before being discarded or transferred to a biobank if required approvals and consent are in place.

For more details, please refer to the *Laboratory Manual* in the Investigator Site File and Appendix 8 of the protocol

11. DATA MANAGEMENT AND DATA HANDLING GUIDELINES

Data will be collected from sites on version controlled case report forms (CRFs) designed for the trial and supplied by UCL CTC.

Source data are contained in source documents and must be accurately transcribed on to trial CRFs. CRFs must be verifiable from source data at site. Examples of source documents are hospital records which include patients' notes, laboratory and other clinical reports, etc.

Please note that, for this trial, patients must consent to their initials, date of birth and NHS number being supplied to the UCL CTC and central laboratories.

Where copies of supporting source documentation (e.g. autopsy reports, pathology reports, CT scan images, etc.) are being submitted to UCL CTC, the patient's trial number must be clearly indicated on all material and any patient identifiers removed/blacked out prior to sending to maintain confidentiality.

11.1. Completing Case Report Forms

All CRFs must be completed and signed by staff who are listed on the site staff delegation log and authorised by the PI to perform this duty. The PI is responsible for the accuracy of all data reported in the CRF.

All entries must be clear, legible and written in ball point pen. Any corrections made to a CRF at site must be made by drawing a single line through the incorrect item ensuring that the previous entry is not obscured. Each correction must be dated and initialed. Correction fluid must not be used.

The use of abbreviations and acronyms should be avoided.

Once completed the CRFs must be sent / faxed to UCL CTC and a copy kept at site.

11.2. Missing Data

To avoid the need for unnecessary data queries CRFs must be checked at site to ensure there are no blank fields before sending to UCL CTC (unless it is specifically stated that a field may be left blank). When data are unavailable because a measure has not been taken or test not performed, enter "ND" for not done. If an item was not required at the particular time the form relates to, enter "NA" for not applicable. When data are unknown enter the value "NK" (only use if every effort has been made to obtain the data).

11.3. Timelines for Data Return

CRFs must be completed at site and returned to UCL CTC as soon as possible after the relevant visit and within 1 month of the patient being seen.

Sites that persistently do not return data within the required timelines may be suspended from recruiting further patients into the trial by UCL CTC and subjected to a 'triggered' monitoring visit. See section 14.3 ('Triggered' On-Site Monitoring) for details.

11.4. **Data Queries**

Data arriving at UCL CTC will be checked for legibility, completeness, accuracy and consistency, including checks for missing or unusual values. Data Clarification Requests will be sent to the data contact at site. Further guidance on how data contacts should respond to data queries can be found on the Data Clarification Forms.

12. PHARMACOVIGILANCE

12.1. Definitions of Adverse Events

The following definitions have been adapted from Directive 2001/20/EC, ICH E2A "Clinical Safety Data Management: Definitions and Standards for Expedited Reporting" and ICH GCP E6:

Adverse Event (AE)

Any untoward medical occurrence in a patient treated on a trial protocol, which does not necessarily have a causal relationship with a trial treatment. An AE can therefore be any unfavourable and unintended sign (including clinically significant abnormal laboratory findings), symptom or disease temporally associated with the use of a trial treatment, whether or not related to that trial treatment. See section 12.2.1 for AE reporting procedures.

Adverse Reaction (AR)

All untoward and unintended responses to a trial treatment related to any dose administered. A causal relationship between a trial treatment and an adverse event is at least a reasonable possibility, i.e. the relationship cannot be ruled out.

Serious Adverse Event (SAE) or Serious Adverse Reaction (SAR)

An adverse event or adverse reaction that at any dose:

- Results in death
- Is life threatening (the term "life-threatening" refers to an event in which the patient was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe)
- Requires in-patient hospitalisation or prolongs existing hospitalisation
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly or birth defect
- Is otherwise medically significant (e.g. important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed above)

See section 12.2.2 for SAE reporting procedures.

Suspected Unexpected Serious Adverse Reaction (SUSAR)

An adverse event meeting the following criteria:

- Serious – meets one or more of the serious criteria above
- Related – assessed by the local investigator and/or Sponsor as causally related to one or more elements of the trial treatment

- Unexpected – the event is not consistent with the applicable reference safety information (RSI)

See section 12.3 for reporting procedures for these events.

Urgent events

Urgent events for this trial are:

- Thrombotic microangiopathy

See section 12.4 for reporting procedures for these events.

Overdose, trial treatment error, abuse, misuse and occupational exposure

See section 8.6 for definitions and reporting procedures for these events.

12.2. **Reporting Procedures**

Adverse Event Term

An adverse event term must be provided for each adverse event. Wherever possible, this should be a valid term listed in the Common Terminology Criteria for Adverse Events (CTCAE) v4.03, available online at:

http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf

Severity grade

The severity grade of each adverse event must be determined by using CTCAE v4.03 as a guideline.

Causality

The relationship between the trial treatment and an adverse event will be assessed.

For AEs, the local PI or their designee will assess whether the event is causally related to trial treatment.

For SAEs, a review will also be carried out by the Sponsor's delegate.

Causal relationship to each trial treatment must be determined as follows:

- Related (reasonable possibility) to a trial treatment
- Not related (no reasonable possibility) to a trial treatment

UCL CTC will consider events evaluated as related to be adverse reactions.

Responsibility for reporting safety events following transfer of care

In the event of transfer between trial sites:

UCL CTC must be informed if a patient's care is transferred to another trial site (see section 15.4 – Transfer of Care). The trial site caring for the patient at the time of awareness of AE, SAE, Urgent Event onset, Pregnancy or Lactational Exposure is responsible for completing and sending relevant reports to UCL CTC. When the patient's care is transferred, the referring site must provide sufficient information about the patient's trial participation (i.e. a copy of the patient's completed CRFs up to the date of transfer) to the new site to allow them to complete SAE reports.

In the event of transfer between a trial site and a non-trial site:

The trial site will remain responsible for completing and sending AE, SAE, Urgent Event, Pregnancy and Lactational Exposure reports to UCL CTC. If a patient is discharged to the care of a non-trial site, the PI/study team at the trial site should ensure that they are sent regular updates on the patient's progress and notified of any admissions or significant medical developments (including relapses and deaths), in order that the site's reporting responsibilities can be fulfilled.

12.2.1 Reporting of Adverse Events

All adverse events that occur between the initiation of trial treatment and 30 days post last trial treatment administration (including maintenance) must be recorded in the patient notes and the trial CRFs. Those meeting the definition of a Serious Adverse Event (SAE) must also be reported to UCL CTC using the trial specific SAE Report. Also refer to section 12.2.2 (Reporting of Serious Adverse Events (SAEs).

Pre-existing conditions do not qualify as adverse events unless they worsen.

12.2.2 Reporting of Serious Adverse Events (SAEs)

All SAEs that occur between the signing of informed consent and 30 days post the last trial treatment administration, including maintenance treatment (or after this date if the site investigator feels the event is related to a trial treatment) must be submitted to UCL CTC by fax or e-mail within **24 hours** of observing or learning of the event, using the trial specific SAE Report.

All sections on the SAE Report must be completed.

If the event is **not being reported within 24 hours** to UCL CTC, the circumstances that led to this must be detailed in the SAE Report to avoid unnecessary queries.

Exemptions from SAE Report submission

For this trial, the following events are exempt from requiring submission on an SAE Report (unless considered to be related to a trial treatment, including maintenance treatment), but must be recorded in the relevant sections of the trial CRFs:

- events that occur more than 30 days post last trial treatment administration unless:

  considered to be a late effect of the trial treatment

  it is a pregnancy related event (see section 12.6)

- disease progression (including disease related deaths)
- any planned surgical procedure that was planned and scheduled prior to study entry
- thrombotic microangiopathy of any grade (including HUS, TTP and MAHA; to be reported as an Urgent Event (see section 12.4))
- alopecia
- non-haematological AEs of grade 2 or less, as defined in CTCAE v4.03
- haematological AEs of grade 2 or less as defined in CTCAE v4.03
- haematological AEs of grade 3 or 4 unless:

  life threatening or fatal

  thrombocytopenia (<50 x 10^9/L) which does not resolve to Grade 2 or less within 14 days of onset (a SAE report will be submitted to the UCL CTC by the site if after 14 days they have not resolved to a Grade 2 or less)
- skeletal events related to myeloma (including bone fractures, spinal cord compression, bone pain and events requiring surgical interventions and/or radiotherapy)
- renal failure related to myeloma
- venous thromboembolic events related to myeloma
- transplant treatment related events (refer to Appendix 6) are exempt from the initiation of high dose Melphalan up to and including day 30 post-transplant

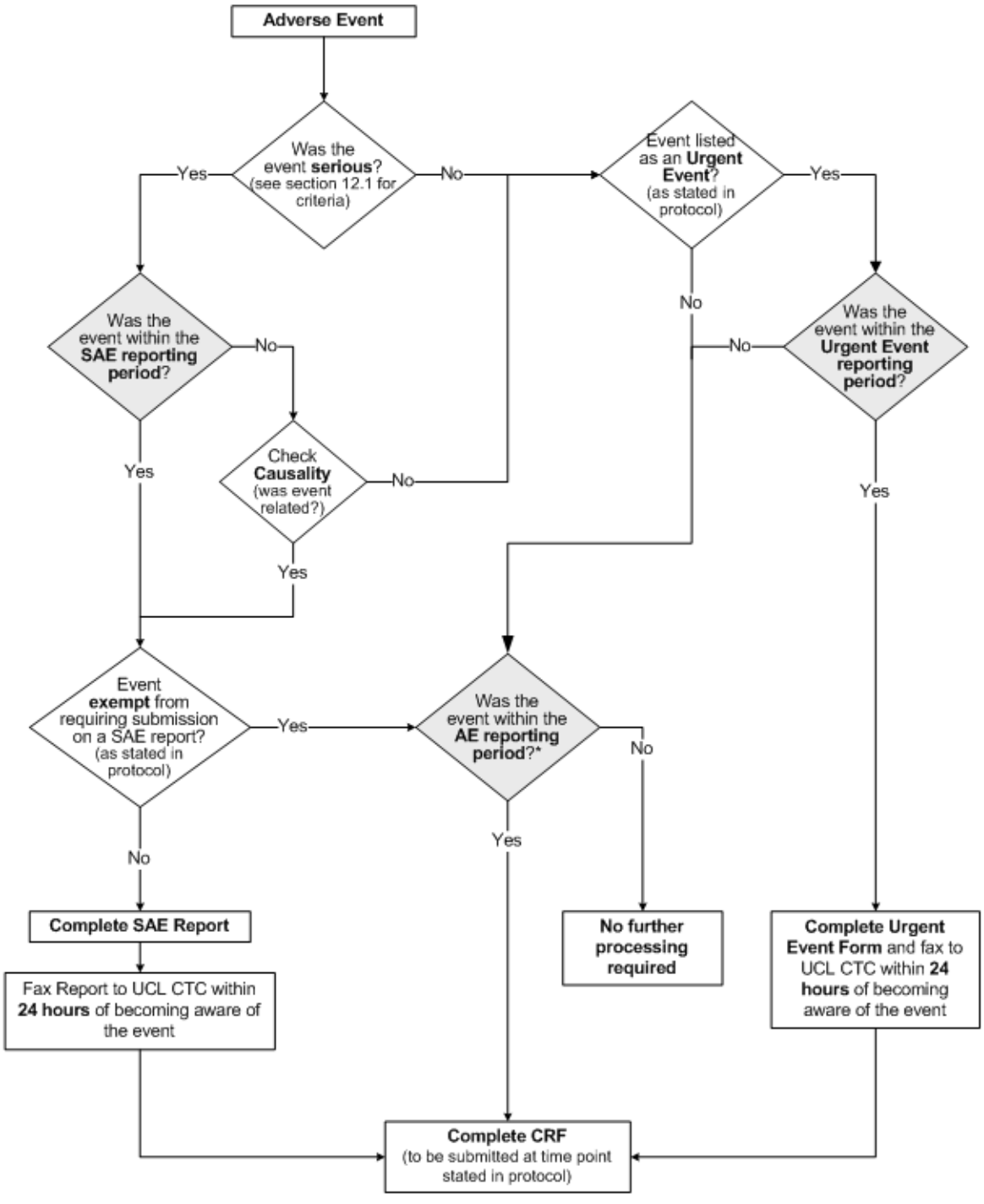
Please note that hospitalisation or prolongation of hospitalisation for elective treatment, for palliative care or for socio-economic/logistical reasons does not qualify as an SAE.

Completed SAE Reports must be faxed or emailed within 24 hours of becoming aware of the event to UCL CTC

Fax: 020 7679 9861
Email: ctc.cardamon@ucl.ac.uk

N.B. If the site is unable to fax, SAE reports may be sent by email. If emailing forms, please ensure any patient identifiable information is redacted before it is emailed.

Adverse Event Reporting Flowchart



*This applies if AE, SAE and Urgent Events reporting periods differs.

SAE Follow-Up Reports

All SAEs must be followed-up until resolution and until there are no further queries. Sites must ensure that any new and relevant information is provided promptly. If the event term changes or a new event is added, the causality must be re-assessed by an investigator. If the event is not being reported to UCL CTC within 24 hours, the circumstances that led to this must be detailed in the SAE report to avoid unnecessary queries.

SAE Processing at UCL CTC

On receipt of the SAE Report, UCL CTC will check for legibility, completeness, accuracy and consistency. Expectedness will be evaluated, to determine whether or not the case qualifies for expedited reporting, using the approved RSI (the list of expected adverse events in the Carfilzomib Investigator Brochure and SPCs for cyclophosphamide and dexamethasone).

The CI, or their delegate (e.g. a clinical member of the TMG), may be contacted to review the SAE and to perform an evaluation of causality on behalf of UCL CTC. If UCL CTC has considered expectedness difficult to determine, the CI, or their delegate, will be consulted for their opinion at this time.

12.3. **SUSARs**

If the event is evaluated as a Suspected Unexpected Serious Adverse Reaction (SUSAR), UCL CTC will submit a report to the MHRA within the required timelines.

Wherever possible, evaluations of causal relationship by both the site and the Sponsor's clinical reviewer will be reported.

Informing Sites of SUSARs

UCL CTC will inform all UK PIs of any SUSARs that occur on the trial in the form of a quarterly line listing.

UCL will also forward updated IBs, 'Dear Investigator' letters and any reports received from Amgen regarding safety updates that have occurred on trials using Carfilzomib to all UK PIs. These must be processed according to local requirements and filed with the applicable IB.

SAE and SUSAR reporting to Amgen

UCL CTC will inform Amgen in writing by e-mail or fax of all SUSARs, on a CIOMS report (or equivalent), within twenty-four (24) hours of submitting the report to the applicable regulatory authority. All forms will be completed and provided to Amgen in English. The Amgen protocol number (IST-CAR-567 / 20159848) and the trial specific EudraCT number will be included on all reports to Amgen.

Additionally, UCL CTC shall provide Amgen with a line listing of all SAEs having occurred during the trial to accompany the Development Safety Update Reports (see section 12.7) and at the end of the trial for reconciliation purposes.

12.4. **Urgent events**

The following treatment related events do not require reporting on an SAE Report but must be reported within **24 hours of becoming aware of the event** on the Urgent Event (TMA) Form.

Urgent Events may still meet the definition of a SUSAR, and will be processed by the UCL CTC in the same manner as SAE reports.

Event	**Description**	**Form required**	**Timeframe**
Thrombotic microangiopathy (TMA)	Thrombotic microangiopathy of any grade, including TTP, HUS or MAHA occurring within 30 days after carfilzomib administration.*	Thrombotic Microangiopathy Urgent Event Form	Within 24 hours of becoming aware of event

Reporting windows vary between trial arms, and are as follows:

Consolidation arm: from start of induction until 30 days after completion of maintenance treatment (or 30 days after last trial treatment administration if sooner).

ASCT arm: from start of induction until 30 days post completion of induction treatment, then from start of maintenance until 30 days after completion of maintenance treatment (or 30 days after last trial treatment administration if sooner).

All confirmed cases of TMA must be reported by faxing or emailing a completed Thrombotic Microangiopathy Urgent Event form to UCL CTC within 24 hours of becoming aware of the event
Fax: 020 7679 9861
Email: ctc.cardamon@ucl.ac.uk

N.B. If the site is unable to fax, Urgent Event (TMA) Forms may be sent by email. If emailing forms, please ensure any patient identifiable information is redacted before it is emailed.

12.5. **Safety Monitoring**

UCL CTC will provide safety information to the Trial Management Group (TMG) and the Independent Data Monitoring Committee (IDMC) on a periodic basis for review.

Trial safety data will be monitored to identify:

- new adverse reactions to the trial treatment regimen or individual trial treatments
- a higher incidence in rare adverse events than is stated in the IB/SPC for a trial treatment
- trial related events that were not considered related to the trial treatment regimen.

If UCL CTC identifies or suspects any issues concerning patient safety at any point during the trial, the CI or TMG will be consulted for their opinion, and if necessary the issue will be referred to the IDMC.

12.6. **Pregnancy and Lactational Exposure**

If a female patient or the female partner of a male trial patient becomes pregnant at any time between starting trial treatment and the end of the pregnancy risk window (12 months post trial treatment), the site must submit a trial specific Pregnancy Report to UCL CTC by fax within **24 hours** of learning of its occurrence.

The site must request consent from the pregnant trial patient or female partner of a male trial patient to report information regarding the pregnancy using:

- For female patients: the trial specific Pregnancy Monitoring Information Sheet and Informed Consent Form for trial patients
- For pregnant partners of male trial patients: the trial specific Pregnancy Monitoring Information Sheet and Informed Consent Form for partners of trial patients.

If consent is not given, the notification that a pregnancy has occurred will be retained by UCL CTC, and Amgen will be notified that a pregnancy has occurred, however no further action will be taken on the information detailed in the report.

If the local clinician suspects that a potential infant exposure to Carfilzomib from lactation has occurred on the trial then a completed trial specific Lactational Exposure Report must be submitted to UCL CTC by fax **within 24 hours** of learning of the event. Consent to report information regarding the lactational exposure must be obtained from the patient. The trial-specific lactational exposure information sheets and informed consent forms for trial patients must be used for this purpose.

All pregnancies and lactational exposures must be reported by faxing or emailing a completed Pregnancy Report/Lactational Exposure Form within 24 hours of becoming aware of the pregnancy/exposure to UCL CTC
Fax: 020 7679 9861
Email: ctc.cardamon@ucl.ac.uk

N.B. If the site is unable to fax, Pregnancy and Lactational Exposure Reports may be sent by email. If emailing forms, please ensure any patient identifiable information is redacted before it is emailed.

Pregnancy Follow-Up Reports

For pregnant patients or partners who consent, pregnancies must be followed-up until an outcome is determined. Follow-up Pregnancy Reports must be submitted to UCL CTC by fax within **24 hours** of learning of the outcome. Reports must include an evaluation of the possible relationship of each trial treatment to the pregnancy outcome.

Any post-natal abnormalities detected in the infant up to 12 months post-end of Carfilzomib treatment and felt by the local investigator to be linked to Carfilzomib should be reported to UCL CTC by fax using the SAE report form within **24 hours** of learning of the event.

SAEs during pregnancy

Any SAE occurring in a pregnant patient must be reported using the trial specific SAE Report, according to SAE reporting procedures. **Refer to section 12.2.2 (Reporting Serious Adverse Events (SAEs) for details.**

Pregnancy Report processing at UCL CTC

UCL CTC will submit a report to the MHRA and the REC should the pregnancy outcome meet the definition of a SUSAR. Refer to section 12.3 (SUSARs) for details.

UCL CTC will fax all Pregnancy Reports and SAE reports associated with pregnancy and potential infant exposure including Lactation, to Amgen within ten (10) calendar days of Sponsor awareness. SUSARs will be reported to Amgen within twenty-four (24) hours of submitting the report to the applicable regulatory authority.

12.7. **Development Safety Update Reports (DSURs)**

Safety data obtained from the trial will be included in DSURs that UCL CTC will prepare and submit to the MHRA and the REC.

UCL CTC will provide Amgen with DSURs that include information regarding carfilzomib.

Amgen will provide the Sponsor with IB updates, Dear Investigator Letters and any other safety updates related to carfilzomib that may affect the safety of the patient.

13. INCIDENT REPORTING AND SERIOUS BREACHES

13.1. Incident Reporting

Organisations must notify UCL CTC of all deviations from the protocol or GCP immediately. An incident report may be requested and a form will be provided, but an equivalent document (e.g. Trust Incident form) is acceptable where already completed.

If site staff are unsure whether a certain occurrence constitutes a deviation from the protocol or GCP, the UCL CTC trial team can be contacted immediately to discuss.

UCL CTC will use an organisation's history of non-compliance to make decisions about future collaborations.

UCL CTC will assess all incidents to see if they meet the definition of a serious breach.

13.2. Serious Breaches

A "serious breach" is defined as a breach of the protocol or of the conditions or principles of Good Clinical Practice which is likely to affect to a significant degree the safety or physical or mental integrity of the trial subjects, or the scientific value of the research.

Systematic or persistent non-compliance by a site with GCP and/or the protocol, including failure to report SAEs occurring on trial within the specified timeframe, may be deemed a serious breach.

In cases where a serious breach has been identified, UCL CTC will inform the MHRA and REC within 7 calendar days of becoming aware of the breach.

Sites must have written procedures for notifying the sponsor of serious breaches (MHRA Guidance on the Notification of Serious Breaches).

14. TRIAL MONITORING AND OVERSIGHT

Participating sites and PIs must agree to allow trial-related on-site monitoring, Sponsor audits and regulatory inspections by providing direct access to source data/documents as required. Patients are informed of this in the patient information sheet and are asked to consent to their medical notes being reviewed by appropriate individuals on the consent form.

UCL CTC will determine the appropriate level and nature of monitoring required for the trial. Risk will be assessed on an ongoing basis and adjustments made accordingly.

14.1. On-Site Monitoring

The degree of on-site monitoring will be proportionate to the objective, purpose, phase, design, size, complexity, endpoints and risks associated with the trial.

Details of monitoring activities will be included in the trial Monitoring Plan which will be provided to sites. The Monitoring Plan will be kept under review throughout the trial and updates provided as necessary.

Sites will be sent a letter in advance confirming when a routine monitoring visit is scheduled to take place. The letter will include a list of the documents to be reviewed, interviews that will be conducted, planned inspections of the facilities, and who will be performing the visit.

Monitoring Follow Up

Following a monitoring visit, the Trial Monitor/Trial Coordinator will provide a follow up email to the site, which will summarise the documents reviewed and a statement of findings, incidents, deficiencies, conclusions, actions taken and/or actions required. The PI at each site will be responsible for ensuring that monitoring findings are addressed in a timely manner by the deadline specified.

14.2. Central Monitoring

Sites will be requested to submit screening logs and staff delegation logs to UCL CTC at the frequency detailed in the trial Monitoring Plan, or on request, and these will be checked for consistency and completeness. Also refer to section 4.2.2 (Required documentation).

Ensuring patient eligibility is the responsibility of the PI or other delegated Investigator(s). Checks of the criteria listed on the registration form will be undertaken by an appropriately trained UCL CTC staff member prior to registration. Also refer to section 6.1 (pre-registration evaluation) and 6.3 (Patient Eligibility).

Details relating to the informed consent process will be collected on the registration form and are subject to review by UCL CTC as part of patient eligibility. Also refer to section 5 (Informed consent).

Copies of completed drug accountability logs must be returned to UCL CTC for all trial patients. Sites will be required to submit logs in accordance with the trial Monitoring Plan.

Sites will be requested to conduct quality control checks of documentation held within the Investigator Site File and Pharmacy Site File at the frequency detailed in the trial monitoring plan. Checklists detailing the current version/date of version controlled documents will be provided for this purpose.

Data received at UCL CTC will be subject to review in accordance with section 11.4 (Data Queries).

Where central monitoring of data and/or documentation submitted by sites indicates that a patient may have been placed at risk (e.g. indication that dose modification rules for an IMP were not observed following an adverse reaction, etc.), the matter will be raised urgently with site staff and escalated as appropriate (refer to section 13 (Incident Reporting and Serious Breaches) and 14.3 ('Triggered' On-Site Monitoring) for further details).

14.3. 'Triggered' On-Site Monitoring

Additional on-site monitoring visits may be scheduled where there is evidence or suspicion of non-compliance at a site with important aspect(s) of the trial protocol/GCP requirements. Sites will be sent a letter in advance outlining the reason(s) for the visit, and confirming when it will take place. The letter will include a list of the documents that are to be reviewed, interviews that will be conducted, planned inspections of the facilities and who will be performing the visit.

UCL CTC will assess whether it is appropriate for the site to continue participation in the trial and whether the incident(s) constitute a serious breach. Refer to section 13 (Incident Reporting and Serious Breaches

14.4. Oversight Committees

Trial Management Group (TMG)

The TMG will include the Chief Investigator, clinicians and experts from relevant specialties and Cardamon trial staff from UCL CTC (see page 3). The TMG will be responsible for overseeing the trial. The group will meet regularly (at least twice a year) and will send updates to PIs (via newsletters or at Investigator meetings) and to the NCRI Haematological Oncology Clinical Studies Group.

The TMG will review substantial amendments to the protocol prior to submission to the REC and MHRA. All PIs will be kept informed of substantial amendments through their nominated responsible individual and are responsible for their prompt implementation.

All TMG members will be required to sign a charter to confirm they agree to undertake the roles and responsibilities of a TMG member.

Trial Steering Committee (TSC)

The role of the TSC is to provide overall supervision of the trial. The TSC will review the recommendations of the Independent Data Monitoring Committee and, on consideration of this information, recommend any appropriate amendments/actions for the trial as necessary. The TSC acts on behalf of the funder and Sponsor.

All TSC members will be required to sign a charter to confirm they agree to undertake the roles and responsibilities of a TSC member.

Independent Data Monitoring Committee (IDMC)

The role of the IDMC is to provide independent advice on data and safety aspects of the trial. Meetings of the Committee will be held at least once a year to review interim analyses (see section 18.6), or as necessary to address any issues. The IDMC is advisory to the TSC and can recommend premature closure of the trial to the TSC.

All IDMC members will be required to sign a charter to confirm they agree to undertake the roles and responsibilities of an IDMC member.

Role of UCL CTC

UCL CTC will be responsible for the day to day coordination and management of the trial and will act as custodian of the data generated in the trial (on behalf of UCL). UCL CTC is responsible for all duties relating to pharmacovigilance which are conducted in accordance with section 12 (Pharmacovigilance).

15. WITHDRAWAL OF PATIENTS

In consenting to the trial, patients are consenting to trial treatment, assessments, collection of biological samples, follow-up and data collection.

15.1. Discontinuation of Trial Treatment

A patient may be withdrawn from trial treatment whenever such treatment is no longer in the patient's best interests, but the reasons for doing so must be recorded in the patient's notes and relevant Case Report Forms. Reasons for discontinuing treatment may include:

- Disease progression whilst on therapy
- Inadequate response to induction treatment (<PR)
- Inadequate stem cell harvest
- Unacceptable toxicity
- Intercurrent illness which prevents further treatment
- Patient decision not to continue with trial treatment and/or procedures
- Any alterations in the patient's condition which justifies the discontinuation of treatment in the site investigator's opinion
- Non-compliance with the trial treatment and/or procedures
- If a female patient becomes pregnant
- If the patient is no longer willing to comply with protocol contraceptive requirements

If a patient is withdrawn from treatment during induction or consolidation treatment, the Treatment Summary CRF must be completed and submitted to UCL CTC promptly.

If a patient is withdrawn from treatment during maintenance, the Maintenance Summary CRF must be completed and submitted to UCL CTC promptly.

Patients will remain within the trial for the purposes of follow-up and data analysis according to the treatment stage they have reached unless they explicitly withdraw consent. The follow up schedule for patients who withdraw from trial treatment is detailed in section 9.7 of the protocol.

If a patient expresses their wish to withdraw from trial treatment, sites should explain the importance of remaining on trial follow-up, or failing this of allowing routine follow-up data to be used for trial purposes and for allowing existing collected data to be used. If the patient gives a reason for their withdrawal, this should be recorded.

15.2. Withdrawal of Consent

If a patient explicitly states they do not wish to contribute further data to the trial their decision must be respected, with the exception of essential safety data, and recorded on the relevant CRF. In this event, data due up to the date of withdrawal must be submitted. Thereafter, no further data, other than essential safety data will be sent to UCL CTC.

UCL CTC will contact the trial laboratories to request return or destruction of the patient's samples, and will email the site to confirm that this has been actioned.

15.3. **Losses to Follow-Up**

If a patient is lost to follow-up at a site every effort should be made to contact the patient's GP to obtain information on the patient's status.

Patients lost to follow up will be tracked by UCL CTC via the Health & Social Care Information Centre.

15.4. **Transfer of Care**

For patients moving from the area, every effort should be made for the patient to be followed up at another participating trial site, and for this new site to take over responsibility for the patient's trial visits and data collection going forward.

The process for transferring care to another participating site is as follows:

- Liaise with the proposed new site and obtain written confirmation that they are willing to take over follow up duties for the patient
- Notify the UCL CTC trial team of the transfer arrangements
- CRFs relating to visits up to the point of transfer must be completed and submitted to UCL CTC
- Provide the new site with copy of the patient's complete CRF up until the point of transfer

The original site remains responsible for submitting all data due up to the date of transfer, and for resolving any data queries relating to those data. The site to whom the patient is transferred will be responsible for completing CRFs pertaining to visits after the date of transfer only.

Details of participating trial sites can be obtained from the UCL CTC study team upon request.

If the patient cannot be transferred to another participating site, the site that registered them into the trial remains responsible for obtaining and submitting follow up and safety data on the patient.

16. TRIAL CLOSURE

16.1. End of Trial

For regulatory purposes the end of the trial will be 10 years after the last patient completes induction treatment, at which point the 'declaration of end of trial' form will be submitted to participating regulatory authorities and Ethics Committee, as required.

Following this, UCL CTC will advise sites on the procedure for closing the trial at the site.

Once the end of trial has been declared, no more prospective patient data will be collected, but sites must cooperate with any data queries regarding existing data to allow for analysis and publication of results.

16.2. Archiving of Trial Documentation

At the end of the trial, UCL CTC will archive securely all centrally held trial related documentation for a minimum of 5 years. Arrangements for confidential destruction will then be made. It is the responsibility of PIs to ensure data and all essential documents relating to the trial held at site are retained securely for a minimum of 5 years after the end of the trial, in accordance with national legislation, and for the maximum period of time permitted by the site.

Essential documents are those which enable both the conduct of the trial and the quality of the data produced to be evaluated and show whether the site complied with the principles of GCP and all applicable regulatory requirements.

UCL CTC will notify sites when trial documentation held at sites may be archived. All archived documents must continue to be available for inspection by appropriate authorities upon request.

16.3. Early Discontinuation of Trial

The trial may be stopped before completion as an Urgent Safety Measure on the recommendation of the TSC or IDMC (see section 14.4). Sites will be informed in writing by UCL CTC of reasons for early closure and the actions to be taken with regards the treatment and follow up of patients.

16.4. Withdrawal from Trial Participation by a Site

Should a site choose to close to recruitment the PI must inform UCL CTC in writing. Follow up as per protocol must continue for any patients recruited into the trial at that site and other responsibilities continue as per the CTSA.

17. QUALITY ASSURANCE (QA)

PET QA for the PET sub-study will be undertaken by the UK PET Core Lab at St. Thomas' Hospital, London. Please refer to the trial Imaging Manual and Appendix 9 (PET-CT Sub-Study) of the protocol for more details.

18. STATISTICS

18.1. Sample Size Calculation

This phase II study has two stages.

In the induction stage there will be a preliminary assessment of response rate (sCR, CR & VGPR). It is anticipated that the objective response rate of the induction regimen is >50%. If the objective response rate is <30%, there is no interest in the induction regimen. Using A'Hern's single-stage phase II design, with a one-sided 5% significance level and 90% power, a sample size of 53 patients is required. Levels of significance and power have been chosen such that the study will not continue unless clear evidence of acceptable efficacy is observed; a minimum of 22 responders are required to continue. Recruitment will not be halted between stages.

In the second stage, patients achieving at least a partial response (PR) to the induction regimen will be randomised to either ASCT or 4 further cycles of CarCyDex, and all patients will receive maintenance. Based on available data on triplet induction regimens incorporating novel agents, followed by ASCT and maintenance, we expect the 2-year PFS to be 85% in this (ASCT) arm (Cavo et al, Lancet 2010). For consolidation CarCyDex (as alternative to ASCT) with maintenance to be of further interest it is required to show non-inferiority (or superiority) to the ASCT arm. Hence it would not be of interest if the 2-year PFS is <75%, i.e. a non-inferiority margin of 10%. Using a one-sided non-inferiority test for two exponential survival curves with 15% significance level, 80% power and a common exponential dropout rate of 10%, we require 105 patients per arm for 43 events. Assuming a ≥PR rate of around 75% (68-89% with CarThaDex and CarLenDex, ASH 2011), with 3 years of recruitment and 2 years of additional follow-up, we would need to recruit a total of 280 patients to the study to randomise 210 patients – 105 to each of the trial arms.

18.2. Population for Analysis

All patients who have completed response assessments or stopped protocol treatment early due to toxicity or insufficient response will be included in the analysis of response to the induction regimen.

Analysis of 2-year PFS will be performed on both an intention-to-treat and a per-protocol basis.

18.3. Analysis of the Primary Endpoint

The number and percentage of patients who achieve disease response (sCR, CR & VGPR) at the end of induction treatment will be presented, with two-sided 95% confidence intervals constructed using exact methods based on the binomial distribution. Response will be assessed by comparing against the highest disease burden reading pre-treatment.

Kaplan-Meier estimates and Cox regression will be used to analyse progression-free survival, defined as the time from date of randomisation to the date of first progression

or date of death from any cause, censoring will occur on the date of last disease assessment.

18.4. **Analysis of Secondary Endpoints**

The number and percentage of patients who suffer a grade 3 or 4 toxicity will be presented by trial arm, the maximum grade of toxicity will also be tabulated for each adverse event. Two-sided 95% confidence intervals will be constructed using exact methods based on the binomial distribution.

The number and percentage of patients who achieve disease response (sCR+CR+VGPR+PR) at the end of induction treatment will be presented, with two-sided 95% confidence intervals constructed using exact methods based on the binomial distribution. Response will be assessed by comparing against the highest disease burden reading pre-treatment.

The number and percentage of patients who achieve conversion from PR or VGPR to CR, and from MRD-positive to MRD-negative on MPF (at a sensitivity of 10^{-4}), will be presented by trial arm with two-sided 95% confidence intervals constructed using exact methods based on the binomial distribution.

Kaplan-Meier estimates and Cox regression will be used to analyse overall survival, defined as the time from date of randomisation to the date of death from any cause, censoring will occur on the date of last study assessment.

Kaplan-Meier estimates and Cox regression will be used to analyse PFS2, defined as the time from date of randomisation to the date of second progression or death from any cause, censoring will occur on the date of last study assessment.

EQ5D, QLQ-C30 and QLQ-MY24 quality of life questionnaires will be analysed using mixed modelling and results reported by each domain with summary statistics. Estimates will be reported with 99% confidence intervals to account for the multiple comparisons.

18.5. **Analysis of PET-CT data**

The PET-CT sub-study is an optional element of the trial. It is anticipated that up to 120 patients will be registered at study entry, with approximately 100 patients being eligible for the second PET-CT scan (end of consolidation/day 100 post-ASCT). Regression modelling, Kaplan-Meier methods and chi-square tests will be used to investigate the following exploratory analyses:

1. Association of baseline PET-CT features
   - Number of focal lesions
   - SUVmax
   - Extramedullary disease
   - Paramedullary disease
   - Diffuse bone marrow activity
   - Lytic lesions on CT

with other disease and risk markers including adverse genetics, response to induction and consolidation, and with PFS and OS.

2. Association of complete metabolic response (CMR) with IMWG response, and the presence/absence of minimal residual disease (MRD)

3. Comparison of the following between ASCT and consolidation arms:
   i) Complete metabolic response (CMR) rate
   ii) Number of focal lesions with residual uptake > liver
   iii) Maximum standardised uptake value (SUVmax) of the single hottest lesion
   iv) Paramedullary disease – number of lesions and SUVmax
   v) Extramedullary disease – number of lesions and SUVmax
   vi) Diffuse bone marrow uptake > liver (if present) at baseline
   vii) Response category (CMR/PMR/SMD/PMD)

4. Association of achieving CMR with PFS and OS5. Assessment of improvement in PET-CT functional response after 6 months of maintenance therapy (only applicable to patients not in CMR at post-ASCT/consolidation scan)

18.6. **Interim Analyses**

A formal review will take place once fifty-three patients have completed response assessment at the end of induction therapy. Recruitment will not be halted during the review period. A report on these patients will be provided to the Independent Data Monitoring Committee (IDMC), who will confirm whether the study can continue or trial closure is justified.

The study will be regularly monitored by trials unit staff, with input from members of the Trial Management Group. A report will be provided to the IDMC, who will review efficacy and toxicity data, at least once each year. Any decision to stop the trial will be communicated to Trial Steering Committee (TSC).

19. ETHICAL AND REGULATORY CONSIDERATIONS

In conducting the trial, the Sponsor, UCL CTC and sites shall comply with all relevant guidance, laws and statutes, as amended from time to time, applicable to the performance of clinical trials including, but not limited to:

- the principles of ICH Harmonised Tripartite Guideline for Good Clinical Practice (CPMP/ICH/135/95) as set out in Schedule 1 (Conditions and Principles of Good Clinical Practice and for the Protection of Clinical Trial Subjects) of the Medicines for Human Use (Clinical Trials) Regulations 2004 and the GCP Directive 2005/28/EC, as set out in SI 2006/1928
- Human Rights Act 1998
- Data Protection Act 1998, and any other applicable UK and EU data protection legislation and regulations
- Freedom of Information Act 2000
- Human Tissue Act 2004
- Human Tissue Act (Scotland) 2006
- Medicines Act 1968
- Medicines for Human Use (Clinical Trials) UK Regulations SI 2004/1031, and subsequent amendments
- Good Manufacturing Practice
- The UK Policy Framework for Health and Social Care Research, issued by the Health Research Authority or the Scottish Health Department Research Governance Framework for Health and Community Care (Second Edition 2006)

Where applicable, UCL CTC and sites will work towards implementation of the EU Clinical Trials Regulation EU/536/2014.

19.1. Ethical Approval

The trial will be conducted in accordance with the World Medical Association Declaration of Helsinki entitled 'Ethical Principles for Medical Research Involving Human Subjects' (1996 version) and in accordance with the terms and conditions of the ethical approval given to the trial.

The trial has received a favourable opinion from the London – City & East Research Ethics Committee (REC) and Health Research Authority (HRA) approval for conduct in the UK.

UCL CTC will submit Annual Progress Reports to the REC, which will commence one year from the date of ethical approval for the trial.

19.2. Regulatory Approval

A Clinical Trial Authorisation (CTA) has been granted for the trial.

The trial will be conducted at approved trial sites in accordance with the trial protocol and the terms of the CTA granted by the MHRA.

19.3. Site Approvals

Evidence of assessment of capability and capacity by the Trust/Health Board R&D for a trial site must be provided to UCL CTC. Sites will only be activated when all necessary local approvals for the trial have been obtained.

19.4. Protocol Amendments

UCL CTC will be responsible for gaining ethical and regulatory approvals for amendments made to the protocol and other trial-related documents. Once approved, UCL CTC will ensure that all amended documents are distributed to sites and CLRNs as appropriate.

Site staff will be responsible for acknowledging receipt of documents and for implementing all amendments.

19.5. Patient Confidentiality & Data Protection

Patient identifiable data, including initials, date of birth and NHS number (or equivalent) will be required for the registration process and will be provided to UCL CTC. UCL CTC will preserve patient confidentiality and will not disclose or reproduce any information by which patients could be identified. Data will be stored in a secure manner and UCL CTC trials are registered in accordance with the Data Protection Act 2018 with the Data Protection Officer at UCL.

Patient identifiable data, including initials, date of birth and NHS number and other trial information will be provided to the central laboratories at the UCL Department of Research Pathology and Myeloma laboratory at the UCL Cancer Institute in order to process the samples. The Department of Research Pathology and Myeloma laboratory will preserve patient confidentiality and will not disclose or reproduce any information by which patients could be identified.

Patient identifiable data, including initials, date of birth and NHS number will be provided to the central laboratory at HMDS in order to process the samples. When logging the samples and identifiers onto their laboratory information system (HILIS) which is linked to the national spine, HMDS will become aware of full patient names. However HMDS will preserve patient confidentiality and will not disclose or reproduce any information by which patients could be identified.

20. SPONSORSHIP AND INDEMNITY

20.1. Sponsor Details

Sponsor Name:	University College London
Address:	Joint Research Office Gower Street London WC1E 6BT
Contact:	Director of Research Support
Tel:	020 3447 9995/2178 (unit admin)
Fax:	020 3447 9937

20.2. Indemnity

University College London holds insurance against claims from participants for injury caused by their participation in the clinical trial. Participants may be able to claim compensation if they can prove that UCL has been negligent. However, as this clinical trial is being carried out in a hospital, the hospital continues to have a duty of care to the participant of the clinical trial. University College London does not accept liability for any breach in the hospital's duty of care, or any negligence on the part of hospital employees. This applies whether the hospital is an NHS Trust or otherwise.

Participants may also be able to claim compensation for injury caused by participation in this clinical trial without the need to prove negligence on the part of University College London or another party. Participants who sustain injury and wish to make a claim for compensation should do so in writing in the first instance to the Chief Investigator, who will pass the claim to the Sponsor's Insurers, via the Sponsor's office.

Hospitals selected to participate in this clinical trial shall provide clinical negligence insurance cover for harm caused by their employees and a copy of the relevant insurance policy or summary shall be provided to University College London, upon request.

21. FUNDING

The trial is endorsed by Cancer Research UK. Amgen are supporting the central coordination of the trial through UCL CTC and providing Carfilzomib free of charge for the trial duration.

Research Part A costs will be reimbursed to sites as per the finance section of the CTSA.

22. PUBLICATION POLICY

The results of the CARDAMON trial will be presented at relevant conferences and published in a peer reviewed journal. The primary publication from CARDAMON will be written by the TMG. Authorship will be in line with the ICMJE recommendations, and will typically include the CI, TMG members, representatives of UCL CTC including the trial coordinator and trial statistician, and PIs at sites that make a significant contribution to patient recruitment.

Abstracts and papers will be reviewed by Amgen prior to submission in accordance with the requirements of the Trial Drug Supply Agreement.

The clinicaltrials.gov number of the trial and the funder reference number will be quoted in all publications.

Sites may not publish data pertaining to CARDAMON patients without prior written permission from the TMG.

Data generated from the CARDAMON trial will be the property of UCL as Trial Sponsor.

23. REFERENCES

1. Kumar SK, Rajkumar SV, Dispenzieri A, et al. Improved survival in multiple myeloma and the impact of novel therapies. Blood 2008;111:2516-20.
2. Koreth J, Cutler CS, Djulbegovic B, et al. High-dose therapy with single autologous transplantation versus chemotherapy for newly diagnosed multiple myeloma: A systematic review and meta-analysis of randomized controlled trials. Biology of blood and marrow transplantation : journal of the American Society for Blood and Marrow Transplantation 2007;13:183-96.
3. Attal M, Harousseau J-L, Stoppa A-M, et al. A Prospective, Randomized Trial of Autologous Bone Marrow Transplantation and Chemotherapy in Multiple Myeloma. New England Journal of Medicine 1996;335:91-7.
4. Child JA, Morgan GJ, Davies FE, et al. High-Dose Chemotherapy with Hematopoietic Stem-Cell Rescue for Multiple Myeloma. New England Journal of Medicine 2003;348:1875-83.
5. Alvares CL, Davies FE, Horton C, et al. Long-term outcomes of previously untreated myeloma patients: responses to induction chemotherapy and high-dose melphalan incorporated within a risk stratification model can help to direct the use of novel treatments. British journal of haematology 2005;129:607-14.
6. van de Velde HJ, Liu X, Chen G, Cakana A, Deraedt W, Bayssas M. Complete response correlates with long-term survival and progression-free survival in high-dose therapy in multiple myeloma. Haematologica 2007;92:1399-406.
7. Barlogie B, Kyle RA, Anderson KC, et al. Standard chemotherapy compared with high-dose chemoradiotherapy for multiple myeloma: final results of phase III US Intergroup Trial S9321. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2006;24:929-36.
8. Harousseau J, Attal M, Leleu X, et al. Bortezomib plus dexamethasone as induction treatment prior to autologous stem cell transplantation in patients with newly diagnosed multiple myeloma: results of an IFM phase II study. Haematologica 2006;91:1498-505.
9. Cavo M, Di Raimondo F, Zamagni E, et al. Short-term thalidomide incorporated into double autologous stem-cell transplantation improves outcomes in comparison with double autotransplantation for multiple myeloma. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2009;27:5001-7.
10. Oakervee HE, Popat R, Curry N, et al. PAD combination therapy (PS-341/bortezomib, doxorubicin and dexamethasone) for previously untreated patients with multiple myeloma. British journal of haematology 2005;129:755-62.
11. Sonneveld P, Schmidt-Wolf IG, van der Holt B, et al. Bortezomib induction and maintenance treatment in patients with newly diagnosed multiple myeloma: results of the randomized phase III HOVON-65/ GMMG-HD4 trial. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2012;30:2946-55.
12. Moreau P, Avet-Loiseau H, Facon T, et al. Bortezomib plus dexamethasone versus reduced-dose bortezomib, thalidomide plus dexamethasone as induction treatment before autologous stem cell transplantation in newly diagnosed multiple myeloma. Blood 2011;118:5752-8; quiz 982.
13. Cavo M, Tacchetti P, Patriarca F, et al. Bortezomib with thalidomide plus dexamethasone compared with thalidomide plus dexamethasone as induction therapy before, and consolidation therapy after, double autologous stem-cell transplantation in newly diagnosed multiple myeloma: a randomised phase 3 study. The Lancet 2010;376:2075-85.
14. Rosinol L, Oriol A, Teruel AI, et al. Superiority of bortezomib, thalidomide, and dexamethasone (VTD) as induction pretransplantation therapy in multiple myeloma: a randomized phase 3 PETHEMA/GEM study. Blood 2012;120:1589-96.

15. Khan ML, Reeder CB, Kumar SK, et al. A comparison of lenalidomide/dexamethasone versus cyclophosphamide/lenalidomide/dexamethasone versus cyclophosphamide/bortezomib/dexamethasone in newly diagnosed multiple myeloma. British journal of haematology 2012;156:326-33.
16. Richardson PG, Weller E, Lonial S, et al. Lenalidomide, bortezomib, and dexamethasone combination therapy in patients with newly diagnosed multiple myeloma. Blood 2010;116:679-86.
17. Kumar S, Flinn I, Richardson PG, et al. Randomized, multicenter, phase 2 study (EVOLUTION) of combinations of bortezomib, dexamethasone, cyclophosphamide, and lenalidomide in previously untreated multiple myeloma. Blood 2012;119:4375-82.
18. Cavo M, Pantani L, Petrucci MT, et al. Bortezomib-thalidomide-dexamethasone is superior to thalidomide-dexamethasone as consolidation therapy after autologous hematopoietic stem cell transplantation in patients with newly diagnosed multiple myeloma. Blood 2012;120:9-19.
19. Attal M, Lauwers-Cances V, Marit G, et al. Lenalidomide Maintenance after Stem-Cell Transplantation for Multiple Myeloma. New England Journal of Medicine 2012;366:1782-91.
20. McCarthy PL, Owzar K, Hofmeister CC, et al. Lenalidomide after Stem-Cell Transplantation for Multiple Myeloma. New England Journal of Medicine 2012;366:1770-81.
21. Bensinger W. Stem-cell transplantation for multiple myeloma in the era of novel drugs. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2008;26:480-92.
22. Wang M, Delasalle K, Feng L, et al. CR represents an early index of potential long survival in multiple myeloma. Bone marrow transplantation 2010;45:498-504.
23. Fermand JP, Ravaud P, Chevret S, et al. High-dose therapy and autologous peripheral blood stem cell transplantation in multiple myeloma: up-front or rescue treatment? Results of a multicenter sequential randomized clinical trial. Blood 1998;92:3131-6.
24. Kumar SK, Lacy MQ, Dispenzieri A, et al. Early versus delayed autologous transplantation after immunomodulatory agents-based induction therapy in patients with newly diagnosed multiple myeloma. Cancer 2012;118:1585-92.
25. Palumbo A, Bringhen S, Rajkumar V, et al. Second primary malignancies (SPM) in newly diagnosed myeloma (MM) patients treated with lenalidomide (Len): Meta-analysis of 6,383 individual patient data (IPD). ASCO Meeting Abstracts 2013;31:8517.
26. Rawstron AC, Gregory WM, de Tute RM, et al. Minimal residual disease in myeloma by flow cytometry: independent prediction of survival benefit per log reduction. Blood 2015;125:1932-5.
27. Regelink JC, Minnema MC, Terpos E, et al. Comparison of modern and conventional imaging techniques in establishing multiple myeloma-related bone disease: a systematic review. British journal of haematology 2013;162:50-61.
28. Bartel TB, Haessler J, Brown TL, et al. F18-fluorodeoxyglucose positron emission tomography in the context of other imaging techniques and prognostic factors in multiple myeloma. Blood 2009;114:2068-76.
29. Zamagni E, Patriarca F, Nanni C, et al. Prognostic relevance of 18-F FDG PET/CT in newly diagnosed multiple myeloma patients treated with up-front autologous transplantation. Blood 2011;118:5989-95.
30. Moreau P, Attal M, Karlin L, et al. Prospective Evaluation of MRI and PET-CT at Diagnosis and before Maintenance Therapy in Symptomatic Patients with Multiple Myeloma Included in the IFM/DFCI 2009 Trial. Blood 2015;126.
31. Zamagni E, Nanni C, Mancuso K, et al. PET/CT Improves the Definition of Complete Response and Allows to Detect Otherwise Unidentifiable Skeletal Progression in Multiple Myeloma. Clin Cancer Res 2015;21:4384-90.

32. Weinhold N, Chavan SS, Heuck C, et al. High Risk Multiple Myeloma Demonstrates Marked Spatial Genomic Heterogeneity Between Focal Lesions and Random Bone Marrow; Implications for Targeted Therapy and Treatment Resistance. Blood 2015;126.
33. Demo SD, Kirk CJ, Aujay MA, et al. Antitumor activity of PR-171, a novel irreversible inhibitor of the proteasome. Cancer research 2007;67:6383-91.
34. Arastu-Kapur S, Shenk K, Parlati F, Bennett MK. Non-Proteasomal Targets of Proteasome Inhibitors Bortezomib and Carfilzomib. ASH Annual Meeting Abstracts 2008;112:2657-.
35. Kirk CJ, Jiang J, Muchamuel T, et al. The Selective Proteasome Inhibitor Carfilzomib Is Well Tolerated in Experimental Animals with Dose Intensive Administration. ASH Annual Meeting Abstracts 2008;112:2765-.
36. Kuhn DJ, Chen Q, Voorhees PM, et al. Potent activity of carfilzomib, a novel, irreversible inhibitor of the ubiquitin-proteasome pathway, against preclinical models of multiple myeloma. Blood 2007;110:3281-90.
37. Vij R, Wang M, Kaufman JL, et al. An open-label, single-arm, phase 2 (PX-171-004) study of single-agent carfilzomib in bortezomib-naive patients with relapsed and/or refractory multiple myeloma. Blood 2012;119:5661-70.
38. Alsina M, Trudel S, Furman RR, et al. A Phase I Single-Agent Study of Twice-Weekly Consecutive-Day Dosing of the Proteasome Inhibitor Carfilzomib in Patients with Relapsed or Refractory Multiple Myeloma or Lymphoma. Clinical Cancer Research 2012;18:4830-40.
39. Alsina M, Trudel S, Vallone M, Molineaux C, Kunkel L, Goy A. Phase 1 Single Agent Antitumor Activity of Twice Weekly Consecutive Day Dosing of the Proteasome Inhibitor Carfilzomib (PR-171) in Hematologic Malignancies. ASH Annual Meeting Abstracts 2007;110:411-.
40. Jagannath S, Vij R, Stewart K, et al. Final results of PX-171-003-A0, part 1 of an open-label, single-arm, phase II study of carfilzomib (CFZ) in patients (pts) with relapsed and refractory multiple myeloma (MM). ASCO Meeting Abstracts 2009;27:8504.
41. Siegel DS, Martin T, Wang M, et al. A phase 2 study of single-agent carfilzomib (PX-171-003-A1) in patients with relapsed and refractory multiple myeloma. Blood 2012;120:2817-25.
42. Siegel D, Wang L, Orlowski RZ, et al. PX-171-004, An Ongoing Open-Label, Phase II Study of Single-Agent Carfilzomib (CFZ) in Patients with Relapsed or Refractory Myeloma (MM); Updated Results From the Bortezomib-Treated Cohort. ASH Annual Meeting Abstracts 2009;114:303-.
43. Wang L, Siegel D, Kaufman JL, et al. Updated Results of Bortezomib-Naive Patients in PX-171-004, An Ongoing Open-Label, Phase II Study of Single-Agent Carfilzomib (CFZ) in Patients with Relapsed or Refractory Myeloma (MM). ASH Annual Meeting Abstracts 2009;114:302-.
44. Vij R, Siegel DS, Jagannath S, et al. An open-label, single-arm, phase 2 study of single-agent carfilzomib in patients with relapsed and/or refractory multiple myeloma who have been previously treated with bortezomib. British journal of haematology 2012;158:739-48.
45. Papadopoulos K, Lee P, Singhal S, et al. A phase 1b/2 study of prolonged infusion carfilzomib in patients with relapsed and/or refractory multiple myeloma: updated efficacy and tolerability from the completed 20/56 mg/m2 expansion cohort of PX-171-007. Blood 2011;118.
46. Lendvai N, Landau H, Lesokhin A, et al. Phase II Study of Infusional Carfilzomib in Patients with Relapsed or Refractory Multiple Myeloma. ASH Annual Meeting Abstracts 2012;120:947-.
47. Berenson JR, Klein L, Rifkin RM, et al. A Phase 1, Dose-Escalation Study (CHAMPION-1) Investigating Weekly Carfilzomib In Combination With Dexamethasone For Patients With Relapsed Or Refractory Multiple Myeloma. Blood 2013;122:1934.
48. Niesvizky R, Wang L, Orlowski RZ, et al. Phase Ib Multicenter Dose Escalation Study of Carfilzomib Plus Lenalidomide and Low Dose Dexamethasone (CRd) in Relapsed and Refractory Multiple Myeloma (MM). ASH Annual Meeting Abstracts 2009;114:304-.

49. Wang M, Martin T, Bensinger W, et al. Final results from the phase Ib/II study (PX-171-006) of carfilzomib, lenalidomide, and low-dose dexamethasone (CRd) in patients with relapsed or progressive multiple myeloma. ASCO Meeting Abstracts 2013;31:8529.
50. Badros AZ, Vij R, Martin T, et al. Carfilzomib in multiple myeloma patients with renal impairment: pharmacokinetics and safety. Leukemia 2013;27:1707-14.
51. Harvey D, Lonial S, Patel P, McCulloch L, Niesvizky R, Kaufman JL. 17th Congress of the European Hematology Association, Amsterdam, The Netherlands, June 14–17, 2012. Haematologica 2012;97:346.
52. Singhal S, Siegel DS, Martin T, et al. Integrated Safety From Phase 2 Studies of Monotherapy Carfilzomib in Patients with Relapsed and Refractory Multiple Myeloma (MM): An Updated Analysis. ASH Annual Meeting Abstracts 2011;118:1876-.
53. Jakubowiak AJ, Dytfeld D, Griffith KA, et al. A phase 1/2 study of carfilzomib in combination with lenalidomide and low-dose dexamethasone as a frontline treatment for multiple myeloma. Blood 2012;120:1801-9.
54. Sonneveld P, Asselbergs E, Zweegman S, et al. Phase 2 study of carfilzomib, thalidomide, and dexamethasone as induction/consolidation therapy for newly diagnosed multiple myeloma. Blood 2015;125:449-56.
55. Asselberg-Hacker E, Zweegman S, van der Holt B, et al. Dose Escalation Phase 2 Trial Of Carfilzomib Combined With Thalidomide and Low-Dose Dexamethason In Newly Diagnosed, Transplant Eligible Patients With Multiple Myeloma. A Trial Of The European Myeloma Network. Blood 2013;122:688.
56. Mikhael J, Reeder CB, Libby EN, et al. A phase I/II trial of cyclophosphamide, carfilzomib, thalidomide, and dexamethasone (CYCLONE) in patients with newly diagnosed multiple myeloma. ASCO Meeting Abstracts 2012;30:8010.
57. Mikhael JR, Reeder CB, Libby EN, et al. Phase Ib/II trial of CYKLONE (cyclophosphamide, carfilzomib, thalidomide and dexamethasone) for newly diagnosed myeloma. British journal of haematology 2015.
58. Jakubowiak AJ, Dytfeld D, Jagannath S, et al. Final Results of a Frontline Phase 1/2 Study of Carfilzomib, Lenalidomide, and Low-Dose Dexamethasone (CRd) in Multiple Myeloma (MM). ASH Annual Meeting Abstracts 2011;118:631-.
59. Sonneveld P, Hacker E, Zweegman S, et al. Carfilzomib Combined with Thalidomide and Dexamethasone (CARTHADEX) As Induction Treatment Prior to High-Dose Melphalan (HDM) in Newly Diagnosed Patients with Multiple Myeloma (MM). A Trial of the European Myeloma Network EMN. ASH Annual Meeting Abstracts 2011;118:633-.
60. Bringhen S, Petrucci MT, Larocca A, et al. Carfilzomib, cyclophosphamide, and dexamethasone in patients with newly diagnosed multiple myeloma: a multicenter, phase 2 study. Blood 2014;124:63-9.
61. Bensinger WI, Vescio R, Gasparetto C, et al. A Multi-Center Phase 1b, Open-Label, Dose-Finding Pilot Study to Evaluate the Combination of Carfilzomib and Cyclophosphamide with Dexamethasone (CCyD) Prior to Autologous Stem Cell Transplant (ASCT) in Patients with Transplant Eligible Newly Diagnosed M…2014.
62. Sonneveld P, Asselbergs E, Van der Holt B, et al. Dose Escalation Phase 2 Trial of Carfilzomib Combined with Thalidomide and Low-Dose Dexamethason in Newly Diagnosed, Transplant Eligible Patients with Multiple Myeloma. a Trial of the European Myeloma Network2014.
63. Lendvai N, Hilden P, Devlin S, et al. A phase 2 single-center study of carfilzomib 56 mg/m2 with or without low-dose dexamethasone in relapsed multiple myeloma. Blood 2014;124:899-906.
64. Papadopoulos KP, Siegel DS, Vesole DH, et al. Phase I Study of 30-Minute Infusion of Carfilzomib As Single Agent or in Combination With Low-Dose Dexamethasone in Patients With Relapsed and/or Refractory Multiple Myeloma. Journal of Clinical Oncology 2014.

65. Barrington SF, Mackewn JE, Schleyer P, et al. Establishment of a UK-wide network to facilitate the acquisition of quality assured FDG-PET data for clinical trials in lymphoma. Annals of oncology : official journal of the European Society for Medical Oncology / ESMO 2011;22:739-45.
66. Rawstron AC, Orfao A, Beksac M, et al. Report of the European Myeloma Network on multiparametric flow cytometry in multiple myeloma and related disorders. Haematologica 2008;93:431-8.
67. Group TIMW. Criteria for the classification of monoclonal gammopathies, multiple myeloma and related disorders: a report of the International Myeloma Working Group. British journal of haematology 2003;121:749-57.
68. Rajkumar SV, Dimopoulos MA, Palumbo A, et al. International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma. The Lancet Oncology 2014;15:e538-e48.
69. Blade J, Samson D, Reece D, 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. British journal of haematology 1998;102:1115-23.
70. Durie BG, Harousseau JL, Miguel JS, et al. International uniform response criteria for multiple myeloma. Leukemia 2006;20:1467-73.
71. Rajkumar SV, Harousseau J-L, Durie B, et al. Consensus recommendations for the uniform reporting of clinical trials: report of the International Myeloma Workshop Consensus Panel 1. Blood 2011;117:4691-5.
72. Greipp PR, Miguel JS, Durie BGM, et al. International Staging System for Multiple Myeloma. Journal of Clinical Oncology 2005;23:3412-20.
73. Mosteller RD. Simplified calculation of body-surface area. The New England journal of medicine 1987;317:1098.
74. Du Bois D, Du Bois EF. A formula to estimate the approximate surface area if height and weight be known. 1916. Nutrition (Burbank, Los Angeles County, Calif) 1989;5:303-11; discussion 12-3.
75. Wang Y, Moss J, Thisted R. Predictors of body surface area. Journal of clinical anesthesia 1992;4:4-10.
76. de Tute RM, Jack AS, Child JA, Morgan GJ, Owen RG, Rawstron AC. A single-tube six-colour flow cytometry screening assay for the detection of minimal residual disease in myeloma. Leukemia 2007;21:2046-9.
77. Rawstron AC, Davies FE, DasGupta R, et al. Flow cytometric disease monitoring in multiple myeloma: the relationship between normal and neoplastic plasma cells predicts outcome after transplantation. Blood 2002;100:3095-100.
78. Boellaard R, Delgado-Bolton R, Oyen WJG, et al. FDG PET/CT: EANM procedure guidelines for tumour imaging: version 2.0. Eur J Nucl Med Mol I 2015;42:328-54.
79. Mesguich C, Fardanesh R, Tanenbaum L, Chari A, Jagannath S, Kostakoglu L. State of the art imaging of multiple myeloma: Comparative review of FDG PET/CT imaging in various clinical settings. Eur J Radiol 2014;83:2203-23.

APPENDIX 1: ABBREVIATIONS

ABPI	Association of British Pharmaceutical Industry
ADL	Activities of Daily Living
AE	Adverse Event
ALP	Alkaline phosphatase
ALT	Alanine transaminase
ANC	Absolute Neutrophil Count
AR	Adverse Reaction
ARSAC	Administration of Radioactive Substances Advisory Committee
AST	Aspartate aminotransferase
ASCT	Autologous stem cell transplantation
AUC	Area Under the Curve
BJP	Bence-Jones protein
BUN	Blood urea nitrogen
CALGB	Cancer And Leukemia Group B
CarCyDex	Carfilzomib, cyclophosphamide, dexamethasone
CarThaDex	Carfilzomib, thalidomide, dexamethasone
CEA	Carcinoembryonic Antigen
CI	Chief Investigator
CIOMS	Council for International Organisations of Medical Sciences
CLRN	Comprehensive Local Research Network
CMR	Complete metabolic response
CR	Complete response
CrCl	Creatinine clearance
CRF	Case Report Form
CT	Computerised Tomography
CT-L	Cytotoxic T Cell
CTA	Clinical Trial Authorisation
CTAAC	Clinical Trials Advisory & Awards Committee
CTCAE	Common Terminology Criteria for Adverse Events
CTSA	Clinical Trial Site Agreement
CXR	Chest X-Ray
DFCI	Dana-Faber Cancer Institute
DFS	Disease Free Survival
DLT	Dose limiting toxicity
DOR	Duration of response
DSUR	Development Safety Update Report
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDTA	Ethylene Diamine Tetra Acetate
EEA	European Economic Area
EudraCT	European Clinical Trials Database
FBC	Full Blood Count
FISH	Fluorescent In Situ Hybridization
G-CSF	Granulocyte Colony Stimulating Factor

GFR	Glomerular Filtration Rate
GIMEMA	Gruppo Italiano Malattie Ematologiche
GLP	Good laboratory practice
Hb	Haemoglobin
HDT	High dose therapy
HMDS	Haematological Malignancy Diagnostic Service
HOVON	Hemato-Oncologie voor Volwassenen Nederland
HUS	Haemolytic uremic syndrome
IB	Investigator's Brochure
ICH GCP	International Conference of Harmonisation-Good Clinical Practice
IDMC	Independent Data Monitoring Committee
IFM	Intergroupe Francophone du Myelome
IMiDs	Immunomodulatory derivatives
IMP	Investigational Medicinal Product
IMWG	International myeloma working group
INR	International Normalised Ratio
ISF	Investigator site file
ISRCTN	International Standard Randomised Controlled Trial Number
IUD	Intra-uterine device
IUS	Intra-uterine system
IV	Intravenous
LDH	Lactate Dehydrogenase
LFT	Liver Function Tests
LLN	Lower Limit of Normal
MAHA	Microangiopathic haemolytic anaemia
MHRA	Medicines and Healthcare products Regulatory Agency
MM	Multiple Myeloma
MPR	Melphalan/Prednisolone/Lenalidomide
MR	Minimal response
MRC	Medical Research Council
MRD	Minimal residual disease
MRI	Magnetic Resonance Image
MTD	Maximum tolerated dose
NCRI	National Cancer Research Institute
NCRN	National Cancer Research Network
NDA	New Drug Application
NGS	Next generation sequencing
NRES	National Research Ethics Service
NYHA	New York Heart Association
ORR	Objective response rate
OS	Overall Survival
PA	Posteroanterior
PBMC	Peripheral Blood Mononuclear Cell
PBSCH	Peripheral blood stem cell harvest
PCR	Polymerase Chain Reaction
PD	Progressive Disease
PET-CT	Positron Emission Tomography – Computerised Tomography

PFS	Progression Free Survival
PI	Principal Investigator
PMD	Progressive metabolic disease
PMR	Partial metabolic response
PN	Peripheral Neuropathy
PO	By mouth
PR	Partial Response
PRES	Posterior reversible encephalopathy syndrome
QA	Quality assurance
RBC	Red blood cells
REC	Research Ethics Committee
RECIST	Response Evaluation Criteria in Solid Tumours
RSI	Reference safety information
RTOG	Radiotherapy Oncology Group
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
sCR	Stringent CR
SD	Stable Disease
(S)FLC	(Serum) free light chain
SMD	Stable metabolic disease
SPC	Summary of Product Characteristics
SSA	Site Specific Assessment
SUSAR	Suspected Unexpected Serious Adverse Reaction
SUV	Standardised Uptake Value
TLS	Tumour lysis syndrome
TMA	Thrombotic microangiopathy
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee
TTP	Thrombotic thrombocytopenic purpura
UCL CTC	CR UK and UCL Cancer Trials Centre
U&E	Urea and Electrolytes
ULN	Upper Limit of Normal
VGPR	Very Good Partial Response
VTD	Bortezomib (Velcade®), thalidomide, dexamethasone
WBC	White Blood Cells
WOCBP	Woman of childbearing potential

APPENDIX 2: DEFINITION OF MYELOMA AND RELATED DISEASES

Criteria as per the International Myeloma Working Group[67,68]

Symptomatic Multiple Myeloma

- Clonal bone marrow plasma cells ≥10% or biopsy-proven bony or histologically proven plasmacytoma* **and**
- Myeloma-related organ or tissue impairment, including one or more of the myeloma defining events below

*Clonality should be established by showing κ/λ-light-chain restriction on flow cytometry, immunohistochemistry, or immunofluorescence. Bone marrow plasma cell percentage should preferably be estimated from a core biopsy specimen; in case of a disparity between the aspirate and core biopsy, the highest value should be used.

Myeloma related organ or tissue impairment (end organ damage)

Evidence of end organ damage that can be attributed to the underlying plasma cell proliferative disorder, specifically:

- Hypercalcaemia: serum calcium >0·25 mmol/L (>1 mg/dL) higher than the upper limit of normal or >2·75 mmol/L (>11 mg/dL)
- Renal insufficiency: creatinine clearance <40 mL per min† or serum creatinine >177 μmol/L (>2 mg/dL)
- Anaemia: haemoglobin value of >20 g/L below the lower limit of normal, or a haemoglobin value <100 g/L
- Bone lesions: one or more osteolytic lesions on skeletal radiography, CT, or PET-CT*

Any one or more of the following biomarkers of malignancy:

- Clonal bone marrow plasma cell percentage***** ≥60%
- Involved:uninvolved serum free light chain ratio****** ≥100
- >1 focal lesions on MRI studies*******

***** If bone marrow has less than 10% clonal plasma cells, more than one bone lesion is required to distinguish from solitary plasmacytoma with minimal marrow involvement.
****** These values are based on the serum Freelite assay (The Binding Site Group, Birmingham, UK). The involved free light chain must be ≥100 mg/L.
******* Each focal lesion must be 5 mm or more in size.

APPENDIX 3: MODIFIED INTERNATIONAL MYELOMA WORKING GROUP UNIFORM CRITERIA OF RESPONSE AND PROGRESSION

Adapted from Bladé et al[69], Durie et al[70] & Rajkumar et al[71]

For patients with measurable secretory disease:

- **If paraprotein ≥10g/L at registration,** the paraprotein alone can be followed for determination of MR, PR or VGPR. Additional urine and marrow studies are required to confirm CR/sCR.
- **If paraprotein <10g/L with measurable light chain disease at registration** (24h urine BJP ≥200mg/24h and/or difference in light chains ≥100mg/l): **either 24h BJP or serum FLC** can be followed for determination of MR, PR or VGPR. Additional serum, urine and marrow studies are required confirm CR/sCR.
- **If soft tissue plasmacytomas are present at baseline** these must also be monitored to confirm response assessment, along with any M-protein

For patients with measurable non-secretory disease:

- **Repeat bone marrow aspirate or trephine is required for response assessment**
- **If soft tissue plasmacytomas are present at baseline** these must also be monitored to confirm response assessment

Serum and/or urinary M-protein responses should only be calculated using sequential measurements made in the **same laboratory using the same method.**

All response categories require 2 consecutive assessments made at any time. Serum and/or urine studies, where applicable, may be repeated at any time, at or between scheduled trial visits to confirm response. Bone marrow assessments do not to be repeated to confirm response.

All response categories also require no known evidence of progressive disease.

1. Minimal response (MR)

a. 25-49% reduction in the level of the serum monoclonal paraprotein level
b. 50-89% reduction in 24 hour urinary light chain excretion, which still exceeds 200 mg/24h
c. For patients with light chain myeloma, 25-49% reduction in the difference between involved and uninvolved serum FLC levels

d. For patients with non-secretory myeloma only, 25-49% reduction in plasma cells in bone marrow
e. 25-49% reduction in the size of soft tissue plasmacytomas by radiological investigations if performed
f. No increase in size number of lytic bone lesions on radiological investigations, if performed.
g. MR also includes patients in whom some, but not all, the criteria for PR are fulfilled

2. <u>Partial response (PR) requires:</u>

a. ≥50% reduction in the level of the serum monoclonal paraprotein level
b. Reduction in 24 hour urinary light chain excretion either by a ≥90% or to <200 mg per 24h, if measured
c. For patients with light chain myeloma: a ≥50% reduction in the difference between involved and uninvolved serum FLC levels
d. In addition, ≥50% reduction in the size of soft tissue plasmacytomas, if present at baseline
e. For patients with non-secretory myeloma only, ≥50% reduction in plasma cells, in a bone marrow, provided baseline percentage was ≥30%
f. No increase in size or number of lytic bone lesions on radiological investigations, if performed.

3. **<u>Very Good Partial Response (VGPR)</u>**

a. Serum and urine M-protein detectable by immunofixation but not on electrophoresis
   Or
b. ≥90% reduction in serum M protein level
c. Reduction in 24 hour urinary light chain excretion, if measured, to <100mg per 24h.
d. No increase in size or number of lytic bone lesions on radiological investigations, if performed
e. For patients with light chain myeloma, >90% decrease in the difference between involved and uninvolved FLC levels.

Clarification 1: The laboratory lower limit of quantification must be considered for VGPR assessment: if a paraprotein is 'too faint to quantify' it may not be possible to demonstrate a ≥90% reduction in serum M protein for patients with low paraprotein levels at diagnosis (i.e., 10-29g/l). In such cases the patient will remain in PR until they fulfil criteria for CR.

4. <u>Complete Response (CR) requires all of:</u>

a. Negative immunofixation of **both** the serum and urine **and**
b. <5% plasma cells in a bone marrow (confirmation with repeat bone marrow is not needed) **and**

c. No increase in size or number of lytic bone lesions on radiological investigations, if performed (development of a compression fracture does not exclude response) **and**
d. Disappearance of soft tissue plasmacytomas.
e. For patients with light chain myeloma only: a normal FLC ratio of 0.26 to 1.65 (or laboratory-specific normal FLC ratio reference range) in addition to the CR criteria above.

Clarification 2. The presence of oligoclonal bands consistent with oligoclonal immune reconstitution (regenerative bands eg. post ASCT) does not exclude CR.
Clarification 3. Both serum and urine studies must be performed and repeated once to confirm CR, even if there was no detectable urinary or serum M-protein at baseline.
Clarification 4: After achieving CR, response remains at CR until M-protein becomes detectable again, i.e. 'too faint to quantify' or higher. Once the M-protein is detectable, the patient will then be assessed as either VGPR or PR unless they fit the criteria for PD.

5. Stringent complete response (sCR) requires that:

CR as defined above plus:
a. Normal FLC ratio
b. Absence of clonal cells in bone marrow by immunohistochemistry or immunofluorescence

6. Stable disease

Not meeting the criteria of either minimal response or progressive disease

7. Progressive disease (PD) requires one or more that:

a. ≥25% increase from lowest response in serum monoclonal paraprotein level which must also be an absolute increase of at least 5g/L and confirmed by at least one repeated investigation.
b. ≥25% increase from lowest response level in 24 hour urinary light chain excretion, if measured, which must also be an absolute increase of at least 200mg/24h and confirmed by at least one repeated investigation.
c. For patients with light chain myeloma (the serum and urine M-protein are unmeasurable), ≥25% increase from the lowest response level in the difference between involved and uninvolved serum FLC levels. The absolute increase must be >100 mg/L and confirmed by at least one repeated investigation.
d. Only in patients without measurable disease (by urine or serum M-protein or serum FLC): ≥25% increase in plasma cells in bone marrow, which must also be an absolute increase of at least 10%
e. Definite increase in the size of existing bone lesions or soft tissue plasmacytomas.
f. Development of new lytic bone lesions or soft tissue plasmacytomas. Development of a compression fracture does not exclude response.

g. Development of hypercalcaemia, corrected serum calcium >11.5mg/dL or 2.8mmol/L, not attributable to any other cause

Clarification 5. The 'lowest response level' or nadir value does not need to be confirmed, i.e., can be from a single disease assessment.

APPENDIX 4: HBV SEROLOGY

Patients with evidence of past infection with the hepatitis B virus (HBV) may be eligible for trial registration at the discretion of the treating clinician and should be managed in accordance with local guidelines.

The table below contains a brief outline for interpretation of HBV serology.

HBsAg	HBsAb	HBcAb	HBV DNA	Interpretation	Eligible Y/N
-	+	-	-	Typically seen when vaccinated; reactivation risk very low	Y
-	+	+	-	Past infection; low risk reactivation	Y at discretion of PI*
-	- (<10IU/L)	+	-	Past infection; higher risk reactivation	Y at discretion of PI*
-	+/-	+	+	Occult infection	N
+	Any results			Chronic carrier or infection	N

HBsAg = Hepatitis B surface antigen
HBsAb = Hepatitis B surface antibody
HBcAb = Hepatitis B core antibody

Sites should liaise with local hepatologists regarding appropriate monitoring and prophylaxis.

APPENDIX 5: International Staging System (ISS) for Multiple Myeloma (MM)

Adapted from Greipp et al[72]

Stage	Criteria
I	Serum β2-microglogulin <3.5mg/L; serum albumin >3.5g/dL
II	Serum β2-microglogulin <3.5mg/L but serum albumin < 3.5g/dL Or Serum β2-microglogulin 3.5 to < 5.5mg/L irrespective of the serum albumin level.
III	Serum β2-microglobulin ≥ 5.5mg/L

APPENDIX 6: EXPECTED ADVERSE EVENTS FOR TRANSPLANT

The following AEs are commonly associated with high dose melphalan and ASCT and will be considered expected for this treatment, even if fatal:

Abnormal hepatic enzymes	Myelosuppression
Abnormal pancreatic enzymes	Nausea
Anorexia/loss of appetite	Oedema
Bone marrow suppression	Premature menopause:
- Anaemia	- Dry skin
- Leucopenia	- Hot flushes
- Neutropenia	- Vaginal dryness
- Thrombocytopenia	Psychological effects:
Cardiac toxicity:	- Altered body image
- Cardiac arrhythmia	- Depression
- Heart failure	- Fear
- Tachycardia	Pulmonary toxicity:
Decreased sex drive	- Cough
Diarrhoea	- Shortness of breath (dyspnoea)
Dry mouth	- Pneumonitis
Electrolyte disturbances	- Pulmonary fibrosis
Fatigue	Reduced thyroid function
Febrile neutropenia	Renal impairment:
Fever	- Renal failure/nephropathy
Gastritis	- Bladder inflammation
Haemorrhage	- Pain when passing urine
Hair loss/alopecia	Secondary neoplasm
High blood pressure	Thromboembolism
Infection: All sites/pathogens	Thrombosis (NB fatal thrombosis is unexpected)
Infertility	Vomiting
Mucositis:	Weakness
- Abdominal discomfort	Weight loss
- Flatulence	
- Mouth sores or ulcers	

APPENDIX 7: BODY SURFACE AREA CALCULATIONS FOR DOSAGE

Body surface area (BSA) should be calculated using either the Mosteller[73] or DuBois and DuBois formula[74,75]:

a. Mosteller Formula for BSA

$$\sqrt{\left(\frac{Height \times Weight}{3600}\right)}$$

where weight is in kilograms and the height is in centimetres

b. Dubois and Dubois Formula

$$(Weight^{0.425} \times Height^{0.725}) \times 0.007184$$

where the weight is in kilograms and the height is in centimetres.

APPENDIX 8: BIOLOGICAL SAMPLES FOR MRD STATUS AND BIOMARKER ANALYSIS

For more details, please refer to the Laboratory Manual in the Investigator Site File.

1. Minimal residual disease (MRD) assessment by multiparameter flow cytometry (MFC)

There is growing evidence for the prognostic value of MRD status by MFC on outcome of ASCT, however similar data on patients treated with chemotherapy alone is lacking. The value of MRD status in risk stratification to ASCT or no is also not established. Thus the prognostic impact of MRD status on patient outcomes in the CARDAMON status remains one of the key study objectives.

Patient BM samples will be assessed for suitability for MRD monitoring at baseline. Follow up samples will then be assessed for MRD at defined time points during their treatment on the CARDAMON study. The MRD assay is routinely used in the laboratory in Leeds[76,77]. Samples are also being stored with a view to subsequent analysis (if required by next generation sequencing (NGS)).

Bone Marrow aspirate - 2 ml in EDTA must be sent to HMDS, Leeds for MRD analysis at the following time points:

- Baseline – prior to starting induction therapy
- Post PBSCH
- Day 100 post ASCT or after 4 cycles of consolidation
- After 6 months of maintenance therapy (or at 6 months after commencing maintenance if patient completes less than 6 months of maintenance therapy)

IT IS ESSENTIAL THAT BONE MARROW SAMPLES ARE SHIPPED IMMEDIATELY AFTER COLLECTION!

Please ensure the following information is provided, to ensure samples are correctly identified and can be processed promptly:

Information required	On sample	On Sample Form
Trial name		X
Patient trial number if allocated	X	X
Patient NHS number	X	X
Patient initials	X	X
Patient date of birth	X	X
Date of sample collection		X
Site name		X
Site contact details		X

to be sent to:

Cardamon Trial c/o Dr Roger Owen

HMDS
Level 3, Bexley Wing
St. James's Institute of Oncology
Beckett Street
Leeds, LS9 7TF

Note: Whilst being prepared to be posted the bone marrow sample should be kept at room temperature. Please send samples on the same day; if same day postage is not possible, keep sample at 4°C overnight until posting.

Please avoid taking or shipping samples on Friday. DO NOT FREEZE the bone marrow sample.

For more details, please refer to the *'Laboratory Manual'* in the Investigator Site File.

2. Genomic and pathway analyses

These cell signalling pathways are central to plasma cell biology and survival. Differential activation of these pathways may dictate response to therapy, in particular protocols that are based on proteasome inhibition. Tumour cells at baseline and at the time of relapse will be obtained and analysed for activation of these pathways, using a combination of molecular (RNA and DNA-based) and cellular assays (Western blotting, flow cytometry). Peripheral blood samples will also be collected to serve as normal comparator for tumour cells in each patient.

Bone Marrow aspirate - 4-6 ml in EDTA- must be sent to UCL Cancer Institute, London at the following time points:

- Baseline – prior to starting induction therapy
- Day 100 post ASCT or after 4 cycles of consolidation
- At relapse

Please refer to the Laboratory Manual for advice regarding how to acquire good quality bone marrow aspirates.

Peripheral blood sample - 8 ml in EDTA - must be sent to UCL Cancer Institute, London at the following time points:

- Baseline – prior to starting induction therapy
- Day 100 post ASCT or after 4 cycles of consolidation
- At relapse

N.B Where possible blood samples should be couriered with the bone marrow aspirate. If sent separately please use first class post with appropriate packaging.

3. Cytogenetics/FISH

Sites not able to perform cytogenetics/FISH at baseline or relapse must send an additional 4-8 ml of bone marrow aspirate in lithium heparin to UCL Cancer Institute, London. This is only applicable to selected sites as agreed with UCL CTC.

Please provide the following information:

Information required	On sample	On Sample Form
Trial name		X
Patient trial number if allocated	X	X
Patient NHS number	X	X
Patient initials	X	X
Patient date of birth	X	X
Date of sample collection	X	X
Site name		X
Site contact details		X

IT IS ESSENTIAL THAT BONE MARROW SAMPLES ARE SHIPPED IMMEDIATELY BY A COURIER!

The courier will be arranged by the Myeloma laboratory at the UCL Cancer Institute. You need to contact the laboratory (tel. no below) with full details of the pickup point (site address) **ONE BUSINESS DAY** in advance of the bone marrow being taken to ensure prompt delivery.

Samples will be shipped to:

Cardamon Trial
Myeloma Lab, ext. 46233
UCL Cancer Institute
3rd floor Haematology
72 Huntley Street
London, WC1E 6BT
Tel: 0207 679 6233 or 0207 679 0993

Avoid taking samples on Friday. If this is not possible, samples must be obtained early in the morning. Samples must arrive at UCL by 2pm at the latest in order to be processed. DO NOT FREEZE the bone marrow or blood samples.

4. Immunohistochemistry for plasma cell phenotype

All patients will have a bone marrow trephine sample taken at screening, alongside the aspirate sample. This is part of routine management. These samples will be processed at local sites and samples will be sent to UCL (see below), for immuno-histochemical staining for plasma cell antigens of interest, including CD20, CD56, CD28, BCMA and cyclin D1 and D2. The impact of expression levels of these antigens will explored to identify useful biomarkers for disease response and outcomes of patients treated on the ASCT or non-ASCT (consolidation) arms.

Samples of diagnostic bone marrow trephine (paraffin-embedded tumour block or 15 unstained slides) must be sent to Department of Research Pathology at UCL as soon as possible once a patient has been registered.

Please provide the following information:

Information required	On sample	On Sample Form
Trial name		X
Patient trial number if allocated	X	X
Patient NHS number	X	X
Patient initials	X	X
Patient date of birth	X	X
Block number	X	X
Date of sample collection		X
Site name		X
Site contact details		X
Whether block to be returned to site		X

to be sent to:

Dr Manuel Rodriguez-Justo, Cardamon Trial
Department of Research Pathology,
UCL - Faculty of Biomedical Sciences,
Rockefeller Building, 21 University Street,
London, WC1E 6JJ

APPENDIX 9: PET-CT SUB-STUDY: METHODS, EVALUATION AND DATA ANALYSIS

Before a PET centre can participate in the trial it must undergo the formal PET site accreditation process. Whole body PET-CT scans will be performed in centres accredited by the UK PET Core Lab, based at St Thomas' Hospital, London [www.ncri-pet.org.uk/] with standardised methods for scanning preparation, acquisition and quality control, used successfully in previous multicentre national and international trials[65].

Further details and written procedures for the site accreditation process will be provided by the UK PET Core Lab based at St Thomas' Hospital, London in the CARDAMON Imaging Manual. Sites should contact the UK PET Core Lab pet-trials@kcl.ac.uk at an early stage to determine the requirements for the accreditation procedure.

Most patients will undergo a total of two PET-CT scans, with a third as directed by results of the second scan. The **first scan** will be at baseline, within 28 days prior to cycle, 1 day 1 of chemotherapy.

The **second scan** will take place 100 days post-ASCT (ASCT arm) or after 4 cycles of consolidation with Carfilzomib, Cyclophosphamide and Dexamethasone [CarCyDex] (consolidation arm).

For patients receiving ASCT, scans should be performed as close to the day 100 time point as possible, but may be performed between day 100-128. Scans must be performed before starting maintenance therapy.

For patients receiving consolidation with CarCyDex, scans should be performed within 14-28 days after completing consolidation, and prior to starting maintenance therapy.

All PET-CT scans will be centrally reviewed for the purposes of trial analysis by staff at the Core Lab. PET is an exploratory endpoint and not used for treatment decisions. Local reports should be routinely issued for PET-CT scans and factors documented that might affect patient management e.g. infection, fracture or any clinical findings that could require immediate attention. For the second scan, the Core Lab will notify the investigator within two weeks of receipt of the scan whether the patient achieved a complete metabolic response (CMR) or not. If not CMR a third scan should be scheduled.
A **third scan** will only be performed in patients who are not in complete metabolic response (CMR) on their PET-CT scans at the post-ASCT/consolidation chemotherapy time point. This third scan will take place after 6 months of maintenance therapy. Scans should again be performed as close to the 6-month time point as possible, and no more

than 28 days after the 6 month time-point. These time points will coincide with bone marrow testing for minimal residual disease (MRD)

As above, all PET-CT scans will be centrally reviewed for the purposes of trial analysis by staff at the Core Lab. PET-CT is an exploratory endpoint and not used for treatment decisions. Local reports should be routinely issued for PET-CT scans and factors documented that might affect patient management e.g. infection, fracture or any clinical findings that could require immediate attention. The patient's management should not be altered on the basis of the result of the third scan unless discussed with, and agreed by, the TMG.

Myeloma imaging and reporting using PET/CT

Whole body imaging will be performed from vertex to toes, if tolerated, with arms down, but at least to the mid-femora using European guidelines for tumour imaging with FDG 60 minutes post-FDG administration[78].

Transfer of images to PET Core Lab

The electronic transfer of anonymised, non-identifiable patient scan images and reports from the multiple centres to the central review site will be coordinated and collated by the UK PET Core Lab based at St Thomas' Hospital. These will be anonymised prior to transfer.

The UK PET Core Lab recommended method for electronic data transfer from NHS PET Centres is via the NHS Secure File Transfer Service. Centres without access to the NHS Secure File Transfer Service can transfer anonymised non-identifiable patient data using the UK PET Core Lab SFTP server which uses secure encryption transfer methods and is password protected.

Further details are provided in the CARDAMON Imaging Manual.

Reporting

Scans will be reported as per local practice, but for trial purposes, all scans will be centrally reviewed at St Thomas' Hospital by Professor Sally Barrington and Dr Victoria Warbey. Scans will be reported using *a priori* criteria proposed at the international workshop on PET in lymphoma and myeloma 2016, based on previous reports and criteria developed for the CassioPET study[31,79].

The following will be reported at baseline:

1. Number of focal lesions
2. Maximum standardised uptake value (SUV max) of the single hottest lesion
3. Number of lytic lesions on CT
4. Paramedullary disease
5. Extramedullary disease
6. Diffuse bone marrow uptake ≥ liver (if present) at baseline

The following will be reported at response:

1. Number of focal lesions with residual uptake > liver
2. Maximum standardised uptake value (SUV max) of the single hottest lesion
3. Paramedullary disease – number of lesions and SUVmax
4. Extramedullary disease – number of lesions and SUVmax
5. Diffuse bone marrow uptake > liver (if present) at baseline
6. Response category CMR/PMR/SMD/PMD *(note: these response categories will be reported to the UCL CTC only; sites will receive a simplified report confirming 'CMR' or 'not CMR' to direct the third scan)*

APPENDIX 10: PROTOCOL VERSION HISTORY

Protocol:		**Amendments:**	
Version no.	**Date**	**Protocol Section**	**Summary of main changes from previous version.**
1.0	01.12.14		
2.0	15.01.15	9.7-9.9	Follow up schedule changed to include longer term follow up
		3.1 & 17.4	Addition of PFS 2 as a secondary endpoint
		8.1	Change of manufacturer, and clarification of dose rounding in aseptic pharmacy in response to comments from CPAS
		12.2	Change of RSI to Carfilzomib IB
		16.1	End of trial will now be 10 years from the date of last patient rather than 3 years to allow long term follow up of patients for PFS2
3.0	24.02.15	2.2, 8.2.1 & 8.2.6	Change of dosage of Carfilzomib to 56mg/m^2 and addition of rationale for increased dose level
		6.3	Clarification to inclusion criteria 8 and 10 regarding growth factor and platelet support
		8.1 & 8.3.1	Dosage should now be calculated based on the BSA at the start of the cycle rather than baseline BSA
		8.2.4 & 9.2	Clarification to the timing of post-PBSCH assessments
		16.2	Change of the archiving requirement for sites from 5 to 25 years
3.1	18.05.15	6.1 & Appendix 7	Clarification to the BM aspirate sample volume required for FISH analysis
		6.3	Clarification to the exclusion criteria to allow patients with prior treatment with local radiotherapy, bisphosphonate or corticosteroids to remain eligible for the trial
		8.1 & 8.3.1	Dose modification will now be based on changes in patient weight rather than BSA in line with the Carfilzomib prescribing information
		8.1 & Appendix 6	Site may now use either the Dubois or Mosteller formula for calculating BSA
		9.1, 9.4 & 9.5	Validity period for FBC increased to 48hrs
		12.2.1	Change to the categorisation of causal relationship of adverse events to an IMP.
4.0	04.04.16	Throughout	Onyx Pharmaceuticals Inc. replaced with Amgen Ltd.
		1.1	Increase in the number of sites to 25
		1.1, 3.1, 17.4	Addition of quality life as a trial endpoint
		6.1	Changes to the validity periods of pre-registration assessments. Skeletal surveys no longer required, sites are now permitted to do other whole body imaging (e.g. MRI, PET-CT) as per their local policy
		7.2	Clarification to randomisation requirements
		8.1	Carfilzomib information updated to reflect licensed status in Europe.
		8.2.1	Guidance added regarding the recommended treatment for patients failing to achieve a PR to induction.
		8.2.3	Clarification to samples needed in the case of an inadequate PBSCH
		8.3.1	Clarification to dose modifications required for CHF and infection Site investigators may now use an additional step up dose where necessary for hypertensive patients

Protocol:		**Amendments:**	
Version no.	**Date**	**Protocol Section**	**Summary of main changes from previous version.**
		8.4	Guidance has been added on pseudohyponatremia. Anti-emetics, anti-diarrhoeals and laxatives may now be given as per institutional guidelines
		12.3	Clarification of the reporting procedure for SUSARs and SAEs
		Appendix 5	Addition of appendix for interpretation of serology results.
		Appendix 8	Change to the labelling of patient samples, sample should now be marked with patient NHS number, initials and date of birth.
4.1 Urgent Safety Measure	13/01/2017	1.2	Trial schema flow chart updated with change to maintenance treatment.
		8.2.7	Maintenance treatment - carfilzomib dose change to 20mg/m^2 on cycle 1 day 1 and 56mg/m^2 for subsequent doses, plus additional dexamethasone to be given as supportive care.
		8.3.1	Carfilzomib dose reductions section updated with instructions for management of suspected or confirmed TMA.
		8.3.3	Dexamethasone dose reductions/adjustments section updated with two tables, one for induction and consolidation, and one for maintenance supportive care dose. Additional guidance given about reducing dose during maintenance.
		8.4	IV Hydration subsection updated with further guidance for maintenance treatment. New subsection added for monitoring, prophylaxis and treatment of TMA. Required concomitant medication section updated to included additional dexamethasone dose during maintenance.
		9.5	Blood pressure and monitoring for signs and symptoms of TMA added to existing table.
		Appendix 2	Changes made in line with changes to section 9.5.
5.0	05/04/2017	1.1, 1.2, 2.1, 3, 3,1, 3.2, 3.3, 4.2, 5, 6.1, 8.2.5, 8.2.6, 8.2.7, 9.3, 9.4, 9.5, 17, 18, appendix 8	Updated to reflect introduction of an optional PET-CT sub-study.
		1.1, 6.3	Clarifications made to inclusion/exclusion criteria.
		4.1, 4.2	Site requirements updated in line with current UCL CTC protocol template.
		6.1	Timeframes for some eligibility investigations amended to draw into line with standard management of myeloma patients. Clarification added about results that may be pending at the time of registration.
		6.1, 7.2	Further clarification added about the requirement to send the local cytogenetics report to UCL CTC for review.
		6.1, 7.2, 8.2.4, 8.2.5, 8.2.6, 8.2.7, 9.2, 9.3, 9.4, 9.5, 9.6, 9.7, 9.8, Appendix 7	Clarification added about sending samples to the central laboratories.

Protocol:		Amendments:	
Version no.	**Date**	**Protocol Section**	**Summary of main changes from previous version.**
		6.3.1	Provision added for patients who have had >160mg steroids to be entered into trial with TMG's approval, and for patients who are on systemic antimicrobial therapy.
		6.4	Pregnancy and contraception guidance updated in line with Clinical Trials Facilitation Group guidance.
		7.2. 8.2.1, 8.2.6	References to diary cards amended to reflect change of process: diary cards will now be given out and collected on a cycle-by-cycle basis.
		7.3	Clarifications added about timing, eligibility and stratification at randomisation.
		8.1	Clarification added about the IMPs and NIMPs for the trial. Detailed preparation and administration guidance for carfilzomib removed; this will now be provided in a separate document (the Summary of Drug Arrangements), thus negating the need for protocol amendments should the manufacturer update their advice. The named distributor of Carfilzomib has been changed
		8.2.1, 8.2.6, 8.3.2, 8.3.3	Provision added for patients to receive IV cyclophosphamide and dexamethasone during induction and consolidation if they are unable to swallow tablets.
		8.2.1, 8.2.3, 9.7	Further information added about requirements for CRF submission and follow up where patients discontinue treatment early or are ineligible for randomisation.
		8.3.1	Clarification added to guidance regarding actions to be taken if patients have suspected of confirmed thrombotic microangiopathy. Additional guidance added regarding actions to be taken in the event of suspected or confirmed cases of posterior reversible encephalopathy syndrome.
		8.4	Minor clarifications added to section on management of thrombotic microangiopathy. Guidance added on monitoring and management of poorly controlled hypertension. Additional guidance added on pre-medication with dexamethasone to mitigate against infusion reactions.
		8.6	Guidance on reporting of drug handling errors added in line with current UCL CTC protocol template.
		9.1, 9.2, 9.3, 9.5, 9.5	Clarifications added regarding assessments required during, and on completion of, trial treatment.
		9.6	Clarifications added regarding assessments required if patients relapse at any time during the trial
		9.7, 9.8	Detailed guidance added on follow up requirements for patients who stop trial treatment early for different reasons, or once treatment has been completed in its entirety.
		10	Clarifications added about analyses to be undertaken on research samples for the trial.
		11, 13, 14, 16, 19, 21, 22	Sections updated in line with current UCL CTC protocol template
		12	Section updated in line with current UCL CTC protocol template. Addition of guidance on reporting thrombotic microangiopathy; these will now be exempt from reporting on the SAE form and rather will be collected in an expedited fashion as an Urgent Event.

Protocol:		Amendments:	
Version no.	**Date**	**Protocol Section**	**Summary of main changes from previous version.**
		15.1	List of reasons to withdraw from trial treatment extended to include outcome of interim response assessments, stem cell harvests and the updated pregnancy and contraceptive requirements.
		15.2	Clarification added about what will be done with trial samples in the event that a patient withdraws consent during the trial.
		Appendix 2	"Quick reference guide to patient assessments" deleted. Assessment summary tables are now contained within section 9 only. Numbering of subsequent appendices updated accordingly.
		Appendix 4	Corrections made in line with current guidelines
		Throughout	Minor typographic and formatting corrections.
6.0	14/03/2018	TMG members	TMG details updated to include a new member
		1.1, 6	Inclusion criteria – permissible ECOG score clarified
		1.1	Measurable disease clarified
		4	Clarification that relevant license(s) must be in place in relation to medical radiation exposure for the PET-CT sub-study
		5	Requirement for patients to have 24 hours to consider partipation in the trial eased if it helps patients to avoid unnecessary visits
		6.1	MUGA scans can be performed in place of echocardiograms if required.
		6.1	4-6mL bone marrow aspirate is required for the UCL Myeloma Lab within 3 months of registration.
		6.1	Baseline PET-CT scan to be performed within 28 days of registration
		6.4	Timelines for males to donate sperm after participation in the trial updated
		7, 12	Allowance added for sites to e-mail registration and randomisation case report forms along with serious adverse event and urgent event forms
		7.2	Trephine block shipment clarified
		8	Dose banding to be permitted for all trial IMPs
		8.2.7	Clarification of review of post 6-months maintenance PET-CT scan for PET positive patients
		8.4	Requirement to capture vitamins and supplements on the concomitant medication page of the CRF removed.
		8.5, 9.5	Clinical monitoring hypertension in patients who experience a TMA clarified
		8.8	Out of hours emergency drug specific advice section removed
		9	Timing of assessments clarified
		9.6	Assessments to be performed at relapse/progression clarified
		12	Guidelines on the responsibility for reporting safety events following the transfer of care for a trial patient added
		15	Guidelines to process the transfer of a patient's care added
		19	Updated to reference applicable laws / regulations / guidelines
		Appendix 2	Text added to clarify the definition of myeloma
		Appendix 3	Updated with guidance for non-secretory patients
		Appendix 7	Labelling requirements for cytogenetic/FISH samples sent centrally clarified
		Appendix 8	Requirement and process for third PET-CT scan clarified

Protocol:		**Amendments:**	
Version no.	**Date**	**Protocol Section**	**Summary of main changes from previous version.**
6.1	13/06/2018	6.1	Clarified MUGA scans can be performed in place of echocardiograms at the end of induction time point
		8.2.6	Incorrect dexamethasone dose updated in the footnote of the protocol
		8.3.3	Duplicate paragraph removed
		9.5	End of maintenance assessment timeframe clarified
		Appendix 9	Version history log for protocol v6.0 updated to include all changes
7.0	05/06/2019	TMG members	TMG member details updated
		1.2	Trial schema updated to reflect addition of step-up doses during consolidation and maintenance
		8.2.1, 8.2.6, 8.2.7	Clarification on start of cycle/within cycle delays during induction, consolidation and maintenance
		8.2.1, 8.2.6	Additional reminder for dexamethasone at 4mg po/IV given prior to carfilzomib doses during cycle 1
		8.2.6	Additional step-up dose of carfilzomib during consolidation cycle 1 on days 1 and 2
		8.2.7, 9.2	Additional guidance for out of time-window research samples
		8.3.1	Additional guidance for missed doses during treatment cycles
		8.3.1	Additional dose reduction guidelines for thrombocytopenia with active bleeding
		8.3.1	Dose modification guidelines for non-haematologic events updated in line with guidelines provided in the Investigator Brochure ed 19.0 for carfilzomib
		8.3.2, 8.3.3	Guidance to refer to the SPC for dose modification guidelines for cyclophosphamide and dexamethasone
		8.3.3	Amended guidance on reducing dexamethasone beyond 6mg and additional guidance on increasing beyond 10mg
		8.4	Additional reminder that dexamethasone 4mg po/IV should be administered before carfilzomib during the 1st cycle of induction and consolidation. During every cycle of maintenance, dexamethasone 10mg should be given on the day of dosing and the day after dosing
		10.0	Clarification on the assessments performed in the central laboratories
		12.2.2	Clarification on events that are exempt from SAE reporting
		16.2	Archiving periods amended in line with applicable regulatory requirements
		19.5	Clarification on the types of patient identifiable data collected in the central laboratories
		Appendix 5	Addition of table for International Staging System for multiple myeloma
7.1	23/07/2019	1.2	Trial schema updated to amend the dose of dexamethasone during consolidation