CATALYST

A single arm open labeled multicentre phase 1b dose escalation study of Carfilzomib taken in combination with Thalidomide and Dexamethasone in relapsed AL amyloidosis (CATALYST Trial)

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The Chief Investigator and the JRO have discussed this protocol. The investigators agrees to perform the investigations and to abide by this protocol.
The investigator agrees to conduct the trial in compliance with the approved protocol, EU GCP and UK Regulations for CTIMPs (SI 2004/1031; as amended), the UK Data Protection Act (1998), the Trust Information Governance Policy (or other local equivalent), the current Research Governance Framework, the GMO (Contained Use) Regulations 2000 (and subsequent amendments), the Sponsor's SOPs, and other regulatory requirements as amended.

Coordinating Centre:

For general queries, supply of trial documentation and central data management please contact:

CATALYST Trial Coordinators:

Geraldine Murden
Clinical Trials Research Unit
Leeds Institute of Clinical Trials Research
University of Leeds
Leeds
LS2 9JT

Tel: 0113 343 9369

Fax: 0113 343 4345

Email: medcatal@leeds.ac.uk

Erin Peat
Clinical Trials Research Unit
Leeds Institute of Clinical Trials Research
University of Leeds
Leeds
LS2 9JT

Tel: 0113 343 1658

Fax: 0113 343 4345

Email: medcatal@leeds.ac.uk

Other trial contacts:

Chief Investigator: Dr Ashutosh Wechalekar
Address: National Amyloidosis Centre
University College Medical School (Royal Free Campus)
Royal Free Hospital, Rowland Hill Street, London, NW3 2PF
Tel: 020 7433 2758
Fax: 020 7433 2817
Email: a.wechalekar@ucl.ac.uk

Co-Investigator: Dr Julian Gillmore
Address: University College Medical School (Royal Free Campus)
Royal Free Hospital, Rowland Hill Street, London, NW3 2PF
Tel: 020 7433 2726
Fax: 020 7433 2817
Email: j.gillmore@ucl.ac.uk

Trial Statistician: Nick Ward,
Address: Clinical Trials Research Unit
Leeds Institute of Clinical Trials Research
University of Leeds
Leeds
LS2 9JT
Tel: 0113 343 4887
Fax: 0113 343 1471
Email: N.Ward@leeds.ac.uk

National Amyloidosis Centre (NAC/UK NAC), Royal Free Hospital

Laboratory Contact – Serum Samples

To be collected, as per standard practice, on Day 1 of each chemotherapy cycle

Name & Address:	Wendy Taylor (Specimen Reception) National Amyloidosis Centre Royal Free & University College Medical School Royal Free Hospital, Rowland Hill Street, London, NW3 2PF
Tel:	020 7433 2890
Fax:	020 7433 2817

Trial Management Group (TMG):

Dr A Wechalekar	Chief Investigator	Royal Free Hospital
Dr J Gillmore	Co-Investigator	Royal Free Hospital
Dr Helen Lachmann	Reader in Medicine	UCL
Dr Sadie Reed	Head of Trial Management	Leeds CTRU
Dr Sarah Brown	Division Director & Scientific Lead	Leeds CTRU

Trial Registration

Only authorised members of staff from the UK NAC have permission to register participants into the trial.

Tel: CTRU 0113 343 1658 (Monday – Friday 9am – 5pm except Public and University holidays). Details of University Holidays can be found in the Investigator Site File.

Reporting Serious Adverse Events (SAEs)

Complete the SAE CRF for all SAEs occurring in the trial and fax to the CTRU within 24 hours of becoming aware of the event:

Fax: CTRU: 0113 343 4345

A receipt will be sent for all received SAEs. ***If a receipt is not received within two working days contact the CTRU.***

Reporting Suspected Unexpected Serious Adverse Reactions (SUSARs)

Complete the SUSAR CRF for all SUSARs occurring in the trial and fax to the CTRU within 24 hours of becoming aware of the event:

Fax: CTRU: 0113 343 4345

A receipt will be sent for all received SUSARs. ***If a receipt is not received within two working days contact the CTRU***.

Reporting Dose Limiting Toxicities (DLTs)

Complete the DLT CRF for all DLTs occurring in cycle 1 of treatment and fax to the CTRU immediately and no later than 24 hours of becoming aware of the event:

Fax: CTRU: 0113 343 4345

A receipt will be sent for all received DLTs. ***If a receipt is not received within two working days contact the CTRU***.

Reporting Pregnancies

Report all pregnancies to the CTRU using the Notification of Pregnancy CRF within 24 hours Fax: CTRU: 0113 343 4345

A receipt will be sent for all received pregnancy reports. ***If a receipt is not received within two working days contact the CTRU***.

Pregnancies resulting in a congenital anomaly must also be reported as an SAE

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1.0 Protocol Summary

1.1 Summary of Trial Design

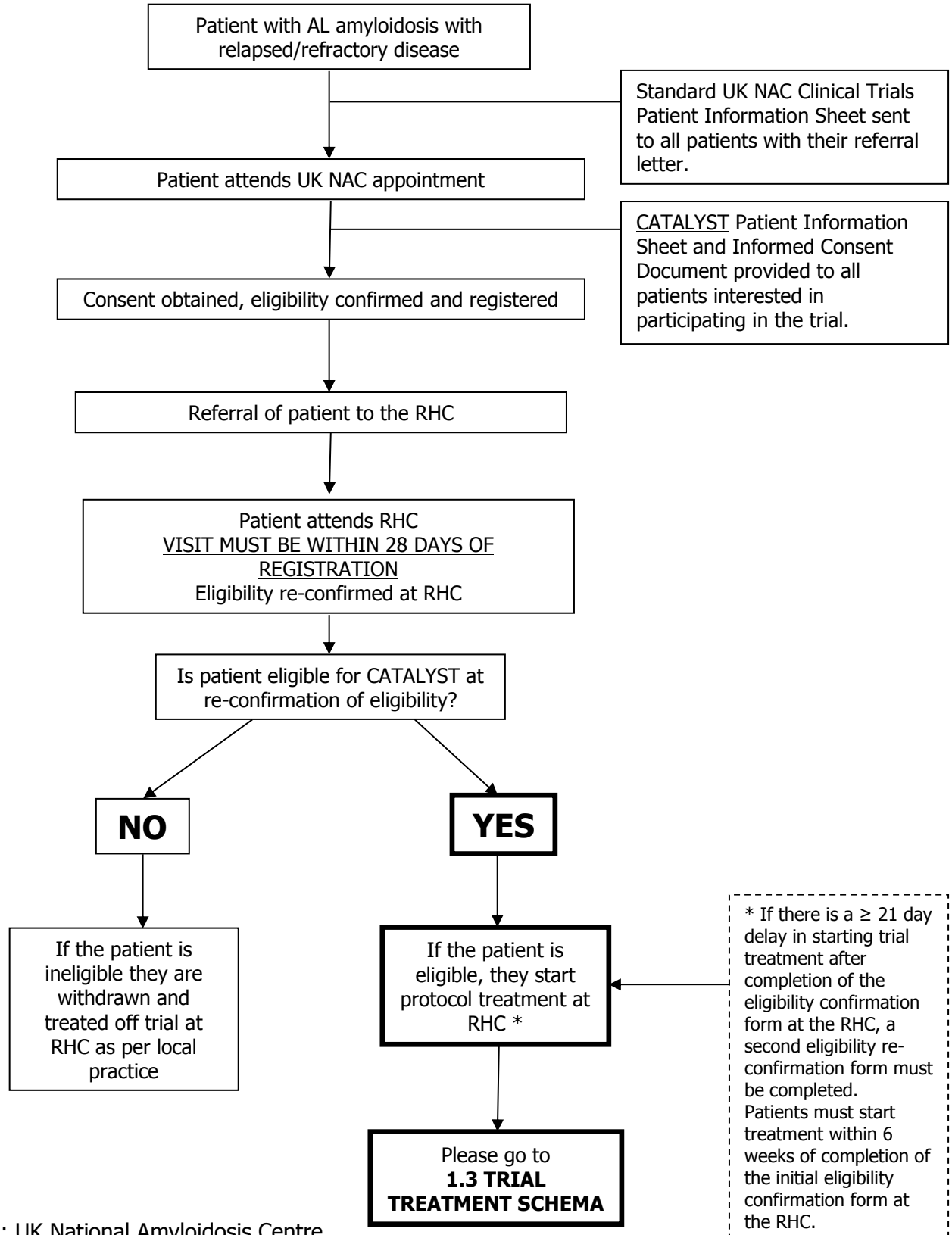
Title:	A single arm open labeled multicentre phase 1b dose escalation study of Carfilzomib taken in combination with Thalidomide and Dexamethasone in relapsed AL amyloidosis (CATALYST Trial)
EudraCT no:	2015-000954-40
Sponsor name & no:	University College London 14/0786
Funder name & no.:	Amgen 20159879
ISRCTN no:	16308011
Design:	Open label, multi-centre, Phase Ib clinical trial
Aims:	To determine the maximum tolerated dose of Carfilzomib withina combination chemotherapy regimen (KTD) and to access the the safety and tolerability of this regimen in patients with relapsed or refractory AL amyloidosis
Primary endpoint:	Define the MTD and RD of Carfilzomib in combination with TD Safety and toxicity of KTD
Secondary endpoints:	Clonal responses Improvement in amyloidotic organ function Overall Survival at 1 year Relapse free survival at 1 year
Subjects:	Any UK patient with a diagnosis of systemic AL amyloidosis with relapsed or refractory disease after first line treatment. During the dose escalation phase a minium of 6 or a maximum of 18 participants will be recruited. Once the MTD and/or RD has been established a maximum of 20 participants will be recruited.
Inclusion & Exclusion criteria	**Inclusion Criteria** Patients with the following characteristics are eligible for this study: 1. Aged 18 years or greater 2. Diagnosis of systemic AL amyloidosis with 3. exclusion of genetic mutations associated with hereditary amyloidosis and immunohistochemical exclusion of AA and TTR amyloidosis as appropraite 4. Amyloid-related organ dysfunction or organ syndrome 5. Measurable clonal disease 6. Clonal relapse after previous chemotherapy or autograft stem cell transplant OR refractory clonal disease to previous chemotherapy or stem cell transplant 7. Capable of providing written, informed consent and willing to follow study protocol 8. Life expectancy ≥ 6 months 9. ECOG performance status of 0-2 10. Platelet count ≥ $50x10^9$/l) 11. Neutrophil count ≥ $1x10^9$/l) 12. Haemoglobin ≥ 8g/dL 13. Bilirubin <2 times or Alkaline phosphatase <4 times upper limit of normal 14. Female participants of child-bearing potential must have a negative pregnancy test prior to treatment and agree to use dual methods of contraception for the duration of the study and for 30 days following completion of study. Male participants must also agree to use a barrier method of contraception for the duration of the study and for 90 days following completion of study if sexually active with a female of child-bearing potential. Women who could become pregnant must have taken precautions not to become pregnant for 1 month before the start of the study

	15. Participants must comply with the Celgene pregnancy prevention programme for Thalidomide **Exclusion Criteria** Patients with the following characteristics are ineligible for this study (see Appendices for definitions): 16. Overt symptomatic multiple myeloma 17. Amyloidosis of unknown or non-AL type 18. Localised AL amyloidosis (in which amyloid deposits are limited to a typical single organ, for example the bladder or larynx, in association with a clonal proliferative disorder within that organ) 19. Trivial or incidental AL amyloid deposits in the absence of a significant amyloid-related organ syndrome (e.g., isolated carpal tunnel syndrome) 20. Refractory to or progressive disease with an IMid and proteasome inhibitor combination 21. Allogeneic stem cell transplantation 22. Solid organ transplantation 23. Severe peripheral or autonomic neuropathy causing significant functional impairment that, in the investigator's opinion, may interfere with protocol adherence 24. eGFR <20ml/min 25. Ejection fraction < 40% or NYHA class III or IV heart failure or uncontrolled hypertension that concerns the investigator 26. Severe pulmonary Hypertension that, in the investigator's opinion, may interfere with protocol adherence 27. Advanced Mayo stage III disease as defined by hs-Troponin T>0.07 and NT-proBNP >700 pMol/L OR NT-proBNP >1000 pMol/L OR supine SBP <100 mm of Hg 28. Myocardial infarction in the proceeding 6 months or unstable angina or conduction abnormalities uncontrolled by medication or devices 29. Concurrent active malignancies, except surgically removed basal cell carcinoma of the skin or other in situ carcinomas 30. Pregnant, lactating or unwilling to use adequate contraception 31. Systemic infection unless specific anti-infective therapy is employed. 32. Known or suspected HIV infection 33. Contraindication to any of the required concomitant drugs or supportive treatments 34. Any other clinically significant medical disease or condition or psychiatric illness that, in the Investigator's opinion, may interfere with protocol adherence or a participant's ability to give informed consent 35. Previous experimental agents within 3 months before the date of registration 36. Known allergies to Carfilzomib, Thalidomide or Dexamethasone 37. Positive hepatitis B viruses (HBV) test
Planned number of sites:	15
Treatment Summary:	**KTD** (maximum of 6 x 28 day cycles) **KTD protocol** Days 1, 8,15 — 30 minute IV infusions of Carfilzomib at current dose level. All patients will receive Carfilzomib at 20mg/m² on day 1 of cycle 1 and then registered dose level on day 8 of cycle 1 onwards. The dose levels are; • level -1- 27mg/m² • level 0 – 36mg/m² • level 1 – 45mg/m²

	• level 2 - 56mg/m^{2s} Days 1-28 50mg Thalidomide, oral preparation for **cycle 1** Up to 100mg can be considered for cycle 2 onwards Days 1, 8,15 20mg Dexamethasone, oral preparation A maximum of 6 cycles will be administered.
Anticipated duration of recruitment:	24 months
Duration of patient follow up:	Minimum 6 months after registration or 1 month after last cycle for each patient.
Definition of end of trial:	The end of trial is defined as the date of the last participant's last data item. At this point, the end of trial notification will be submitted to the relevant regulatory authorities (e.g. UK MHRA) and ethics committees.
Statistical summary:	**Sample Size** In the dose escalation phase of this study, a minimum of 6 (3 at dose level 0 and 3 at dose level -1)and a maximum of 18 (6 at dose level 0, 1, and 2) patients will recruited in a 3+3 design with cohorts of between 3 and 6 patients, in order to determine maximum tolerated dose (MTD) and recommended dose (RD). At the recommended dose level identified, a further 20 patients will be recruited to further assess safety and toxicities at the RD. **Analysis sets and dose cohorts** All patients that receive at least one dose of Carfilzomib will be included in the safety analysis set. The per protocol analysis set will include all patients with at least one post baseline efficacy assessment who receive at least one dose of Carfilzomib and have no protocol deviations with relevant impact on efficacy. Determination of the MTD in the dose escalation phase of the trial will be based on those patients who have received at least one cycle KTD and will be evaluated between the time of receiving the first dose of Carfilzomib in cycle 1 and the first dose of treatment in cycle 2. The safety review committee will review each DLT and attribute the DLT to the loading dose or the registered dose; any DLT attributed to the loading dose will be excluded when determining the MTD. KTD Patients who do not receive one complete cycle due to experiencing a DLT will be included in the analysis; patients who do not receive at least one complete cycle for reasons other than toxicity, without experiencing a DLT, and who miss a dose of Carfilzomib, more than 14 doses of Thalidomide or 2 doses of Dexamethasone in the first cycle, will be replaced. Evaluability will be considered by the safety review committee on an individual basis to account for attributing DLTs and missed doses to the loading or the registered dose. The RD cohort will include all patients who are registered to receive and receive at least one dose of Carfilzomib at the RD. This cohort will include patients from the dose escalation and dose expansion phases of the study. All patients who do not fulfill this criteria will be included in the non-RD cohort. All safety analyses will be based upon the safety analysis set; safety data from patients not included in this analysis set will be listed separately. All Efficacy analyses will be based upon the per protocol set. **Primary endpoints and analysis** The number of patients experiencing DLTs within the first cycle of KTD will be presented, with descriptive summaries of the specific DLTs observed. Summaries will be presented for each dose level. This data will be presented for patients registered to the dose escalation phase of the study only.

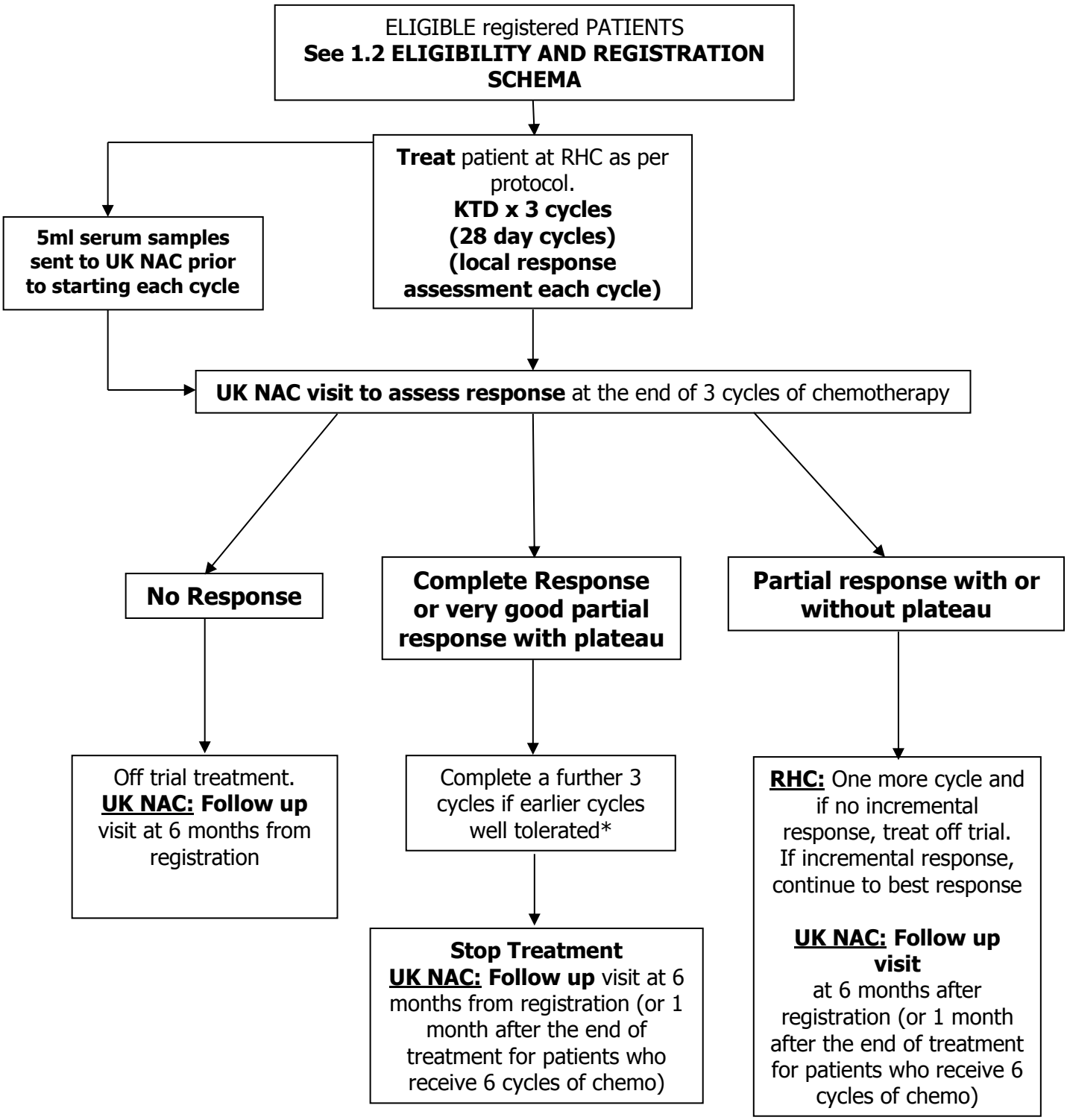
	Further summaries of longer-term tolerability will also be presented for patients registered to the dose escalation phase to include the maximum toxicity grade experienced within the first three cycles of treatment, overall and by cycle. Individual listings of the toxicities, grade and cycle of all toxicities experienced within the first three cycles will be presented. The number of patients experiencing any grade 3 or 4 CTCAE toxicity within all cycles of treatment will be summarised. This will be presented overall and by dose cohort, across all cycles as well as by each cycle. **Secondary endpoints and analysis** • Clonal response rate within 3m, at 3m, within 6m and at 6m • Amyloidotic organ response rate within 3m and 6m • Time to amyloidotic organ response • Number of deaths at 6 months • Number of patients progression free at 6 months • Maximum response • Time to maximum response • Number of patients withdrawing from treatment • Number of patients experiencing dose delays, and compliance profile of KTD. • Relative Dose intensity The secondary objective of assessing activity will be primarily assessed by the clonal response rate. Secondary endpoints will be descriptive with no formal hypothesis testing.

1.2 Eligibility & Registration Schema



UK NAC: UK National Amyloidosis Centre
RHC: Regional Haematology Centre

1.3 Trial Treatment Schema



UK NAC: UK National Amyloidosis Centre
RHC: Regional Haematology Centre

* If tolerance is poor, stop after one cycle after best response

2.0 Introduction

2.1 Background

Amyloidosis is a disorder of protein folding in which normally soluble proteins are deposited as abnormal, insoluble fibrils that progressively disrupt tissue structure and impair function. Systemic AL amyloidosis, which is the commonest amyloid type, is a malignant disorder occurring in a small proportion of individuals with monoclonal B cell dyscrasias and AL amyloidosis is a myeloma defining criteria according to the international working group definition of myeloma 2003 (1). AL amyloidosis occurs at an incidence of 3-5 cases per million population and is the cause of death of between 0.5-1 per thousand individuals in the UK. AL fibrils are derived from monoclonal immunoglobulin light chains which are unique in each patient underlying the remarkably heterogeneous clinical picture in this particular form of amyloidosis; virtually any organ or combination of organs other than the brain may be affected. Treatment in AL amyloidosis is aimed at suppression of the underlying B cell dyscrasia using chemotherapy regimens based on those used for multiple myeloma. Without therapy it is inexorably progressive and until recently the median survival was just 6-15 months. Survival for patients who achieve a less than VGPR or refractory patients is even poorer (2).

2.1.1 Assessing the risk and response to therapy

Many studies have demonstrated a link between hematologic responses and improved organ function and survival. Stopping the production of the toxic light chain species can translate into significant benefit for most patients except those with most advanced organ involvement, while stable hematologic disease despite therapy means it is likely that the effects of the toxic light chain species will continue. Consensus criteria for hematologic and cardiac response have been recently developed and validated (2). Advanced cardiac and extensive organ involvement limit benefits that can be derived from treatment including eligibility for autologous stem cell transplantation (ASCT) and can shorten survival despite treatment (3, 4). Another treatment limitation is related to the type of organ involvement predisposing patients to the adverse effects of specific drugs. In AL amyloidosis clinical trials, it has been a challenge to distinguish drug-specific side effects from disease-mediated organ dysfunction (5)

2.1.2 Treatment of AL amyloidosis

The treatment of systemic AL amyloidosis has evolved to a risk adapted approach based on the end organ damage, particularly cardiac involvement, and the functional status of the patient. Intensive therapies like high dose melphalan followed by an autologous stem cell transplant are considered for patients with limited organ involvement, younger age and excellent functional status. Majority of patients with AL amyloidosis will not be candidates for ASCT and are generally treated with combination chemotherapy.

High dose therapy in AL amyloidosis

Although a systematic review and meta-analysis to evaluate the efficacy of ASCT for AL did not establish that high-dose therapy is superior to conventional chemotherapy in improving survival, many investigators believe that stem cell transplantation is a preferred option if it can be performed safely. Much of the transplant-related research over the past five years has focused on improving patient selection to ensure a safe outcome. ASCT outcomes have improved significantly when comparing patients transplanted before and after 2006. Much of this reduction in mortality relates to refinement in patient selection. Patients who have a troponin T >0.07 μg/L (6) or an NT-proBNP level >5000 pg/mL at diagnosis should not be considered for high-dose therapy (7). The reported ten-year survival after autologous stem cell transplantation is 43% (4), and in patients with hematologic CR, is 60% (8). Patients with cardiac involvement can be safely transplanted if their biomarkers are below the thresholds listed above, and their systolic blood pressure is $\geq$ 100 mmHg, with a median overall survival of 52 months (9). Incorporating refined selection criteria, treatment-related mortality can be reduced from 17 to 4% (10). High-dose therapy does not preclude the use of highly active novel agents following transplant for patients who do not achieve an adequate response. Bortezomib-Dexamethasone following stem cell transplantation improves responses, resulting in high complete response rates and organ improvement (11).

Standard and Novel Agent-Based Chemotherapy

Melphalan and Dexamethasone is considered the standard oral alkylator-based regimen. In a trial using melphalan and Dexamethasone orally in patients ineligible for stem cell transplantation, the hematologic response rate was 67%, complete response rate was 33%, and treatment-related mortality was 4%, with a median survival of 5.1 years (12, 13). The outcome seen in patients treated with melphalan and Dexamethasone is highly dependent on the fraction of patients with advanced cardiac amyloidosis (14). All new regimens should be compared with oral melphalan and Dexamethasone.

Thalidomide and lenalidomide have been used in the treatment of light chain amyloidosis. Treatment-related toxicity was frequent when high dose Thalidomide was used. However, lower doses of Thalidomide appear safer particularly when used in combination with other agents. Thalidomide has been combined with cyclophosphamide and Dexamethasone (15). The hematologic response rate was 74%, and the median overall survival was 41 months and the toxicity of the dose adapted regime is manageable. CTD was the standard treatment for all patients with AL amyloidosis in the UK until the last 3 years since when bortezomib has been increasingly used.

Lenalidomide has been combined with Dexamethasone to treat AL. The nonhematologic toxicity is greater than reported in myeloma trials. Cytopenias, rash, fatigue, and cramps are commonly seen (16). A hematologic response rate of 41% has been reported (17). Lenalidomide has been combined with melphalan and prednisone or Dexamethasone. The maximum tolerated dose of lenalidomide in this combination is 15 mg (18). The hematologic response rate is 58%, complete in 42%. Lenalidomide responses have been reported to be durable (19). Lenalidomide, melphalan and Dexamethasone was recently reported in 16 patients. Hematologic responses were achieved by 43%, with a progression-free survival of 24 months. Grade 3 to 4 toxicities were experienced by 88%, and dose reductions occurred in 85% (20). Lenalidomide has been combined with cyclophosphamide and Dexamethasone and produced an overall hematologic response rate of 60%, including 40% very good partial responses or better and organ responses in 29%. The progression-free survival was 28.3 months. Nonhematologic toxicity $\geq$ grade 3, however, was seen in 71% with 20% of patients dying on study (21). Lenalidomide and Dexamethasone alone has a reported response rate of 41% in patients who have failed both bortezomib and Thalidomide (22). The toxicity of immunomodulatory drugs in amyloidosis patients is significant. Lenalidomide-treated patients also have a higher risk for NT-proBNP rises and early drug discontinuation compared to controls. It is unclear whether immunomodulatory-based therapy leads to increased fluid retention and cardiac toxicity, or whether cardiac response can be accurately assessed patients on immunomodulatory drug therapy (23).

Pomalidomide, with its higher potency, may be better tolerated in patients with light chain amyloidosis. Pomalidomide in patients with previously treated light chain amyloidosis confirmed a hematologic response rate of 48% with a rapid median time to response of 1.9 months. Pomalidomide caused rises in the NT-proBNP. The most common adverse effects, however, were neutropenia and fatigue. This drug warrants further exploration in the treatment of amyloid (24).

Bortezomib is a first in class proteasome inhibitor which appears particularly effective in AL amyloidosis. The first phase-1 dose-escalation study of bortezomib specifically excluded corticosteroids, to ensure that the response was attributable to the proteasome inhibitor, and hematologic responses were seen in 50% (20% complete) of relapsing/refractory patients (25). In this safety study, patients with New York Heart Association class 3-4 heart failure were excluded. Therefore, the safety of bortezomib in patients with advanced cardiac amyloidosis is difficult to gauge. Hypotension has been reported in 12 to 15% of myeloma patients treated with bortezomib, and congestive heart failure has been reported in up to 15% of patients; the impact on patients with cardiac amyloidosis is unknown, and caution needs to be exercised (26). Good clonal responses to Bortezomib have been reported to successfully improve cardiac function in AL amyloidosis (27); and as alluded to earlier, posttransplant consolidation with bortezomib and Dexamethasone is safe and effective. A significant advantage of bortezomib is its ability to rapidly decrease the burden of light chain with a median time to response of less than two months. Both weekly and twice-weekly schedules of bortezomib have been investigated with no significant differences in response rates or progression-free survival, but with significantly less side effects, particularly neuropathy, in patients treated weekly (28). Cyclophosphamide, bortezomib, and Dexamethasone produce rapid and complete hematologic responses in patients with light chain amyloidosis with 71% achieving complete hematologic response, and 3 patients of 17 originally not eligible for stem cell transplantation becoming eligible (29). Data on long-term outcomes with bortezomib are currently lacking; therefore, it cannot be directly compared to melphalan Dexamethasone or high-dose therapy.

2.1.3 Carfilzomib background

Carfilzomib (PR-171) is a tetrapeptide ketoepoxide-based inhibitor specific for the chymotrypsin-like active site of the 20S proteasome. 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.
There is limited data on the use of Carfilzomib in AL amyloidosis, we therefore propose a gradual dose escalation study. There is an ongoing study of Carfilzomib in AL amyloidosis.

2.1.3.1 Phase 1 Experience with Carfilzomib as a Monotherapy in Myeloma

A Phase 1 clinical trial, PX-171-002, testing Carfilzomib in subjects with relapsed/refractory hematologic malignancies, has been completed (30). During the dose escalation portion of the trial, 36 subjects received Carfilzomib on Days 1, 2, 8, 9, 15, and 16 of a 28-day cycle. Subjects with Multiple Myeloma (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.

Hematologic 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 maximize 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 (30). 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. The median number of prior therapies for subjects on this trial was five, and responses were seen in subjects who had relapsed from (including some refractory to) bortezomib and/or immunomodulatory agents. Stable disease also occurred in four NHL and five MM subjects, with subjects on therapy for up to 409 days. Such prolonged therapy, at "full" twice-weekly doses, is not possible with bortezomib.

2.1.3.2 Phase 2 Experience with Carfilzomib as a monotherapy in Myeloma

Two Phase 2 clinical studies are now complete 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. 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, anemia, thrombocytopenia (primarily cyclical), gastrointestinal, and dyspnea. Almost all were Grades 1 or 2. There were reported cases of increased 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 (31).
The response rate in PX-171-003-A0 was 18% 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) (31).

A "stepped up" dosing schedule, referred to as 20/27 mg/m², has subsequently been incorporated into the PX-171-003 study (referred to as PX-171-003-A1) in order to maximize the clinical benefit of Carfilzomib. Patients receive 20 mg/m² for the first cycle and 27 mg/m² thereafter. The study completed enrollment of 266 patietns by the end of 2009 and formed the basis for an accelerated approval NDA filing. To date, this dosing schedule has been well tolerated (30). An independent Safety Oversight Group (SOG) evaluated the safety data from the 40 of 250 patients to be enrolled on the 20/27 schedule and agreed that the trial should proceed without modification. No cases of TLS were observed and rates of BUN and creatinine elevation dropped sharply, with Grade 3/4 renal impairment dropping to 2.2% in A1(from 15% in A0), 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 with 15% Grade 1/2 and one (0.7%) Grade 3/4 event reported to date on PX-171-003-A1[8]. In addition, anemia rates in the PX-171-003-A1 (higher dose) were lower than those reported in the PX-171-003–A0 portion of the study, possibly indicating that the higher dose of Carfilzomib is achieving better clearing of neoplastic cells in the bone marrow allowing superior normal marrow reconstitution. Rates of thrombocytopenia and neutropenia were similar in the two cohorts, with Grade 3 neutropenia in ~5% without any Grade 4 neutropenia to date (31).

In PX-171-004, a first cohort of patients received 20 mg/m². The subset of patients (N=54) that had not seen bortezomib had an ORR of 46% (2% CR, 9% VGPR and 35% PR), while the bortezomib treated patients (N=33) had an ORR of 18% (3% CR, 3% VGPR and 12% PR)(32, 33). The median TTP was 7.6 and 5.3 months in these two groups, respectively. Thus, Carfilzomib can induce very high levels of response in patients who have not previously been treated with bortezomib and, even in bortezomib-treated patients, substantial anti-tumor activity is observed. 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.
The protocol was amended to allow patients to increase to 27 mg/m² in Cycle 2 or later based on tolerability, similar to that used in PX-171-003 – A1.

In a phase 2 study, Carfilzomib was administered 20 mg/m² on days 1 to 2 of cycle 1, 56 mg/m² thereafter (30-minute infusion), in relapsed refractory myeloma (R/RMM) with the option of adding Dexamethasone (20 mg) for suboptimal response/progression (34). Forty-four patients were enrolled, all having prior bortezomib and immunomodulatory drugs and a median of 5 prior regimens. Of 42 response-evaluable patients, 23 (55%) achieved at least partial response (PR). Median (95% confidence interval) duration of response, progression-free, and overall survival were 11.7 (6.7-14.7), 4.1 (2.5-11.8), and 20.3 months (6.4-not estimable), respectively. High-risk cytogenetics did not impact outcomes. Treatment was active in bortezomib-refractory subgroups, but these patients tended to have poorer outcomes. Four/10 patients with prior allogeneic transplant achieved at least PR. Of 6 patients who responded, progressed and had Dexamethasone added, 4 achieved at least stable disease. The most frequent grade 3/4 adverse events (AEs) possibly related to Carfilzomib included lymphopenia (43%), thrombocytopenia (32%), hypertension (25%), pneumonia (18%), and heart failure (11%). Seven patients (16%) discontinued treatment due to AEs. Carfilzomib 56 mg/m² +/- Dexamethasone was tolerable and provided durable responses.

2.1.3.3 Carfilzomib combination therapy in myeloma

PX-171-006 was a Phase 1b study in patients with relapsed multiple myeloma in which Carfilzomib is administered in combination with lenalidomide (Revlimid®) and Dexamethasone. "Low-dose" Dexamethasone 40 mg/day is given on Days 1, 8, 15, and 22 in all cases. Carfilzomib is administered IV on Days 1, 2, 7, 8, 15, and 16; lenalidomide is administered PO on Days 1 through 21. Enrollment has closed in this study, and no MTD was reached. The maximum per protocol doses of Carfilzomib (27mg/m²) with lenalidomide 25mg and low dose Dexamethasone are being used (35).

In a phase 1/2 study in patients with newly diagnosed multiple myeloma (N = 53) assessed CRd--Carfilzomib (20, 27, or 36 mg/m², days 1, 2, 8, 9, 15, 16 and 1, 2, 15, 16 after cycle 8), lenalidomide (25 mg/d, days 1-21), and weekly Dexamethasone (40/20 mg cycles 1-4/5+)--in 28-day cycles (36). After cycle 4, transplantation-eligible candidates underwent stem cell collection (SCC) then continued CRd with the option of transplantation. The maximum planned dose level (Carfilzomib 36 mg/m²) was expanded in phase 2 (n = 36). Thirty-five patients underwent SCC, 7 proceeded to transplantation, and the remainder resumed CRd. Grade 3/4 toxicities included hypophosphatemia (25%), hyperglycemia (23%), anemia (21%), thrombocytopenia (17%), and neutropenia (17%); peripheral neuropathy was limited to grade 1/2 (23%). Most patients did not require dose modifications. After a median of 12 cycles (range, 1-25), 62% (N = 53) achieved at least near-complete response (CR) and 42% stringent CR.

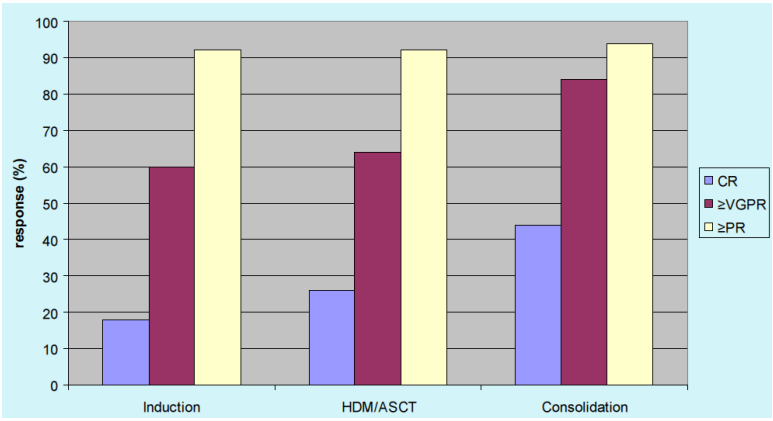
Responses were rapid and improved during treatment. In 36 patients completing 8 or more cycles, 78% reached at least near CR and 61% stringent CR. With median follow-up of 13 months (range, 4-25 months), 24-month progression-free survival estimate was 92%. CRd was well tolerated with exceptional response rates.

Updated efficacy data are presented in the following table:

	CRd: Cohorts 1–5 (CFZ: 15 to 20 mg/m² ; LEN: 10 to 25 mg)		
Response	**Relapsed (n=16)**	**Refractory (n=13)**	**Overall (n=29)**
≥ CR/nCR	5 (31)	1 (8)	6 (21)
≥ VGPR	7 (44)	4 (31)	11 (38)
≥ PR	9 (56)	8 (62)	17 (59)
≥ MR	11 (67)	10 (77)	21 (72)

Together, these results suggest that Carfilzomib, lenalidomide, and low-dose Dexamethasone (CRd) in combination are active and well tolerated and that there are no significant overlapping toxicities (in the dose ranges tested). Importantly, lenalidomide-associated neutropenia and thrombocytopenia do not appear to be exacerbated by concurrent treatment with Carfilzomib, even up to 27mg/m², suggesting that Carfilzomib will combine well with other anti-cancer agents.

The combination of Carfilzomib with cyclophosphamide and Dexamethasone was studied in elderly (≥ 65 years) newly diagnosed patients with myeloma in a multicenter, open-label phase 2 trial (37). Patients (N = 58) received CCyd for up to 9 28-day cycles, followed by maintenance with Carfilzomib until progression or intolerance. After a median of 9 CCyd induction cycles (range 1-9), 95% of patients achieved at least a partial response, 71% achieved at least a very good partial response, 49% achieved at least a near complete response, and 20% achieved stringent complete response. After a median follow-up of 18 months, the 2-year progression-free survival and overall survival rates were 76% and 87%, respectively. The most frequent grade 3 to 5 toxicities were neutropenia (20%), anemia (11%), and cardiopulmonary adverse events (7%). Peripheral neuropathy was limited to grades 1 and 2 (9%). Fourteen percent of patients discontinued treatment because of adverse events, and 21% of patients required Carfilzomib dose reductions. In summary, results showed high complete response rates and a good safety profile.



Carfilzomib- Thalidomide- Dexamethasone regime was studied by the HOVON Group (38). This multicenter phase 2 study of the European Myeloma Network investigated the combination of Carfilzomib, Thalidomide, and Dexamethasone (KTd) as induction/consolidation therapy for transplant-eligible patients with previously untreated multiple myeloma (N = 91). During KTd induction therapy, patients received 4 cycles of Carfilzomib 20/27 mg/m² (n = 50), 20/36 mg/m² (n = 20), 20/45 mg/m² (n = 21), or 20/56 mg/m² (n = 20) on days 1, 2, 8, 9, 15, and 16 of a 28-day cycle; Thalidomide 200 mg on days 1 to 28; and Dexamethasone 20 mg on days 1, 2, 8, 9, 15, and 16. After autologous stem cell transplantation, patients proceeded to KTd consolidation therapy, where the target doses of Carfilzomib were 27 mg/m², 36 mg/m², 45 mg/m² or 56 mg/m²), respectively, and Thalidomide 50 mg. Common grade 3/4 adverse events included respiratory (15%), gastrointestinal (12%), and skin disorders (10%); polyneuropathy was infrequent (1%). Complete response rates after induction and consolidation treatment were 25% and 63%, respectively; rates of very good partial response or better after induction and consolidation were 68% and 89%, respectively. At a median follow-up of 23 months, the 36-month progression-free survival rate was 72%. The KTd induction and consolidation regimens were active, safe, and well tolerated.

Safety data for single-agent Carfilzomib have been analyzed for 526 patients with advanced multiple myeloma who took part in one of 4 phase II studies (PX-171-003-A0, PX-171-003-A1, PX-171-004, and PX-171-005) (39). Overall analyses of adverse events and treatment modifications are presented, as well as specific analyses of adverse events by organ system. Overall, the most common adverse events of any grade included fatigue (55.5%), anemia (46.8%), and nausea (44.9%). In the grouped analyses, any grade adverse events were reported in 22.1% for any cardiac (7.2% cardiac failure), 69.0% for any respiratory (42.2% dyspnea), and 33.1% for any grouped renal impairment adverse event (24.1% increased serum creatinine). The most common non-hematologic adverse events

were generally Grade 1 or 2 in severity, while Grade 3/4 adverse events were primarily hematologic and mostly reversible. There was no evidence of cumulative bone marrow suppression, either neutropenia or thrombocytopenia, and febrile neutropenia occurred infrequently (1.1%). Notably, the incidence of peripheral neuropathy was low overall (13.9%), including patients with baseline peripheral neuropathy (12.7%). Additionally, the incidence of discontinuations or dose reductions attributable to adverse events was low. These data demonstrate that single-agent Carfilzomib has an acceptable safety profile in heavily pre-treated patients with relapsed/refractory multiple myeloma. The tolerable safety profile allows for administration of full-dose Carfilzomib, both for extended periods and in a wide spectrum of patients with advanced multiple myeloma, including those with pre-existing comorbidities.

Recently a phase III trial of Carfilzomib-Lenalidomide-Dexamethasone compared with Lenalidomide-Dexamethasone was reported. 792 patients with relapsed multiple myeloma were randomised to Carfilzomib with Lenalidomide and Dexamethasone (Carfilzomib group) or Lenalidomide and Dexamethasone alone (control group). The primary end point was progression-free survival. Progression-free survival was significantly improved with Carfilzomib (median, 26.3 months, vs. 17.6 months in the control group; hazard ratio for progression or death, 0.69; 95% confidence interval [CI], 0.57 to 0.83; P=0.0001). The median overall survival was not reached in either group at the interim analysis. The Kaplan–Meier 24-month overall survival rates were 73.3% and 65.0% in the Carfilzomib and control groups, respectively (hazard ratio for death, 0.79; 95% CI, 0.63 to 0.99; P=0.04). The rates of overall response (partial response or better) were 87.1% and 66.7% in the Carfilzomib and control groups, respectively (P<0.001; 31.8% and 9.3% of patients in the respective groups had a complete response or better; 14.1% and 4.3% had a stringent complete response). Adverse events of grade 3 or higher were reported in 83.7% and 80.7% of patients in the Carfilzomib and control groups, respectively; 15.3% and 17.7% of patients discontinued treatment owing to adverse events. The authors concluded that In patients with relapsed multiple myeloma, the addition of Carfilzomib to lenalidomide and Dexamethasone resulted in significantly improved progression-free survival at the interim analysis and had a favorable risk–benefit profile. (40)

2.1.3.4 Carfilzomib in AL amyloidosis

There is limited data on Carfilzomib in AL amyloidosis. The first results of a multi-center, Phase I, dose-finding study of Carfilzomib in AL amyloidosis were presented in ASH 2014. Patients had relapsed AL after ≥1 prior therapy. Patients with advanced cardiac involvement (Mayo stage III, LVEF<40%, or NYHA Class III/IV) were excluded. A standard 3+3 dose escalation schedule was used, with planned cohorts of 27, 36, 45, and 56 mg/m². Carfilzomib was given as a 30-minute infusion on days 1, 2, 8, 9, 15, 16 of a 28-day cycle, starting at 20 mg/m² on cycle 1, days 1,2, then escalating starting day 8. Three patients each were treated at 20/27 and 20/36 mg/m², with no DLTs. In the 20/45 mg/m² cohort, there were 2 DLT's of grade 3 fatigue ≥7 days in 4 patients, establishing 20/36 mg/m² in a twice weekly schedule as the MTD. Two additional patients were enrolled at MTD in the PI-exposed expansion cohort. Median number of cycles is 5 (range 1+-13+), with 7 patients still on study, and 5 discontinuing (3 AE, 2 patient withdrawal). Drug-related AEs occurring in >20% of patients (n=11 evaluable) included fatigue (45%), nausea (36%), anemia, dyspnea, and diarrhea (27% each). Seven patients had at least one Grade ≥3 AE (any cause), including cardiac (n=4 patients), fatigue (n=3), diarrhea (n=2), and nausea, hypoalbuminemia, and pneumonia (n=1 each). There have been 3 AE's possibly related to drug: 1 grade 4 cardiac arrest due to ventricular tachycardia during cycle 5; 1 grade 4 restrictive cardiomyopathy and CHF after cycle 3 (with negative endomyocardial biopsy for amyloid); 1 grade 3 drop in ejection fraction after cycle 7. Rising NTproBNP levels correlated with clinical and/or echocardiographic manifestations of CHF in these latter 2 patients. A 4th patient had exacerbation of atrial fibrillation during pneumonia, deemed unrelated. No deaths were reported. Of 9 evaluable patients, 7 responded hematologically, including 6 VGPR (≥PR rate=78%;). Responses were seen at all dose levels. Two patients had Dexamethasone added after cycle 4, both improving response to VGPR. With median follow-up of 5.1 months (range 0.2 to 12.3), no organ responses were observed (41).

2.2 Carfilzomib Dosing

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 27 mg/m². Maximum proteasome inhibition was seen at doses 11 mg/m² and higher in whole blood samples taken 1 hour after the first dose. Carfilzomib is rapidly cleared from plasma with an elimination half life of < 60 minutes at the 20 mg/m² dose. Large, single arm studies of the 27 mg/m² dose are ongoing and suggest that this dose is very well tolerated with patients being treated for >10 cycles without cumulative toxicities.

A total of 266 patients with relapsed and refractory multiple myeloma were enrolled in the PX-171-003-A1 study, with a "stepped up" dosing schedule of 20/27 mg/m² (39). The goal of dose escalating to 27 mg/m² beginning with Cycle 2 is to improve ORR, DOR, and TTP.

In multiple preclinical studies, the tolerability of Carfilzomib in rats has been shown to be significantly higher when administered as a 30 min infusion as compared to a rapid IV bolus. Toxicities observed with IV bolus injection of Carfilzomib *above the MTD* at a dose of 48 mg/m² include evidence of prerenal azotemia (transient increases in BUN > creatinine) as well as lethargy, piloerection, dyspnea, and gastrointestinal bleeding. Notably, death occurred in ~50% of animals at 48 mg/m² when Carfilzomib was given as a bolus. Administration of the same dose (48 mg/m²) as a 30 min continuous infusion was well tolerated, with no changes in BUN and creatinine and substantially reduced signs of lethargy, piloerection, or dyspnea. Moreover, all animals in the infusion treatment groups survived. The only toxicity observed following infusion of Carfilzomib for 30 min was gastrointestinal bleeding. The reduced toxicity seen with dosing by infusion may reflect the reduced C_{max} of Carfilzomib vs that with bolus dosing. Inhibition of the pharmacological target of Carfilzomib (the chymotrypsin-like activity of the proteasome) was equivalent in the bolus and infusion treatment groups.

In the clinic, the MTD of Carfilzomib has not been reached in the multiple myeloma (MM) setting, particularly when administered as a 30' infusion. 27mg/m² of 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.

Patients with relapsed and/or refractory multiple myeloma (MM) were administered single-agent Carfilzomib on days 1, 2, 8, 9, 15, and 16 of a 28-day cycle (42). Cycle one day 1 and 2 doses were 20 mg/m², followed thereafter by dose escalation to 36, 45, 56, or 70 mg/m². Additionally, Carfilzomib was combined with low-dose Dexamethasone (40 mg/wk). Thirty-three patients were treated with single-agent Carfilzomib. Dose-limiting toxicities in two patients at 70 mg/m² were renal tubular necrosis and proteinuria (both grade 3). The MTD was 56 mg/m². Nausea (51.5%), fatigue (51.5%), pyrexia (42.4%), and dyspnea and thrombocytopenia (each 39.4%) were the most common treatment-related toxicities. Overall response rate (ORR) was 50% (56- mg/m² cohort). Increasing Carfilzomib dosing from 20 to 56 mg/m² resulted in higher area under the plasma concentration-time curve from time zero to last sampling and maximum plasma concentration exposure with short half-life (range, 0.837 to 1.21 hours) and dose-dependent inhibition of proteasome chymotrypsin-like activity. In 22 patients treated with 45 or 56 mg/m² of Carfilzomib plus low-dose Dexamethasone, the ORR was 55% with a safety profile comparable to that of single-agent Carfilzomib. Carfilzomib administered as a 30-minute IV infusion at 56 mg/m² (as single agent or with low-dose Dexamethasone) was generally well tolerated and highly active in patients with relapsed and/or refractory MM. These data have provided the basis for the phase III randomized, multicenter trial ENDEAVOR

A phase II study suggests that Carfilzomib is safe in patients with renal impairment (43). Carfilzomib was administered on days 1, 2, 8, 9, 15 and 16 in 28-day cycles: mg/m² (Cycle 1), mg/m² (Cycle 2) and 27 mg/m² (Cycles 3+). There were no differences in Carfilzomib clearance or exposure among patients with normal renal function and any group with renal impairment. were similar among groups. At 15 mg/m², proteasome inhibition up to 85% was observed and did not differ among groups. Although nearly 50% of patients were refractory to both bortezomib and lenalidomide, end of study partial response or better (overall response rate) was 25.5% with 7.9 months median duration of response. The authors concluded that the pharmacokinetics and safety of Carfilzomib were not influenced by the degree of baseline renal impairment, including in patients on dialysis, and Carfilzomib was well tolerated in patients with renal impairment.

2.3 Proposed Trial

2.3.1 Summary and Rational for Therapeutic Study

Proteasome inhibitors are associated with highest response rates in AL amyloidosis. Bortezomib has toxicity and limitations in AL amyloidosis. In particular, the high specificity of Carfilzomib for proteosome inhibition and it's favorable toxicity profile makes it very appealing in AL amyloidosis. For instance, toxicities which commonly complicate Bortezomib use, such as autonomic and peripheral neuropathy, appear uncommon with Carfilzomib. Combination of proteosome inhibitors with Immunomodulatory Drug (IMiDs) appears to be synergistic in myeloma and the phase II data using Carfilzomib with lenalidomide or Thalidomide appears promising. In the UK, we have extensive experience using Thalidomide in the treatment of patients with AL amyloidosis. Combining Carfilzomib with Thalidomide offers an attractive treatment option for patients with relapsed refractory disease

due to their non-overlapping toxicity profile. Low dose Thalidomide is generally well tolerated by patients with AL amyloidosis but as single agent has limited efficacy. However, in combination with other agents, response rates are high as we have documented by using risk adapted CTD regime. This study is designed to improve the response rates seen with CTD protocol by using Carfilzomib in combination with Thalidomide and Dexamethasone.

Since there is limited data on use of Carfilzomib in AL amyloidosis, we propose a gradual dose escalation study. In the ongoing phase I study of Carfilzomib in AL amyloidosis, a dose of 36mg/m^2 twice weekly (total weekly Carfilzomib of 72 mg/m^2) was considered as MTD when used as single agent or with Dexamethasone. Based on this, we propose to use half of this dose at 36mg/m^2 once weekly as our dose level 0 increasing to a maximum of 56 mg/m^2 once weekly. The synergy Thalidomide and Carfilzomib should allow for lower doses of both drugs to be used.

Within the design of the trial, several procedures may be carried out at a higher frequency than would be expected with standard treatment. Information about these risks and associated advice for patients are discussed at length in the Patient Information Sheet. In accordance with the MRC/DH/MHRA Joint Project Risk-adapted Approaches to the Management of Clinical Trials of Investigational Medicinal Products, this trial is categorised as Type B, somewhat higher than standard medical care.

3.0 Trial Design

This will be a single arm open label multicentre phase Ib study with dose escalation and expansion phases. Patients will receive treatment with Carfilzomib in escalating dose cohorts along with a fixed dose of Dexamethasone and Thalidomide (KTD). The dose escalation phase of the study will use a 3+3 dose escalation design. Cohorts of 3-6 participants will be treated with KTD as outlined in the Section 8. Carfilzomib doses will be increased between cohorts until the occurrence of dose limiting toxicities (DLTs) define the MTD. The Safety Reviev Committee will review the safety and ethics of the trial by reviewing interim data after each cohort of treatment during recruitment to the Dose Escalation Cohort. Once the MTD and/or RD has been established a maximum of 20 participants will be recruited for entry into the expansion phase of the study at the RD. The study will run in 15 UK centres. The study duration is expected to be approximately 42 months – including 6 months of set up, 24 months of recruitment, 6 months of follow-up and 6 months of analysis/write-up.

3.1 Aims

The Catalyst (*Ca*rfil-*t*hal-Dex in *AL* Am*y*loido*s*is *t*reatment) Trial aims to assess the safety and tolerability of KTD (Carfilzomib-Thalidomide-Dexamethasone) using the phase 1 dose escalating component to define the maximum tolerated dose (MTD) and recommended dose (RD) and the expansion cohort to further assess the safety and tolerability and to gain an understating of efficacy to allow design for further trials.

Primary:

Dose escalation

To define the MTD and RD of Carfilzomib used in combination with Thalidomide and Dexamethasone in patients with relapsed or refractory AL amyloidosis

Dose expansion

To further assess the safety and tolerability of KTD at the RD of Carfilzomib identified in the dose escalation phase

Secondary:

To make a preliminary assessment of the activity of KTD in patients with relapsed refractory AL amyloidosis

3.2 Trial Activation

Leeds Clinical Trials Research Unit (CTRU) 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)
- Adequate funding for central co-ordination
- Adoption into NIHR portfolio
- NHS permission
- Confirmation of sponsorship
- Adequate insurance provision

4.0 Selection of Sites/Site Investigators

4.1 Site (Regional Haematology Centre) selection

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

Sites must be able to comply with:

- Trial treatments, clinical care, follow up schedules and all requirements of the trial protocol
- Requirements of the Research Governance Framework and the Medicines for Human Use (clinical trials) Act (SI 2004/1031 and all amendments)
- Monitoring requirements, as outlined in the protocol (section 16.0 and Trial Monitoring Plan)
- Data collection requirements including adherence to CRF submission timelines as per section 12.0
- Sample collection and processing requirements

4.1.1 Selection of Principal Investigators and other investigators at sites

Sites must have an appropriate Principal Investigator (PI) i.e. a health care professional authorised by the site, ethics committee and regulatory Authority to lead and coordinate the work of the trial on behalf of the site. Other investigators at site wishing to participate in the trial must be trained and approved by the PI. All investigators must be medical doctors and have experience of treating amyloidosis.

4.1.2 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.

CVs for all staff must be kept up-to-date, signed and dated and copies held in the Investigator Site File (ISF). An up-to-date, signed copy of the CV for the PI must be forwarded to CTRU 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 CTRU 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.

The site initiation will be performed by site visit or teleconference.

4.2.2 Required documentation

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

- Trial specific Feasibility/Site Registration Form (identifying relevant local staff and contact details)
- All relevant institutional approvals (e.g. local NHS permission)
- A completed authorised personnel log and pharmacy personnel logthat is signed and dated by the PI
- A copy of the PI's current CV that is signed and dated
- A copy of the PI's GCP certificate
- PI declaration that is signed and dated
- Lead pharmacist declaration that is signed and dated
- Local lab ranges and lab accreditations
- Trial specific prescriptions & labels

In addition, the following agreement must be in place:

- a fully signed model non-commercial agreement (mNCA) between the Sponsor and the relevant institution (usually a NHS Trust)

4.2.3 Site activation

Once the CTRU trial team at Leeds has received all required documentation and the site has been initiated, **a site activation email** will be issued to the PI and other key site contacts, at which point:

- If the site in question is the UK National Amyloidosis Centre (UK NAC), they may start to approach patients
- If the site is a Regional Haematology Centre (RHC), the UK NAC can begin to refer patients to them.

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

- adherence to the most recent approved 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
- that the site has facilities to provide **24 hour medical advice** for trial patients

Please note, for the CATALYST trial, all patients will be approached by the UK National Amyloidosis Centre (UK NAC) and referred by UK NAC to a suitable Regional Haematology Centre (RHC)/Site. No patients may be referred to an RHC/Site that is not activated by Leeds CTRU. Leeds CTRU will provide UK NAC with an up to date list of activated RHCs.

5.0 Informed consent

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

The UK NAC 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 UK NAC PI, or, where delegated by the PI, other appropriately trained site staff (trained on the study protocol, Patient Information Sheet and are GCP trained), 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 (including the aims, methods, possible benefits and possible disadvantages of taking part). The patient will be allowed as much time as needed to consider and discuss their participation in the trial. Patients will be given the option to take the patient information sheet and consent form away and return it by post (this is standard practice at UK NAC). Upon receipt at UK NAC, the consent form must be checked for completeness and then signed by the appropriate investigator. Dated entries for this consent process must be recorded in the patient's medical notes. No clinical trial procedures will be conducted prior to obtaining consent. Consent will not denote enrolment to the trial. If new safety information results changes in the significant risk/benefit the consent will be reviewed and updated and patients will be given an opportunity to re-consent to participating in the study.

Healthcare professionals have specific obligations that must be followed when prescribing or dispending thalidomide. As such, patients must be fully educated on the risks of thalidomide in accordance with the Celgene Pregnancy Prevention Programme. This should be done by an authorised member of staff at the research centre at the time the patient is given a full verbal explanation of 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.

UK NAC staff are responsible for:

- Checking that the correct (current approved) version of the patient information sheet and consent form are used
- Checking that information on consent forms is complete and legible
- Checking that the patient has completed/initialled all relevant sections and signed and dated the consent 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 card and Red Flag card
- Adding details of all consented patients to the informed consent form log
- Following registration and confirmation of eligibility: 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
- Sending a copy of the completed consent form to the CTRU and the appropriate RHC following registration (see 4.1 & 6.1)

The original signed consent form must be stored at the UK NAC, one copy forwarded to the CTRU, one copy forwarded to the Regional Haematology Centre (RHC), and a copy given to the patient.

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 14.0 (Withdrawal of patients).

5.1 Referral of patients to Regional Haematology Centres

Following consent and registration (see section 7.1), patients will be referred to the appropriate Regional Haematology Centre (RHC). The choice of RHC will be discussed and agreed with the patient during their UK NAC visit.

UK NAC are responsible for forwarding a copy of the signed informed consent form (fax or email is acceptable) to the RHC in order that trial specific activities may be undertaken, with an additional copy being sent to the CTRU.

Following referral the RHC will contact the patient to arrange their first visit (to include confirmation of eligibility to the trial). This visit must be within 28 days of the patient's registration.

Authorised members of the study team at the RHC should give the participant an opportunity to ask any further questions about the trial and to check they are still willing to take part in the trial.(as part of the re-confirmation of eligibility visit)

6.0 Selection of Patients

6.1 Pre-treatment Evaluation

Patients referred to the UK NAC with AL amyloidosis are routinely sent a 'General Clinical Research Information Sheet' with their UK NAC appointment letter. Nationally, patients are followed up at the UK NAC as part of standard practice, where a full 'Amyloid Evaluation' is undertaken, usually over a period of two days; follow up visits are approximately 6 monthly. The Amyloid Evaluation includes Serum Amyloid Protein component (SAP) scintigraphy, echocardiography, full haematological, biochemical and urine examinations for evidence of organ dysfunction, clonal disease, a bone marrow (if indicated) and cardiac biomarkers. This standard amyloid assessment will form the baseline pre-treatment evaluation. The patient will also have a blood test to check hepatitis B status. Patients who may receive thalidomide treatment or other chemotherapy outside of the trial have this test as standard of care. Any UK patient with a diagnosis of systemic AL amyloidosis who has relapsed disease is potentially eligible for entry into the trial (see 6.3 for patient eligibility).

Please see protocol section 11 for assessment summary and Appendix 6 for diagnostic sample requirements and investigations.

UK NAC will confirm eligibility for the trial and consent patients, following this, registration will take place at Leeds CTRU. All registered patients will have a brief pre-treatment evaluation to reconfirm eligibility at their allocated RHC (Regional Haematology Centre).

6.2 Screening Log

A screening log must be maintained by the UK NAC and kept in the UK NAC CATALYST Site File. This must record each patient screened for the trial/all patients identified with proven systemic AL amyloidosis and the reasons why they were not registered in the trial if this is the case.

The log must be sent to Leeds CTRU from UK NAC when requested, with patient identifiers removed prior to sending.

Individual RHC sites will not be asked to maintain a screening log.

6.3 Patient Eligibility

There will be no exception to the eligibility requirements at the time of registration. Ensuring patient eligibility is the responsibility of the UK NAC PI or other delegated Investigator(s). Queries in relation to the eligibility criteria must be addressed prior to calling/faxing registration. Patients are eligible for the trial if all the inclusion criteria are met and none of the exclusion criteria applies.

6.3.1 Inclusion Criteria

Patients with the following characteristics are eligible for this study:

1. Aged 18 years or greater
2. Diagnosis of systemic AL amyloidosis with
    i. exclusion of genetic mutations associated with hereditary amyloidosis and immunohistochemical exclusion of AA and TTR amyloidosis as appropraite
    ii. Amyloid-related organ dysfunction or organ syndrome (see Appendix 2)
3. Measurable clonal disease
4. Clonal relapse after previous chemotherapy or autograft stem cell transplant OR refractory clonal disease to previous chemotherapy or stem cell transplant
5. Capable of providing written, informed consent and willing to follow study protocol
6. Life expectancy ≥ 6 months
7. ECOG performance status of 0-2
8. Platelet count ≥ $50x10^9/l$
9. Neutrophil count ≥ $1x10^9/l$
10. Haemoglobin ≥ 8g/dL
11. Bilirubin <2 times or Alkaline phosphatase <4 times upper limit of normal.
12. Female participants of child-bearing potential must have a negative pregnancy test prior to treatment and agree to use dual methods of contraception for the duration of the study and for 30 days following completion of study. Male participants must also agree to use a barrier method of contraception for the

duration of the study and for 90 days following completion of study if sexually active with a female of child-bearing potential. Women who could become pregnant must have taken precautions not to become pregnant for 1 month before the start of the study. Because of the increased risk of venous thromboembolism in patients, combined oral contraceptive pills are not recommended.

13. Participants must be willing to comply with the Celgene pregnancy prevention programme for Thalidomide

6.3.2 Exclusion Criteria

Patients with the following characteristics are ineligible for this study (see Appendices for definitions):

1. Overt symptomatic multiple myeloma
2. Amyloidosis of unknown or non-AL type
3. Localised AL amyloidosis (in which amyloid deposits are limited to a typical single organ, for example the bladder or larynx, in association with a clonal proliferative disorder within that organ)
4. Trivial or incidental AL amyloid deposits in the absence of a significant amyloid-related organ syndrome (e.g., isolated carpal tunnel syndrome)
5. Refractory to or progressive disease with an IMid and proteasome inhibitor combination
6. Allogeneic stem cell transplantation
7. Solid organ transplantation
8. Severe peripheral or autonomic neuropathy causing significant functional impairment that, in the investigator's opinion, may interfere with protocol adherence
9. eGFR <20ml/min
10. Ejection fraction < 40% or NYHA class III or IV heart failure or uncontrolled hypertension that concerns the investigator
11. Severe pulmonary Hypertension that, in the investigator's opinion, may interfere with protocol adherence
12. Advanced Mayo stage III disease as defined by hs-Troponin T>0.07 and NT-proBNP >700 pMol/L OR NT-proBNP >1000 pMol/L OR supine SBP <100 mm of Hg
13. Myocardial infarction in the preceeding 6 months or unstable angina or conduction abnormalities uncontrolled by medication or devices
14. Concurrent active malignancies, except surgically removed basal cell carcinoma of the skin or other in situ carcinomas
15. Pregnant, lactating or unwilling to use adequate contraception
16. Systemic infection unless specific anti-infective therapy is employed
17. Known or suspected HIV infection
18. Contraindication to any of the required concomitant drugs or supportive treatments
19. Any other clinically significant medical disease or condition or psychiatric illness that, in the Investigator's opinion, may interfere with protocol adherence or a participant's ability to give informed consent
20. Previous experimental agents within 3 months before the date of registration
21. Known allergies to Carfilzomib, Thalidomide or Dexamethasone
22. Positive hepatitis B viruses (HBV) test

6.3.3 Pregnancy and Birth Control

The risks to the human embryo or foetus from exposure to Carfilzomib are currently unknown. Thalidomide is teratogenic. 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 affects 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. Corticosteroids may pass into breast milk, although no data are available for Dexamethasone. Infants of mothers taking high doses of systemic corticosteroids for prolonged periods may have a degree of adrenal suppression.

All patients will have to comply with the Thalidomide pregnancy prevention programme.

Pregnancy Testing

All women of child bearing potential who are at risk of becoming pregnant must undergo a pregnancy test prior to commencing the trial drugs and prior to start of each cycle.
Sterilisation of either partner is not usually regarded as completely reliable enough to ensure that pregnancy can never occur.

A woman of childbearing potential 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 24 consecutive months (i.e. who has not had menses at any time in the preceding 24 consecutive months without an alternative medical cause)

Contraceptive advice

Due to the effects of the trial treatment during pregnancy and lactation, patients must consent to use one of the following acceptable methods of contraception during the study and for 30 days (in the case of female participants) or 90 days (in the case of male participants) after the end of the study treatment. Women who could become pregnant must have taken precautions not to become pregnant for 1 month before the start of the study
Acceptable methods of effective contraception for this trial are:

- Established use of oral methods of contraception. **Because of the increased risk of venous thromboembolism in patients, combined oral contraceptive pills are not recommended.**
- Placement of an intrauterine device (IUD) or intrauterine system (IUS).
- Barrier methods of contraception: condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository. The use of barrier contraceptives should always be supplemented with the use of a spermicide. The following should be noted:
    - Failure rates indicate that, when used alone, the diaphragm and condom are not highly effective forms of contraception. Therefore the use of additional spermicides does confer additional theoretical contraceptive protection.
    - However, spermicides alone are inefficient at preventing pregnancy when the whole ejaculate is spilled. Therefore, spermicides are not a barrier method of contraception and must not be used alone.
- Male sterilisation (with appropriate post-vasectomy documentation of the absence of sperm in the ejaculate). For female patients, the vasectomised male partners must be the sole partner for that patient. Please note that sterilisation is not usually regarded as completely reliable enough on its own to ensure that pregnancy can never occur.
- Absolute and continuous abstinence: When this is in line with the preferred and usual lifestyle of the patient. Please note that periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

Because of the potential for serious undesirable effects in breast-fed infants, lactation should be discontinued during trial treatment. Women should not breastfeed for 3 months following their last dose of study treatment.
The method(s) of contraception used must be stated in the patient medical notes.

Should a pregnancy occur, either to a female patient or to a female partner of a male patient while on the trial Leeds CTRU must be informed immediately (Please refer to section 13.5 Pregnancy for details on the reporting procedure).

7.0 Registration Procedures

7.1 Patient Registration

Patient registration will be administered by telephone at Leeds CTRU. Patients should be assessed for eligibility prior to consent and registration as part of the amyloid evaluation at the UK NAC. Patients must be consented and registered prior to trial-specific assessments.

Following pre-treatment evaluations (as detailed in section 6.1), confirmation of eligibility and consent of a patient at the UK NAC, the registration form must be fully completed. The following information will be required at registration:

- Hospital name and NIHR site code (RHC details)
- Name of person registering the participant
- Name of treating clinician
- Patient details, including initials, date of birth, and gender
- Confirmation of eligibility
- Confirmation of written informed consent

A trial number will be assigned for the patient and details added to the form.

Direct line for participant registration
0113 343 1658
Monday – Friday 9am-5pm except Public and University holidays
Please ensure you have completed the Registration CRF before phoning
Authorisation codes and PINs will be provided to the UK NAC for registration

Immediately after registration, please fax the Consent Form, Registration CRF and Eligibility Checklist to CTRU

Fax: 0113 343 4345

UK NAC/Leeds CTRU registration process:

1. A standard amyloid evaluation will be carried out at the UK NAC. Eligibility will be assessed and written informed consent obtained
2. Upon receipt of a completed consent form (see section 5.0) for an eligible patient, UK NAC will register the patient using the CTRU direct registration line. A trial number will be assigned to the patient during registration and these details will need to be added to the form
3. A fully completed registration form will be sent to Leeds CTRU. A copy of the consent form and eligibility checklist will also need to be sent to Leeds CTRU to confirm patient eligibility
4. If there are any queries about eligibility, trial staff at Leeds CTRU will contact UK NAC immediately

Registration confirmation to UK NAC and RHC

5. Following registration, the UK NAC will refer the patient to their allocated RHC (sections 5.1 & 11.1.2) and forward consent form and patient trial information to the RHC
6. Leeds CTRU will also fax registration confirmation to the UK NAC and to the key contacts at the RHC

Re-confirmation of eligibility at the RHC

7. The RHC will contact the patient to arrange the first RHC visit (sections 5.1 & 11.1.2), which must be within 28 days of registration, and at which eligibility for the trial must be reconfirmed

8. For patients still eligible for the trial, the RHC will fax a fully completed eligibility confirmation form to Leeds CTRU (see point 12 below). If there are any queries about eligibility, trial staff at Leeds CTRU will contact staff at the RHC immediately
9. Leeds CTRU will confirm the patient's inclusion in the trial and also confirm their registered dose level by fax to the main contact at site and the site pharmacy
10. During the dose escalation phase, the treatment start date must be confirmed and agreed with Leeds CTRU. A minimum of 15 days must have elapsed between the start of treatment of the first patient in each cohort and subsequent patients
11. For patients found to be ineligible for the trial, the RHC will fax a fully completed withdrawal form to Leeds CTRU
12. If there is a ≥ 21 day delay in starting trial treatment after completion of eligibility confirmation form at the RHC, a second eligibility confirmation form must be completed. Patients must start treatment within 6 weeks of completion of the initial eligibility confirmation form at the RHC
13. If after registration a patient decides to withdraw consent to the trial, or is found not to satisfy the eligibility criteria, the site must inform CTRU. Sites must complete a withdrawal form to confirm withdrawal details

Please see protocol section 11 for assessment summary and Appendices 6 and 7 for diagnostic sample requirements and investigations.

Once a patient has been 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
- A patient Red Flag card. A list of symptoms which need urgent medical attention

8. Trial Treatment

For the purpose of this protocol, the IMPs are **Carfilzomib, Thalidomide and Dexamethasone.**

All trial patients must be treated according to the following schedule in order to isolate the effects of the Carfilzomib.

Please refer to the current Carfilzomib IB and SPCs for Thalidomide and Dexamethasone, provided in the Investigator Site File and Pharmacy Site File, for drug/drug or drug/food interactions.

8.1 Treatment Schedule Summary

8.1.1 KTD Regimen

All treatment will take place at the patient's RHC/Site.

If there is a ≥ 21 day delay in starting trial treatment after completion of eligibility confirmation form at the RHC, a second eligibility confirmation form must be completed. Patients must start treatment within 6 weeks of completion of the initial eligibility confirmation form.

Treatment will be as below with three regimes based on gradually increased dose and addition of Dexamethasone based on clonal response at end of each cycle.

KTD protocol – dose escalation phase

Carfilzomib 30 minute IV infusions of Carfilzomib at a dose according to table 1 below.
Days 1, 8,15 A maximum of 6 cycles will be administered. All patients will be recommended oral hydration with 250 ml of fluids 2 hours before and one hour after the infusion at day 1.Oral hydration with 250 ml of fluids 2 hours before the infusion is recommended from day 8 onwards. Post infusion hydration is optional and at the discretion of the treating physician for patients at risk of tumour lysis syndrome and/or dehydration. Patients should be monitored closely for fluid overload.

All patients will receive Carfilzomib at 20mg/m² on day 1 of cycle 1 and then at the allocated dose level on day 8 and day 15 of cycle one, and during all subsequent cycles.

Thalidomide 50mg Thalidomide, oral preparation (potentially increasing to 100mg if well Days
1-28 tolerated - to be discussed with the Chief Investigator before increasing dose)

Dexamethasone 20mg Dexamethasone, oral preparation. This should be taken prior to all
Days 1, 8,15 Carfilzomib doses.

Table 1: Dose Levels

Dose level	Carfilzomib IV (mg/m²) (Days 1, 8 & 15)	Thalidomide (mg) (Days 1-28)	Dexamethasone (mg) (Days 1, 8 & 15)
-1	27	50	20
0	36	50	20
1	45	50	20
2	56	50	20

A minimum of 15 days must have elapsed between the start of treatment of the first patient in each cohort and subsequent patients.

KTD protocol – dose expansion phase
The dose escalation phase will then be extended once maximum tolerated dose (MTD) and the Recommended Dose (RD) has been established. All patients will then receive Carfilzomib-Thalidomide -Dexamethasone as follows (repeated every 28 days)

Carfilzomib Carfilzomib intravenous infusion at Recommended Dose (RD) .
Days 1, 8,15 A maximum of 6 cycles will be administered.

All patients will receive Carfilzomib at 20mg/m² on day 1 of cycle 1 and then RD from day 8 onwards

Thalidomide 50 mg, p.o Thalidomide (consider increase to 100 mg from cycle 2 if well
Days 1-28 tolerated. To be discussed with the Chief Investigator before increasing dose

Dexamethasone 20mg Dexamethasone, oral preparation. This should be taken prior to all
Days 1, 8,15 Carfilzomib doses.

8.1.2 Changes in Body Surface Area (BSA)

Participants must be weighed prior to the start of each cycle of treatment but the BSA should only be recalculated if weight changes by greater than 10% (loss or gain). BSA to be calculated as per standard practice.

8.1.3 Dose Escalation

Dose escalation will begin at DL0 and will proceed until MTD or the highest planned dose level has been reached. Toxicity data for each cohort will be reviewed by the Safety Review Commitee prior to dose escalation, according to the following schema (Table 2).

Table 2. Scheme for dose escalation decision

Identifying MTD	
Number of patients with a DLT following 1 cycle at a given dose level	**Escalation decision rule**
0 out of 3	Enter 3 patients at the next highest dose level. If current dose level is the highest dose level, this is the MTD; proceed to identifying RD
≥2 out of 3	Dose escalation stopped and next lowest dose identified as MTD. Proceed to identifying RD. If current dose level is lowest dose, no MTD identified.
1 out of 3	Enter 3 more patients at the current dose level. • If 0 out of these additional 3 experience DLT (i.e. total DLTs 1/6), proceed to the next highest dose level. If current dose level is the highest dose level, this is the MTD & current dose level is identified as RD • If 1 or more of these additional 3 experience DLT (i.e. total DLTs >1/6), dose escalation stopped

	and next lowest dose identified as MTD. Proceed to identifying RD

Identifying RD

Once the MTD is identified, at least 6 patients must have completed cycle 1 at the RD before enrolment to the dose expansion phase can commence.

The RD is defined as the highest dose level at which at most 1/6 patients experience a DLT. If only 3 patients have been treated at the next lowest dose an additional 3 patients are recruited to this dose level. If >1/6 DLTs are then experienced at this dose level, dose level de-escalation continues until the RD is identified.

If the MTD is identified as the highest dose level with 0/3 DLTS then an additional 3 patients are recruited to this highest dose level. If >1/6 DLTs are then experienced at this dose level, dose level de-escalation continues until the RD is identified. If ≤1/6 DLTs are experienced then the highest dose level is identified as the RD.

If no MTD is identified, no RD is identified and the study will not continue to the dose expansion phase.

8.1.4 Dose Limiting Toxicities

Dose limiting toxicities (DLTs) will be collected from the time of receiving the first dose of Carfilzomib in cycle 1 up to the first dose of treatment administered in cycle 2. Only DLTs that are attributed to the registered dose of Carfilzomib will be included when determining the MTD (i.e those attributed to the loading dose will be excluded) (see section 19.2). A DLT will be defined as any of the following events that are determined to be related to trial drug administration:

1. Any non-haematological toxicity ≥ Grade 3 according to NCI CTCAE Version 4.03 which fails to return to ≤Grade 1 or baseline after 7 days. Nausea, vomiting, diarrhoea and electrolyte imbalances will be considered DLTs only if they reach ≥ Grade 3 severity despite adequate supportive care measures. Similarly, fluid retention or worsening symptoms of heart failure will be considered as DLTs if they are persistent ≥Grade 3 despite increase in oral diuretics or there is an increase in dyspnoea by ≥ 2 NYHA grades within 12 hours of administration of Carfilzomib which persists for > 6 hours or needs hospital admission
2. Grade 4 neutropenia lasting > 7 days or Grade 4 neutropenia with sepsis despite adequate supportive measures.
3. Any grade 4 thrombocytopenia which fails to return to Grade 2 within 7 days without platelet support
4. Delay of >8 days within cycle 1 or delay of commencement of 2nd cycle by more than 14 days, due to significant toxicity or tolerability issue*
5. Any other event which, in the opinion of the Safety Review Committee, is considered to be clinically significant and related to treatment

*This will not be defined as a DLT if the delay is due to one of the other specified DLT criteria.

8.1.5 Definition of Maximum Tolerated Dose (MTD)

The highest dose level at which no more than 1 patient experiences a DLT, from the time of receiving the first registered dose of Carfilzomib in cycle 1 up to the first dose of treatment administered in cycle 2, i.e. the dose level below that at which 2 or more patients experiences a DLT. If no more than one patient experiences a DLT at the highest dose level then this will be considered as the MTD.

8.1.6 Definition of Recommended Dose (RD)

Once the MTD has been established, a minimum of 6 patients will be treated at this dose level in order to establish the RD. The RD is the dose which will be used in the dose expansion phase of the study to evaluate activity.

9.0 Trial Medicinal Product Management

9.1 Investigational Medicinal Products (IMPs).

The following are classified as Investigational Medicinal Products (IMPs).

- **CARFILZOMIB (IMP)**

  Lyophilized Carfilzomib for Injection

  Composition: Lyophilized parenteral drug product in 60 mg single use vials. Upon reconstitution, Carfilzomib for injection consists of 2 mg/mL solution.

  Carfilzomib will be supplied solely for use in this trial by Amgen free of charge. Please refer to the trial supplied Investigator Brochure

- **DEXAMETHASONE (IMP)**

  Dexamethasone Tablet
  Composition: 2.0 mg Dexamethasone.
  Generic supply of Dexamethasone as determined by individual hospital sites. Please refer to the trial supplied summary of product characteristics.

- **THALIDOMIDE (IMP)**

  Thalidomide Capsule
  Composition 50 mg Thalidomide
  Generic supply of Thalidomide as determined by individual hospital sites. Thalidomide will be ordered through the Celgene-approved process for Thalidomide risk management and pregnancy prevention, as for standard hospital supplies. Please refer to the trial supplied summary of product characteristics..

9.2 Supportive Measures

The following supportive measures should be considered for all patients in the trial:

a. **Antiviral** such as oral acyclovir 400 mg twice daily (or as per local standard practice) with dose modified according to renal function or appropriate alternative. Acyclovir should be continued for three months after the last dose of Carfilzomib if medically appropriate.

b. **Medication to prevent gastric irritation** such as oral Lansoprazole 15 mg once daily or Omeprazole 20mg once daily or appropriate alternative

c. **Antibiotic**s such as oral Co-trimoxazole 480 mg twice daily given three times weekly (unless contraindicated). Prophylaxis to be continued for the duration of chemotherapy

d. **Allopurinol** is recommended to be prescribed, unless contraindicated (e.g. allergy). to all participants at 300 mg po daily (or dose adjusted for renal impairment), 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 300 mg 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 Lead Principal Investigator. In some circumstances (e.g. participants are exceptionally high risk of TLS); rasburicase may be used at the investigator's discretion.

e. **Oral hydration**. Participants must be well hydrated (i.e., volume replete).All patients will be recommended oral hydration with 250 ml of fluids 2 hours before and one hour after the infusion at day 1.Oral hydration with 250 ml of fluids 2 hours before the infusion is recommended from day 8 onwards. Compliance will be reviewed with the participant and documented by the site personnel prior to initiating treatment with Carfilzomib; treatment may be delayed or withhthromobeld. In patients with poorly controlled heart failure, this can be reduced at the clinicans discretion.

f: **Routine Anticoagulation** All patients will need routine thromboprophylaxis during the study. Patients not considered at high risk of thrombosis can receive aspirin 150 mg daily as thromboproplylaxis. Patients considered at high risk of thrombosis will need formal anticoagulation with LMW heparin, warfarin or a thrombin inhibitor.

All side-effects will be managed as per standard care by the treating clinician. Discontinuation of supportive measures may be considered if deemed appropriate in light of the toxicities seen by the treating clinician.

Antiemetics should be administered as per local protocols. Oral domperidone or ondansteron should be given on as required basis.

9.3 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 CATALYST trial is for CATALYST patients only and must not be used outside the context of this protocol.

9.3.1 Labelling and IMP handling

Carfilzomib supplies will contain a trial specific label, in line with Directive 2001/20/EC and the Medicines for Human Use (Clinical Trials) Regulations 2004 (amended 2006). It must be ring fenced for this trial in a separate area to non-trial products and records retained in the Pharmacy Site File noting the location of the storage.

Dexamethasone tablets and Thalidomide capsules will be sourced from hospital stock as the marketed product and a labelling exemption has been has been granted as part of the Clinical Trial Authorisation. Please refer to the Pharmacy and IMP Management Trial Site Operating Procedure for full details of the trial IMP management requirements.

9.3.2 IMP Preparation

All IMPs will be prepared and handled in line with manufacturers' recommendations and the SPCs. IMPs requiring reconstitution will be reconstituted under conditions approved by the hospital pharmacy.

9.3.3 IMP Administration and Risk Management

Carfilzomib

Carfilzomib for Injection is supplied as a lyophilized parenteral product in single-use vials. The lyophilized product is reconstituted with Water for Injection to a final Carfilzomib concentration of 2 mg/mL prior to administration. The dose will be calculated, as per standard practice, using the participant's actual BSA at baseline . Participants with a BSA > 2.2 m^2 will receive a dose capped at 2.2 m^2 BSA.

- At least 48 hours before Cycle 1 Day 1, oral hydration may be given as follows: 500 mls of extra fluid per day and 250 mls 2 hours before the time of treatment. Participant compliance will be assessed before initiating treatment, which may be delayed if oral hydration is not adequate. In participants considered at risk for TLS, oral hydration may be continued in Cycle 2 and beyond as required by the participant's medical condition and at the Investigator's discretion.

- Oral hydration is at the discretion of the treating physician for patients at risk of tumour lysis syndrome and/or dehydration. Patients should be monitored closely for fluid overload.

- If the participant 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 approximately 30 minutes. The dose will be administered at a facility capable of managing hypersensitivity reactions. Participants will remain at the clinic under observation for at least 1 hour following each dose of Carfilzomib in Cycle 1 and following the dose on Cycle 2 Day 1.

- Dexamethasone will be administered prior to all Carfilzomib doses to prevent infusion reactions.

- Known risks of Carfilzomib therapy include adverse drug reactions. Please refer to the latest IB for full tables of known adverse drug reactions associated with Carfilzomib.

The most common adverse reactions observed (frequency of greater than 15%) include anaemia, thrombocytopenia, neutropenia, diarrhoea, nausea, constipation, vomiting, fatigue, pyrexia, peripheral oedema, respiratory tract infections, increased blood creatinine, hypokalemia, anorexia, back pain, muscle spasms, headaches, insomnia, dyspnoea, and cough.

Important identified risks include pulmonary hypertension, new or worsening cardiac failure, acute renal failure, tumour lysis syndrome, infusion reactions, hepatic toxicity, TTP/HUS, and PRES.

Please refer to 10.12, "Carfilzomib safety considerations", for details of how the risks of tumour lysis syndrome, decreased creatinine clearance, infection, anaemia, thrombocytopenia, and gastro-intestinal toxicities will be managed. The incidence of other toxicities should be managed as outlined in 10.4 and 10.5.

Specific management is in place for cardiac toxicities are outlined in 10.10.

Thalidomide

Thalidomide is available as a capsule and a supply will be provided to patients for use in this trial. Thalidomide should be taken as per the provided instructions (50mg p/o per day, potentially increasing to 100mg per day, if well tolerated) at bed time to reduce the impact of somnolence. This medication may be taken by the patient with or without food. If less than 12 hours has elapsed since missing a dose, the patient can take the dose. If more than 12 hours has elapsed since missing a dose at the normal time, the patient should not take the dose, but take the next dose at the normal time on the following day.

Known risks of Thalidomide therapy include adverse drug reactions. Please refer to the SPC for Thalidomide for an exhaustive list of known risks.

Very common side effects (≥10%) include neutropenia, leukopenia, anaemia, lymphopenia, thrombocytopenia, peripheral neutopathy, tremor, dizziness, paraestheia, dysaesthesia, somnolence, constipation, and peripheral oedema.

Foetal teratogenicity, should women of child-bearing potential become pregnant during treatment, is well described, and there is also a risk of PRES, venous and arterial thrombo-embolitic events, and the development of MDS and AML.

Viral reactivation of the varicella-zoster virus or hepatitis B virus (HBV) has been documented. Some of these cases have resulted in disseminated herpes zoster and acute hepatic failure, respectively. Patients who test positive for HBV will not be eligibile for the CATALYST trial.

Patients will be closely monitored throughout the trial as per the protocol to detect haematological toxicities, which may then be treated as per local practice.

To prevent pregnancy and the risk of foetal malformation, The Celgene Pregnancy Prevention Programme should be adhered to by patients at all times.

The risk of embolism will be managed by the administration of routine thromboprophylaxis during the study, as outlined in section 9.2.

Dexamethasone

Dexamethasone is available as a tablet and should be administered 30 minutes to 4 hours prior to all Carfilzomib doses during all cycles of treatment. If a patient misses a dose of Dexamethasone, this can be taken only if the patient becomes aware of the missed dose within 24 hours of the time the dose was due.
Known risks of Dexamethasone therapy include adverse drug reactions. Please refer to the SPC for Dexamethasone for an exhaustive list of known risks.

Known side effects of Dexamethasone include immunosuppressive effects and associated recurrence of dormant infection, osteoporosis, hyper-tension, psychiatric reactions, ocular reactions, dyspepsia, dermatological problems, allergic reactions, and water retention.

Refer to 10.6, Dexamethasone toxicity, for details on how risks will be managed when patients are administered Dexamethasone. The occurrence of fluid retention and other toxicities should be subject to close monitoring. Fluid retention may be treated with diuretics. Dexamethasone discontinuation and replacement with other corticosteroids may be implemented.

9.3.4 Drug accountability

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 LEEDS CTRU for review and authorisation for use prior to patient enrolment.

Copies of completed drug accountability logs must be submitted to LEEDS CTRU for all trial patients at the end of treatment or upon request. Also refer to section 16.1 (Central Monitoring).

Used vials can be immediately destroyed by aseptic pharmacy. Unused Carfilzomib (packets or vials) will be destroyed/disposed of as per local policy upon authorisation by Leeds CTRU. Authorisation for displosal will be granted after accountability has been verified by CTRU.

For accountability of Thalidomide and Dexamethasone, sites are permitted to use their standard procedure for recording drug allocation and dispensing. Patients will also be instructed to keep a drug diary to detail all taken and missed doses. The information collected must adhere to local policy and be made available to the Sponsor upon request. Information regarding dosing and any reductions/delays of non IMPs will be collected in the CRFs.

Patients must be instructed to return any dispensed unused Thalidomide and Dexamethasone to hospital pharmacy for appropriate destruction/disposal according to local policy.

9.3.5 Temperature Excursions

All temperature excursions outside the storage conditions for Carfilzomib specified in the IB must be reported to LEEDS CTRU.

Upon identifying an excursion:

- all affected trial stock must be quarantined IMMEDIATELY
- the 'Notification of Temperature Excursion' form must be completed and e-mailed to medcatal@leeds.ac.uk or faxed to 0113 343 4345.

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

9.4 Clinical Management after Treatment Discontinuation

Patients whose underlying plasma cell dyscrasia does not respond by the end of three cycles or who have a clonal progression on treatment will be treated and followed up off trial at the discretion of the treating clinician but will have a final follow-up visit 6 months after registration.

Patients that receive 6 cycles of chemotherapy will be followed up 1 month after end of trial treatment.

Also refer to section 14 (Withdrawal of Patients) for further details regarding treatment discontinuation, patient withdrawal from trial treatment and withdrawal of consent to data collection.

9.5 Out-of-hours medical care

Medical care, including out-of-hours medical care is the responsibility of the site. Sites must ensure that all patients registered onto the have received a CATALYST patient card and Red Flag card (which lists symptoms needing immediate medical attention) with out-of-hours contact details.

10.0 Dose delays and modifications

The dose of Carfilzomib should be delayed and / or reduced according to the guidelines given below (CTCAE v4.03). Dose re-escalation may occur if the toxicities were considered to be disease related, however dose re-escalation should only be undertaken following discussion with the CI.

Please see appendix 8 for known risk and discomforts from Carfilzomib.

10.1 Cycle 1 - dose escalation phase only

If toxicity occurs between day 1 of cycle 1 and first dose of treatment administered in cycle 2 treatment of the dose escalation phase, please refer to Section 8.1.4 for DLT definitions.

Any patient experiencing a DLT during cycle 1 of the dose escalation phase will have his or her treatment withheld until toxicity resolves to baseline or Grade ≤1. Upon resolution, the patient may have therapy re-instituted at the next lowest dose level, unless this occurs dose level -1, where patients will stop therapy.

If a patient experiences an SAE or grade 3/4 toxicity after the day 1 dose of cycle 1 (loading carfilzomib dose) treatment should be delayed until toxicity has resolved to baseline or Grade ≤1 and then discussed with the CI to see whether it is safe to proceed as planned.

If there is a greater than 8 day delay in dosing due to toxicity attributable to the loading dose of Carfilzomib, the safety review committee will be notified.

10.2 Subsequent cycles (all patients)

In summary treatment should be delayed for any patient experiencing:

- Grade 4 thrombocytopnia with active bleeding
  Grade 4 anaemia and Grade 4 thrombocytopenia (without active bleeding) do not require the Carfilzomib dose to be withheld. Participants should receive supportive measures in accordance with institutional guidelines.
- Grade 4 neutropenia or neutropenic fever
- Grade 3/4 non-haematological toxicity

Treatment should continue to be withheld until the neutrophil count and platelet count return to ≥0.75 x 109/L and ≥25 x 109/L, respectively (during a cycle). Drug-induced non-haematological toxicities have to have reached baseline, or become Grade ≤1 prior to re-treatment. Treatment may be delayed up to 8 days to allow sufficient time for recovery from toxicities. Please check table 3 and table 5 for dose reduction guidelines.

If the haematological or non-haematological AE has not resolved within 14 days the patient must discontinue from therapy, if the haematological or non-haematological toxicities have resolved within 14 days, the patient may have their therapy re-instituted at the next lowest dose level. Please check table 3 and table 5 for dose reduction guidelines.

A dose delay of up to 14 days (up to 3 weeks for infection treatment) is permitted at the beginning of a cycle to allow resolution of toxicity. If there is no resolution of toxicity as stated above after 2 weeks of withholding treatment (3 weeks for infection treatment), the participant will be discontinued from treatment. Withholding treatment for more than 2 weeks for other reasons, eg elective surgery such as vertebroplasty, may be permitted after discussion with the CI.

No more than three dose reductions or delays in two consecutive cycles will be permitted in an individual participant on study. If toxicity continues or recurs after three dose reductions or delays, the participant should be discontinued from treatment.

If a patient vomits after taking a dose of an oral agent, no repeat dose should be taken and patient will continue as per schedule but the clinical team should consider prophylactic antiemetics.

All previously established or new toxicities observed at any time, with the exception of neuropathic pain and peripheral sensory neuropathy, are to be managed as detailed in table 3 recommended action for haematologic toxicities and table 5 dose adjustment guidelines for non-haematological toxicities.

10.3 Haematological Parameters

The following parameters must be met on the **first day of a new cycle** (other than cycle one, when the inclusion for initial registration parameters must be met):

- Platelet count ≥50x10^9/L, Haemoglobin ≥8g/dl, (prior red blood cell transfusion or recombinant Human Erythropoietin usage is allowed), ANC ≥1x10^9/L.

On any day of Carfilzomib administration **during a cycle** (other than day one of each cycle), the haematological results must be:

- Platelet count ≥25x10^9/L, Haemoglobin ≥8g/dl (prior red blood cell transfusion or recombinant Human Erythropoietin usage is allowed), ANC ≥0.75x10^9/L.

10.4 Dose Reduction For Haematologic Toxicities

Patients will have a FBC prior to each dose of Carfilzomib during treatment.

Carfilzomib will be withheld from participants with:

- Grade 4 thrombocytopenia with active bleeding
- Grade 4 neutropenia

The following table outlines the dose reduction guidelines for Carfilzomib for thrombocytopenia and neutropenia:

Table 3: Recommended Action for Haematologic Toxicities

Haematologic Toxicity	Recommended Action	
Thrombocytopenia		
When platelets fall to ≤ 25 x 10^9 / L	If platelets 10 – 25 x 10^9 / L without evidence of bleeding	Continue at same dose
	If evidence of bleeding or platelets < 10 x 10^9 / L	Withhold dose until platelets return to ≥ 10 x 10^9 / L and/or bleeding is controlled, then resume at same dose.
For each subsequent drop to ≤ 25 x 10^9 / L	If platelets 10 – 25 x 10^9 / L without evidence of bleeding	Continue at same dose
	If evidence of bleeding or platelets < 10 x 10^9 / L	Withhold dose until platelets return to ≥ 10 x 10^9 / L and/or bleeding is controlled, then resume at 1 dose decrement
Neutropenia		
When ANC falls to ≤ 0.75 x 10^9 / L	If ANC 0.5-0.75 x 10^9 / L	Continue at same dose

	If ANC <0.5 x 10^9 / L	Withhold dose until ANC returns to ≥ 0.5 x 10^9 / L, then resume at same dose.
For each subsequent drop to ≤ 0.75 x 10^9 / L	If ANC 0.5-0.75 x 10^9 / L	Continue at same dose
	If ANC <0.5 x 10^9 / L	Withhold dose until ANC returns to ≥ 0.5 x 10^9 / L, then resume at 1 dose decrement.
Neutropenic fever	If < 1000/mm^3 and single temperature > 38.3^{0}C OR temperature > 38.0^{0}C for more than one hour.	Withhold dose until ANC returns to baseline grade, then resume at same dose.

Please note; if doses of carfilzomib need to be delayed then the dexamethasone dose must also be delayed so that it can be taken prior to the carfilzomib dose. Thalidomide can be taken continuously unless there is toxicity directly attributable to Thalidomide.

10.5 Dose Reductions for Non-Haematologic Toxicities

Carfilzomib should be withheld for events ≥ Grade 3 until resolved to ≤ Grade 1 or return to baseline.

After resolution of the event to ≤ Grade 1 or return to baseline, if the adverse event was not treatment-related, subsequent treatment with Carfilzomib may resume at full dose. If the event was treatment-related, subsequent treatment with Carfilzomib will resume at one level dose reduction except for nausea, vomiting or diarrhoea which can be attributed to Carfilzomib (see table 5 below). 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, the participant should be discontinued from treatment.

Dose reduction guide for Carfilzomib:

Table 4: Dose Reduction Guide for Carfilzomib Dosing

Current dose	**Reduce to**
27mg/m^2	**20mg/m^2**
36 mg/m^2	27 mg/m^2
45 mg/m^2	36 mg/m^2
56 mg/m^2	45 mg/m^2

If the participant tolerates the reduced dose for two cycles, participant may be dose escalated to the dose prior to reduction following discussion with the CI and CTRU.

Dose adjustment guidelines for non-haematologic toxicities are summarised as follows:

Table 5: Dose Adjustment Guidelines for Non-Haematological Toxicities.

Symptom	**Recommended Action** **Carfilzomib**
Allergic reaction/hypersensitivity Grade 2 – 3	Withhold until ≤ Grade 1, reinstitute at full dose.
Grade 4	Discontinue (refer to section 14)
Tumour lysis syndrome (≥ 3 of following: ≥ 50% increase in creatinine, uric acid, or phosphate; ≥ 30% increase in potassium; ≥ 20% decrease in calcium; or ≥ 2-fold increase in LDH	Withhold Carfilzomib until all abnormalities in serum chemistries have resolved. Reinstitute at full doses.

Infection Grade 3 or 4	Withhold Carfilzomib until systemic treatment for infection complete and infection resolves. If no neutropenia, restart at same dose. If neutropenic, follow neutropenia instructions.
Herpes zoster of any grade	Withhold Carfilzomib until lesions are dry. Reinstitute at full dose
Grade 3 Nausea or vomiting despite maximal anti-emetic therapy or diarrhoea	Withhold Carfilzomib until this resolves and re-start at full dose. If recurrent, re-start at one dose level lower
Grade 2 treatment emergent neuropathy with pain or Grade 3 neuropathy	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
≥ Grade 3 elevation in LFTs (AST, ALT, or total bilirubin)	Withhold dose. Resume at 1 dose decrement when toxicity has resolved to baseline.
Grade 4 neuropathy	Discontinue (refer to section 14)
Renal Dysfunction Serum creatinine equal to or greater than 2 x baseline, or CrCl < 15mL/min (or CrCl decreases to ≤50% of baseline) or need for dialysis.	Withhold dose and continue monitoring renal function (serum creatinine or serum creatinine clearance). If attributable to Carfilzomib, resume when renal function has recovered to within 25% of baseline. Start at 1 dose level reduction. If not attributable to Carfilzomib, dosing may be resumed at the discretion of the physician. If tolerated, the reduced dose may be escalated to the previous dose at the discretion of the physician. For patients on dialysis during Carfilzomib, the dose is to be administered after the dialysis procedure.
Congestive heart failure and other cardio-pulmonary disorders.	See section 10.10. Any participant with marked worsening of symptoms of congestive heart failure, whether or not drug related, must have the dose withheld until resolution or return to baseline, after which treatment may continue at a reduced dose, or the subject may be permanently discontinued
Other non-haematologic toxicity assessed as Carfilzomib-related ≥ Grade 3	Withhold dose until toxicity resolves to ≤ Grade 2 or baseline. Restart at 1 dose decrement. If tolerated, the reduced dose may be escalated to the previous dose at the discretion of the physician.
PRES (posterior reversible encephalopathy syndrome with symptoms including headaches, altered mental status, seizures, visual loss, and hypertension).	If PRES suspected, withhold Carfilzomib. Consider evaluation with neuroradiological imaging for onset of visual or neutrological symptoms suggestive of PRES. If PRES diagnosis is excluded, Carfilzomib administration may resume if clinically appropriate.

10.6 Dexamethasone Toxicity

Fluid retention is common with Dexamethasone in patients with amyloidosis. Optimisation and close monitoring of fluid balance including alteration of diuretic therapy according to daily weights should be considered as the first step. For fluid retention, switching to an alternative corticosteroid, e.g. methylprednisolone, is unlikely to be of major benefit as the mineralocorticoid action is greater for most other corticosteroids than for Dexamethasone at comparable doses.

If a patient experiences grade 3 or 4 toxicity directly attributable to Dexamethasone a dose reduction should be considered. Dose adjustments should be at the discretion of the treating physicians in view of appreciable variability in the manifestation of such side effects. Dexamethasone should be reduced in 4mg steps.

Please see the SPC for expected toxicities.

10.7 Thalidomide Toxicity

Cases of viral reactivation, some serious, have been reported following treatment with thalidomide, particularly in patients previous infected with the varicella zoster virus or hepatitis B virus (HBV). Some of the cases of reactivation resulted in disseminated herpes zoster, requiring antiviral treatment and thalidomide treatment

interruption. Some cases of HBV reactivation progressed to acute hepatic failure and resulted in thalidomide treatment discontinuation.
Hepatitis B virus status should be established before initiating treatment with thalidomide. For patients who test positive for HBV, consultation with a physician with expertise in the treatment of hepatitis B is recommended. Previously infected patients should be closely monitored for signs and symptoms of viral reactivation, including active HBV infection, throughout therapy. Patients who test positive for HBV will not be eligibile for the CATALYST trial.

Cases of pulmonary hypertension, some fatal, have been reported following treatment with thalidomide.

If a patient experiences grade 3 or 4 toxicity directly attributable to Thalidomide a dose reduction should be considered. Dose adjustments should be at the discretion of the treating physicians in view of appreciable variability in the manifestation of such side effects. Patients receiving 100mg should be reduced to 50mg. Patients receiving 50mg should have their dose discontinued.
Please see the SPC for expected toxicities.

10.8 Increased Creatinine or Decreased CrCl

Carfilzomib should be withheld for CrCl < 15 mL/min, and re-commenced as detailed in Table 5. Patients whose renal function fails to recover may re-commence therapy after discussion with the CI.

10.9 Infections

Participants with active or suspected infections of grade III or greater should have treatment withheld until infection has resolved and anti-infective treatment has been completed. After the infection has resolved and anti-infective treatment has been completed, treatment may continue at the original dose. If there is no resolution of toxicity to ≤ Grade 1 or baseline after 3 weeks, the participant will be discontinued from treatment (see section 14).

10.10 Congestive Heart Failure

New or worsening cardiac failure, myocardial ischaemia, and myocardial infarction have occurred following Carfilzomib administration, with the risk of cardiac failure increased in elderly subjects (≥ 75 years). Worsening of congestive cardiac failure and other cardiopulmonary disorders including pulmonary oedema, and decreased ejection fraction will need careful assessment in relation to baseline cardiac status for the patient since many amyloid patients will have stable heart failure prior to trial entry.

If left ventricular ejection fraction (LVEF) decreases occur (for resting LVEF < 40% or reduction of LVEF to <55% if the drop is greater than 20% from baseline), withhold Carfilzomib until LVEF returns to > 40% or, if held due to a drop, < 55% within 15% of baseline. Resume at a 1-dose decrement.

Any participant with marked worsening of symptoms of congestive heart failure, whether or not drug related, must have the dose withheld until resolution or return to baseline, after which treatment may continue at a reduced dose, or the subject may be permanently discontinued. If no resolution after 2 weeks, participant will be permanently discontinued.

Any participant with significant worsening symptoms of CHF which has not resolved with an increase in diuretics prior to the next dose, or any other acute cardiac event, whether or not drug related, must have treatment withheld until resolution. After the event has resolved, treatment may continue at the previous dose, or one dose level lower than the previous dose. If there is no resolution of worsening of CHF after 2 weeks or further worsening after the next dose, the participant will be discontinued from treatment.

10.11 Conditions Not Requiring Dose Reduction

The following conditions are exceptions to the above guidelines. Carfilzomib dosing does not need to be withheld in the following cases:

- Grade 3 nausea, vomiting or diarrhoea (unless persisting >5 days with adequate use of anti-emetics or anti-diarrhoeal medication)
- Grade 3 fatigue (unless persisting for >14 days)

- Alopecia
- ≥ Grade 3 hyperglycaemia attributed to Dexamethasone

10.12 Carfilzomib 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. methylprednisolone 50–100 mg) is recommended. In addition, intravenous fluids, vasopressors, oxygen, bronchodilators, and acetaminophen should be available for immediate use and instituted, as medically indicated.
- Dexamethasone will be administered prior to all Carfilzomib doses to prevent infusion reactions. See section 9.3.3 for more details.
- 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. Carfilzomib must be withheld for participants with a CrCl < 15 mL/min at any time during study participation.
- Participants with active or suspected infection of any kind that required systemic treatment should not be dosed with Carfilzomib until the infection has resolved.
- Cases of gastrointestinal, pulmonary, and intracranial haemorrhage have been reported in patients treated with Carfilzomib, and are often associated with thrombocytopenia. Thrombocytopenia has been transient, with platelet nadirs seen between Day 8 and Day 15 of dosing, and typically resolves to baseline by the start of the next cycle. Platelet counts should be monitored frequently during treatment with Carfilzomib. For platelet counts ≤ 10 x 10^9/L with evidence of bleeding, Carfilzomib dosing must be withheld. 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 10.4.
- Thromboembolic events, including deep vein thrombosis and pulmonary embolisms, have been reported in patients taking Carfilzomib, and some events have had fatal outcomes. Thromboprophylaxis, as outlined in section 9.2, should be administered to all participants receiving Carfilzomib.
- Participants should have anaemia corrected in accordance with the Institutional 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.
- Posterior reversible encephalopathy syndrome (PRES), formerly termed reversible posterior leukoencephalopathy syndrome (RPLS), is a rare neurological disorder, which can present with seizure, headache, lethargy, confusion, blindness, altered consciousness, and other visual and neurological disturbances, along with hypertension. The diagnosis is confirmed by neuro-radiological imaging. If diagnosed early and treated, the symptoms of PRES may be reversed. Cases of PRES have been reported in subjects receiving Carfilzomib. Discontinue Carfilzomib if PRES is suspected. Refer to the study protocol for further instructions regarding dose modifications. The safety of reinitiating Carfilzomib therapy in subjects previously experiencing PRES is not known.
- Cases of thrombocytopenic thrombotic purpura/hemolytic uremic syndrome (TTP/HUS) including those with fatal outcome have been reported in subjects who received Carfilzomib. Monitor for signs and symptoms of TTP/HUS. If the diagnosis is suspected, stop Carfilzomib and manage per standard of care including plasma exchange as clinically appropriate. If the diagnosis of TTP/HUS is excluded, Carfilzomib can be restarted.
- Hypertensive crises have been infrequently reported in subjects treated with Carfilzomib. Hypertensive crises can present as hypertensive urgency or as a hypertensive emergency. Hypertensive urgency is defined as sustained or persistent systolic blood pressure 180mmHg or higher or diastolic blood pressure 110mmHg or higher, with no associated organ damage. A hypertensive emergency occurs when blood

pressure reaches levels that result in end organ damage. All patients should be routinely evaluated for hypertension and treated as needed. If the hypertension cannot be controlled Carfilzomib should be reduced, per protocol. In cases of hypertensive crises, stop Carfilzomib until resolved or returned to baseline and consider whether to restart Carfilzomib based on a risk/benefit assessment.

- Cases of pulmonary hypertension have been commonly reported in subjects treated with Carfilzomib. Pulmonary hypertension is generally defined as a mean pulmonary arterial pressure ≥ 25mmHg at rest. Echocardiography is usually the first test to suggest pulmonary hypertension. Pulmonary hypertension can be a progressive, fatal disease if untreated, although the rate of progression is highly variable. Amyloid patients often have pulmonary hypertension at baseline. Stop Carfilzomib until pulmonary hypertension has resolved or returned to baseline and consider whether to restart Carfilzomib based on a risk/benefit assessment. Cases of interstitial lung disease (including pneumonitis), acute respiratory failure and Acute Respiratory Distress Syndrome (ARDS) have been uncommonly reported in subjects. Evaluate and stop Carfilzomib until resolved and consider whether to restart Carfilzomib based on a risk/benefit assessment.
- Acute respiratory distress syndrome, acute respiratory failure, and acute diffuse infiltrative pulmonary disease such as pneumonitis and interstitial lung disease have been reported in subjects receiving Carfilzomib. Suspected acute respiratory conditions should be evaluated and Carfilzomib stopped until resolution. Consider whether to re-start Carfilzomib based on a risk/benefit assessment.
- Dyspnoea is commonly reported in participants receiving Carfilzomib, and should be evaluated to exclude cardiopulmonary conditions (cardiac failure, pulmonary syndromes). Carfilzomib shall be stopped for Grade 3 or 4 dyspnoea until resolves or returned to baseline. Consider whether to re-start Carfilzomib based on a risk/benefit assessment.
- Cases of Tumor Lysis Syndrome (TLS) including fatal outcome, have been reported in subjects who received Carfilzomib. Subjects with a high tumor burden should be considered to be at greater risk for TLS. Ensure that subjects are well hydrated before administration of Carfilzomib in Cycle 1 and in subsequent cycles as needed. Uric acid-lowering drugs should be considered in subjects at high risk for TLS. Monitor for evidence of TLS during treatment, including regular measurement of serum electrolytes, and manage promptly. Interrupt Carfilzomib until TLS is resolved. Refer to the study protocol for further instructions regarding dose modifications.

Please refer to the trial supplied Investigator Brochure to see the full adverse drug reaction tables.

11.0 Assessments

The trial consists of an initial treatment period of up to 6 cycles of chemotherapy treatment (approximately 7 months) for all patients. Follow up will be 6 months after registration or 1 month after the end of treatment if 6 cycles of chemotherapy was adminisitered.

Trial data will be recorded by UK NAC and RHCs research staff on the CRFs and submitted to the LEEDS CTRU. It is the responsibility of each trial site to retain copies of all completed CRFs and to maintain their Investigator Site File which contains all essential documentation for the trial that is required at site.

5ml serum samples will be sent to the UK NAC by the RHCs for central testing as part of routine clinical practice; as noted in the following sections of the protocol. Packs, containing appropriately labelled sample tubes for the central testing associated with this trial, will be provided to participating RHCs by the UK NAC.

The central investigations are of key importance in relation to the in-depth assessment of the disease, prognostic factors, and the analysis of response to treatment and outcome.

See Trial Contacts at the beginning of the protocol for addresses for sending samples for central analysis and CRFs.

Assessment summary table:

Investigation	Baseline (Registration at UK NAC)	Re-confirmation of Eligibility (at RHC)[e]	Treatment Carfilzomib and Dexamathasone days 1, 8 , 15 Thalidomide days 1-28			Prior to beginning of 4th Cycle (at UK NAC)	End of treatment visit (at RHC)	Follow up visit (at UK NAC)
			Prior to each treatment cycle (at RHC)[f]	Day 8	Day 15			
Informed consent	X							
Patient details (including initials, date of birth, sex)	X							
Medical History	X							
Physical Examination[a]	X	X	X			X	X	X
Laboratory tests[b]	X[b]	X	X	X[j]	X[j]	X	X	X[b]
Pregnancy test	X	X	X[h]			X	X	X[i]
Assessment of response at UK NAC						X		X
Echocardiography incl. Tissue Doppler	X		X[g]			X[g]		X
24 Hour Holter monitor	X							
Bone marrow examination[c]	X							
Adverse Events	X	X	X	X	X	X	X	X
Concomitant Medication	X	X	X	X	X	X	X	X
Hepatitis B test	X							
5ml serum sample to UK NAC[d] Used to assess response to treatment			On Day 1 of treatment cycle 1, 2, 3, 5, 6 (to be taken at RHC and sent to UK NAC) AND within a week of the planned start date of the 4th cycle					

[a] Including height, weight, lying and 5 minute standing blood pressure, ECOG performance status
[b] Including haematology, biochemistry, paraprotein and immunoglobulins (see Appendix 6 for details)
[c] Only if clinically indicated
[d] Send to UK NAC as per standard practice. Results will be used to assess haematological response and relapse.
[e] visit must be within 28 days of registration
[f] Patient must receive 1st cycle of treatment within 6 weeks of reconfirmation of eligibility at the RHC (see 11.1.2).
[g] Repeat echocardiogram at end of cycle 2 only (echocardiograms at baseline, prior to cycle 4 and end of treatment will be done at NAC). Echocardiogram to be repeated at any cycle if clinically indicated for unexpected worsening of cardiac function.
[h] To be supervised and performed on the day of prescription or in the 3 days prior to the visit to the prescriber.
[I] To be supervised and performed four weeks after the end of treatment during the follow-up visit
[j] FBC and creatine levels to be checked at day 8 and day 15 (see appendix 6 for details)

11.1 Eligibility assessments

PLEASE ALSO SEE APPENDIX 6

11.1.1 Assessments at National Amyloidosis Centre (UK NAC)

Once written informed consent has been obtained, patients will be registered as described in section 7.1. The results of investigations and assessments carried out as part of the standard Amyloid Evaluation by the UK NAC (detailed in **Appendix 6**) will be recorded as part of the trial dataset as baseline evaluation.

11.1.2 Assessments at RHC to reconfirm eligibility

Following consent and registration, patients will be referred by UK NAC to a Regional Haematology Centre (RHC), see section 5.1. Upon attendance at the relevant RHC, patient eligibility for the trial will be reconfirmed by the treating Haematologist. This visit must be within 28 days of registration. The following investigations and assessments will be carried out by the RHC to confirm eligibility of the patient for the trial:

- Physical examination
- FBC (including Hb, White Cell Count, Platelets), clotting screen (PT, APTT, Factor X (if indicated)), biochemistry (including creatinine, eGFRcalcium, phosphate, CRP, ALP, GGT, AST, ALT, bilirubin, albumin, sodium, potassium)
- Pregnancy test

For all patients who still fulfil the eligibility criteria for the trial, the RHC must complete the eligibility confirmation form and fax to LEEDS CTRU. LEEDS CTRU will confirm patient's entry into trial and upon receipt of this at RHC, the patient will receive the protocol treatment regimen.

If there is a ≥ 21 day delay of reconfirmation of eligibility, the RHC will have to carry out the above investigations and assessments again and complete another eligibility confirmation form, to allow the patient to continue on the trial. If the patient is unable to start treatment within 6 week of completion of the first eligibility confirmation form completed by the RHC, he/she will be withdrawn from the trial.

Patients who are no longer eligible for the trial will be withdrawn from the trial and treated according to standard local practice (the RHC site staff will complete the Withdrawal Form and fax to LEEDS CTRU).

LEEDS CTRU will inform UK NAC of all patients entering/withdrawing from the trial at this point.

11.2 Assessments during treatment

Prior to each chemotherapy cycle

During treatment the patient should be seen prior (within 3 days) to each chemotherapy cycle and the following assessments performed:

- Physical examination, including lying and 5 minute standing blood pressure.
- FBC (Hb, White Cell Count, Platelets), clotting screen (PT, APTT, Factor X (if indicated)), biochemistry (urea, creatinine, eGFR, calcium, phosphate, CRP, ALP, GGT, AST, ALT, bilirubin, albumin, sodium, potassium).
- Assess and record any adverse events
- Record concomitant medications
- Repeat echocardiogram at end of cycle 2 only (echocardiograms at baseline, prior to cycle 4 and end of treatment will be done at UK NAC). Echocardiogram to be repeated at any cycle if clinically indicated for unexpected worsening of cardiac function.
- Pregnancy test
- **A 5ml serum sample must be sent to the UK NAC as per standard practice prior to the start of each chemotherapy cycle ***

*The 5 ml serum sample is used by the UK NAC to assess haematological response and relapse (through biochemical tests including serum free light chain assessments), the results of which will be used as part of the trial dataset. The sample will be frozen and stored at the UK NAC indefinitely as per standard practice (separate written

consent is obtained for this as per standard clinical practice for all patients attending UK NAC). In addition, the following data will be collected for each treatment cycle:

- Treatment cycle number and cycle details, including dose given, dose alterations, and reasons
- Toxicities relating to treatment

Day 8 and day 15 of cycle

Patients will also be seen on day 8 and day 15 of each cycle and the following assessement performed:

- FBC (Hb, White Cell Count, Platelets) and creatinine
- Assess and record any adverse events
- Record concomitant medications

All patients with stage III disease will be assessed once weekly for the first three cycles for signs or symptoms of worsening heart failure or "red flag" symptoms ** .
All patients will be given a card for "red flag" symptoms with advice to seek urgent medical attention**

** **Red Flag symptoms**: Significant worsening dyspnoea, hypotension, unexplained persistent dizziness, syncopal episodes.

The continuation of chemotherapy in this trial beyond the third cycle depends on assessment and classification of response at the end of the third cycle of treatment. An Investigator at the UK NAC will send a confirmatory letter from the UK NAC about the classification of response and further treatment though treatment for the next cycle may commence immediately if indicated.

Patients will be seen at the UK NAC after three cycles and either 6 months after registration or in patients receiving a full 6 cycles of chemotherapy, 1 month after the final cycle of treatment.

Thereafter, patients will be monitored off protocol as per their clinical need.

11.3 Assessments during follow up

Follow up investigations will be carried out at 6 months after registration or one month after the last cycle of chemotherapy, if all 6 cycles were received, as detailed in the Assessment Summary table in section 11.0.

12.0 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 LEEDS CTRU. Data entered onto CRFs must be verifiable from source data at site.

Source data are contained in source documents and must be accurately transcribed on to the CRF. Examples of source documents are hospital records which include laboratory and other clinical reports etc.

Where copies of supporting source documentation (e.g. autopsy reports, pathology reports, etc) are being submitted to LEEDS CTRU, 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. The exception to this is the participant consent form, where the participant name and signature must not be obliterated. If signed consent forms are posted to CTRU, they must be sent in a separate envelope and not accompanied by any CRFs containing clinical data.

12.1 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 initialled. Correction fluid must not be used.

The use of abbreviations and acronyms must be avoided.

Once completed the original CRFs must be sent to LEEDS CTRU and a copy kept at site.

12.2 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 the LEEDS CTRU. When data is 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).

12.3 Timelines for data return

CRFs must be completed at site and returned to LEEDS CTRU as soon as possible after patient visit and within 2 weeks of the patient being seen.
Sites who persistently do not return data within the required timelines may be suspended from recruiting further patients into the trial by LEEDS CTRU and subjected to a 'for cause' monitoring visit. See section 16.2 ('For cause' on-site monitoring) for details.

Completed SAE Reports must be faxed within 24 hours of becoming aware of the event to LEEDS CTRU
Fax: 0113 343 4345

12.4 Data Queries

Data arriving at LEEDS CTRU will be checked for legibility, completeness, accuracy and consistency, including checks for missing or unusual values. Query Reports 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 Query Reports.

13.0 Pharmacovigilance

13.1 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 or effect 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 an abnormal laboratory finding), symptom or disease temporally associated with the use of a trial treatment, whether or not related to that trial treatment.

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 subject 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.)

Suspected Unexpected Serious Adverse Reaction (SUSAR)
A Suspected Unexpected Serious Adverse Reaction (SUSAR) is a Serious Adverse Reaction which also demonstrates the characteristics of being unexpected, the nature, seriousness, severity or outcome of which is not consistent with the information about the medicinal product in question set out in the Summary of Product Characteristics or Investigator Brochure.

13.2 Reporting Procedures

13.2.1 All Adverse Events (AEs)

All adverse events that occur between informed consent and 30 days post last trial treatment administration 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 LEEDS CTRU within 24 hours of becoming aware of the event using the trial specific SAE Report. Also refer to section 13.2.2 (Serious Adverse Events (SAEs)).

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

Overdoses

All accidental or intentional overdoses, whether or not they result in adverse events, must be recorded in the patient notes and CRFs. Overdoses resulting in an adverse event are classified as SAEs and must be reported to LEEDS CTRU according to SAE reporting procedures. The fact that an overdose has occurred must be clearly stated on the SAE Report. Also refer to section 13.2.2 (Serious Adverse Events (SAEs)).

Sites must inform LEEDS CTRU immediately when an overdose has been identified. Also refer to section 17 (Incident Reporting and Serious Breaches).

Adverse Event Term

An adverse event term needs to be provided for each adverse event, preferably using the term listed in the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03, available online at: http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf

Severity

Severity for each adverse event will be determined by using the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 as a guideline, wherever possible. The criteria are available online at: http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf. Appendix 5 also details some toxicity criteria.

In those cases where the CTCAE criteria do not apply, severity should be coded according to the following criteria:

1 = Mild (awareness of sign or symptom, but easily tolerated)
2 = Moderate (discomfort enough to cause interference with normal daily activities)
3 = Severe (inability to perform normal daily activities)
4 = Life threatening (immediate risk of death from the reaction as it occurred)
5 = Fatal (the event resulted in death)

Causality

The PI, or other delegated site investigator, must perform an evaluation of causality for each adverse event. Causal relationship to each trial treatment must be determined as follows:

- **None**

There is no evidence of any causal relationship.

- **Unlikely**

There is little evidence to suggest a causal relationship (e.g. because the event did not occur within a reasonable time after administration of a trial treatment). There is another reasonable explanation for the event (e.g. the patient's clinical condition, other concomitant treatments).

- **Possibly**

There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of a trial treatment). However, the influence of other factors may have contributed to the event (e.g. the patient's clinical condition, other concomitant treatments).

- **Probably**

There is evidence to suggest a causal relationship and the influence of other factors is unlikely.

- **Definitely**

There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.

13.2.2 Serious Adverse Events (SAEs)

All SAEs that occur between informed consent and 30 days after the last trial treatment administration (or after this date if the site investigator feels the event is related to the trial treatment) must be submitted to LEEDS CTRU by fax 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 LEEDS CTRU, the circumstances that led to this must be detailed in the SAE Report to avoid unnecessary queries.

Events not classed as SAEs

The following events **will not** be recorded as SAEs within this trial:
Hospitalisation for:

- Routine treatment or monitoring of the studied indication not associated with any deterioration in condit ion.
- Treatment which was elective or pre-planned, for a pre-existing condition not associated with any deterioration in condition.
- Admission to hospital or other institution for general care, not associated with any deterioration in condition.

- Treatment on an emergency, outpatient basis for an event not fulfilling any of the definitions for serious as given above and not resulting in hospital admission.
- Disease progression

Deaths attributable to amyloidosis beyond 30 days of the last administration of the study agent

Expected SAEs related to Amyloidosis:

- Hypercalcaemia
- Pain control necessitating admission to hospital
- Infections requiring intravenous antibiotics
- Blood product support necessitating admission to hospital
- Spinal cord compression
- Renal failure
- Fractures and / or corrective surgery

Expected SAEs common to all treatments:

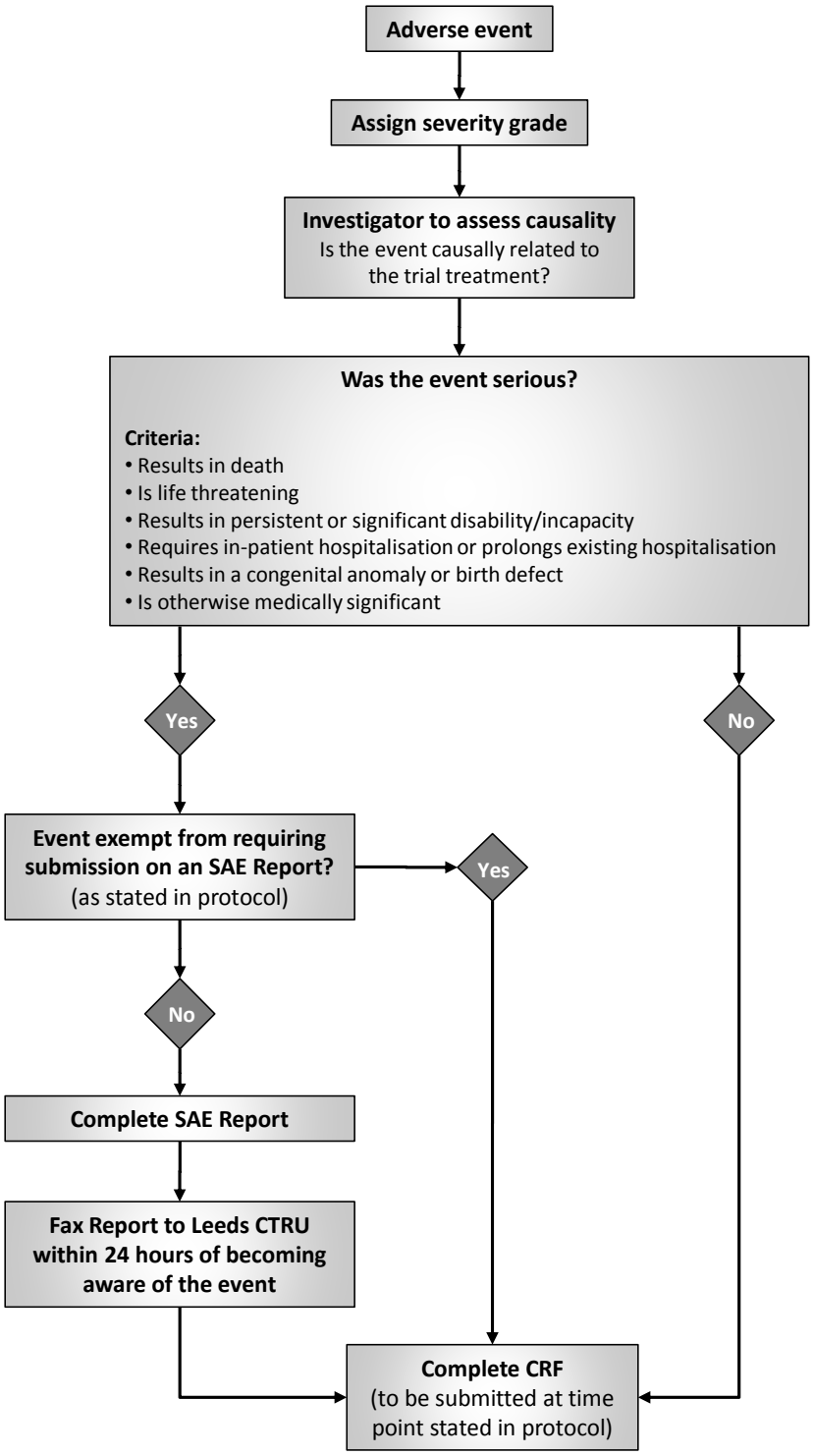
- Anaemia
- Neutropenia
- Thrombocytopenia
- Infections requiring intravenous antibiotics
- Nausea/Vomiting
- Bowel disturbance
- Extravasation

Expected SAEs for specific drugs/treatments:

When determining whether an SAE is expected or not, please refer to the version of the SPC / IB supplied in the Investigator Site File or the latest updated version as instructed by the CTRU.

Completed SAE Reports must be faxed within 24 hours of becoming aware of the event to LEEDS CTRU
Fax: 0113 343 4345

Adverse Event Reporting Flowchart



SAE Follow-Up Reports

All SAEs must be followed-up until resolution and until there are no further queries. The PI, or other delegated site investigator, must provide follow-up SAE Reports if the SAE had not resolved at the time the initial report was submitted.

SAE Processing at LEEDS CTRU

On receipt of the SAE Report, LEEDS CTRU 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 list of expected adverse events in the current Investigator Brochure for Carfilzomib and current SPC for Thalidomide and Dexamethasone.

The CI, or their delegate (e.g. a clinical member of the TMG), will be contacted to review the SAE and to perform an evaluation of causality on behalf of LEEDS CTRU. The CI or delegate will also assign a code to all SAEs using the MedDRA Body System Organ Class coding If LEEDS CTRU has considered expectedness difficult to determine, the CI, or their delegate, will be consulted for their opinion at this time.

LEEDS CTRU will report AEs and SAEs in annual line listings in line with the requirements of the MHRA.

13.3 SUSARs

All SARs and SUSARs occurring for all participants from the time of consent until the end of the trial must be recorded on the SAE / SUSAR Form and faxed to the CTRU within 24 hours of the research staff becoming aware of the event.

For each SAE / SUSAR, the following information will be collected:

- full details in medical terms with a diagnosis, if possible
- its duration (start and end dates if applicable)
- action taken
- outcome
- causality (i.e. relatedness to trial drug / investigation), in the opinion of the investigator)*
- whether or not the event would be considered expected or unexpected*

*Assessment of causality and expectedness must be made by a doctor. If a doctor is unavailable, initial reports without causality and expectedness assessment should be submitted to CTRU within 24 hours, but must be followed up by medical assessment as soon as possible thereafter.
Please ensure that each event is reported separately and not combined on one SAE form.

Any follow-up information should be faxed to the CTRU within 24 hours of the research team becoming aware of the information. Events will be followed up until the event has resolved or a final outcome has been reached.

If the event is evaluated by either the site or LEEDS CTRU as a Suspected Unexpected Serious Adverse Reaction (SUSAR), LEEDS CTRU will submit a report to the MHRA (via eSUSAR) and the REC within 7 calendar days for fatal/life threatening events, with a follow-up report within a further 8 calendar days, and 15 calendar days for all other events. Where there are conflicting evaluations of causal relationship by the site and LEEDS CTRU/CI, both opinions will be reported.

LEEDS CTRU will submit individual case SUSAR reports to Amgen concurrent with submission to the MHRA and the REC.

Informing Sites of SUSARs

LEEDS CTRU will inform all PIs of any SUSARs which occur on the trial. All PIs should review the SUSAR when received, sign and date as reviewed, and file in their site file. PIs will receive a quarterly line listing which must be processed according to local requirements.

13.4 Safety Monitoring

LEEDS CTRU will provide safety information to the TMG and the SRC on a periodic basis for review. Please refer also to section 20.0 Monitoring of data.

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 or SPCs for a trial treatment;
- trial related events that are not considered related to the trial treatment regimen;

Should LEEDS CTRU identify or suspect any issues concerning patient safety at any point throughout the trial, the TMG and SRC will be consulted for their opinion. The SRC will review the safety and ethics of the study by regularly reviewing safety data during the dose escalation stage. The decision about whether to expand the cohort or open up the next level will be based on the frequency of observed toxicity and the definitions of DLT and MTD in Section 8. The Group will meet or communicate via teleconference approximately monthly.

13.5 Pregnancy

Patients taking part in the trial should adhere to the Celgene Pregnancy Prevention Programme for use with Thalidomide. The Pregnancy Prevention Programme outlines the risks of pregnancy while taking Thalidomide and must be followed at all times.

If a participant or partner of a participant becomes pregnant or is suspected to be pregnant at any point during the trial, a completed trial specific Pregnancy Report must be submitted to LEEDS CTRU by fax within **24 hours** of learning of its occurrence. Leeds CTRU will notify Amgen Drug Safety within 24 hours of learning of the pregnancy or suspected pregnancy. Any female participant who becomes pregnant, must be withdrawn from trial.

If the participant is pregnant or is suspected to be pregnant, Carfilzomib, Thalidomide and Dexamethasone must be stopped immediately.

Participants or partner of a participant will be followed through the outcome of the pregnancy. The Investigator will be required to report all pregnancies to the Sponsor.

All pregnancies must be reported by faxing a completed Pregnancy Report within 24 hours of becoming aware of the event to LEEDS CTRU
Fax: 0113 343 4345

Sites are also responsible for reporting pregnancies to the MHRA via the yellow card scheme as per standard practice.

13.5.2 SAEs During Pregnancy

If the outcome of the pregnancy meets a criterion for immediate classification as an SAE - spontaneous abortion (any congenital anomaly detected in an aborted foetus is to be documented), stillbirth, neonatal death, or congenital anomaly—the Investigator should repeat the procedures for expedited reporting of SAEs as outlined in section 13.2.2 (Serious Adverse Events (SAEs)).

13.5.3 Pregnancy Report Processing at LEEDS CTRU

LEEDS CTRU will fax all Pregnancy Reports concerning exposure to Carfilzomib to Amgen within 1 business day.

LEEDS CTRU will submit a report to the MHRA and the REC should the pregnancy outcome meet the definition of a SUSAR. Refer to section 13.3 (SUSARs) for details.

13.6 Development Safety Update Reports (DSURs)

Safety data obtained from the trial will be included in DSURs that LEEDS CTRU will submit to the MHRA and the REC.

LEEDS CTRU will provide Amgen with DSURs that include information regarding Carfilzomib.

14.0 Withdrawal of patients

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

14.1 Discontinuation of Trial Treatment

14.1.1 Withdrawal due to clinical reasons

The site investigator may withdraw a patient from the trial treatment whenever continued participation is no longer in the patient's best interests, but the reasons for doing so must be recorded. Reasons for discontinuing treatment may include:

- Disease progression whilst on therapy
- Unacceptable toxicity
- Intercurrent illness which prevents further treatment
- The patient withdraws consent to further treatment
- Any alterations in the patient's condition which justifies the discontinuation of treatment in the site investigator's opinion

In these cases patients remain within the trial for the purposes of follow-up and data analysis according to the treatment option to which they have been allocated and for allowing existing collected data to be used. If the patient gives a reason for their withdrawal, this should be recorded.

14.1.2 Patient withdrawal from trial treatment

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.

14.2 Future Data Collection

If a patient explicitly states that they do not wish to contribute further data to the trial their decision must be respected, with the exception of safety data, and recorded on the relevant CRF. In this event details should be recorded in the patient's hospital records, no further CRFs must be completed and no further data other than safety data sent to LEEDS CTRU.

14.3 Losses to follow-up

If a patient moves 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 the responsibility for the patient. Details of participating trial sites can be obtained from the LEEDS CTRU trial team who must be informed of the transfer of care and follow up arrangements.

15.0 Trial Closure

15.1 End of Trial

For regulatory purposes the end of the trial is defined as the date of the last participant's last data item. At this point, the end of trial notification will be submitted to the relevant regulatory authorities (e.g. UK MHRA) and ethics committees.

Following this, LEEDS CTRU will advise sites on the procedure for closing the trial at the site.

15.2 Early discontinuation of trial

The trial may be stopped before completion as an Urgent Safety Measure on the recommendation of the SRC. Sites will be informed in writing by LEEDS CTRU of reasons for early closure and the actions to be taken with regards the treatment and follow up of patients.

15.3 Withdrawal from trial participation by sites

Should a site choose to close to recruitment the PI must inform LEEDS CTRU in writing. Follow up as per protocol must continue for all patients recruited into the trial at that site.

15.4 Archiving of Trial Documentation

At the end of the trial, the LEEDS CTRU will archive securely all centrally held trial related documentation for a minimum of 15 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 for a minimum of 15 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 Good Clinical Practice and all applicable regulatory requirements.

LEEDS CTRU 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.

16.0 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.

LEEDS CTRU 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.

16.1 Central monitoring

UK NAC will be requested to submit screening logs for the trial to LEEDS CTRU on request. UK NAC and RHC/sites will be requested to submit staff delegation logs for the trial to LEEDS CTRU at the frequency detailed in the trial monitoring plan or on request and these logs will be checked for consistency and completeness. Also refer to sections 4.2.2 (Required documentation).

Ensuring patient eligibility is the responsibility of the UK NAC PI and confirmation by the Site (RHC) PI or other delegated Investigator(s). Checks of the criteria listed on the registration form will be undertaken by an appropriately trained LEEDS CTRU staff member prior to registration. Also refer to section 7.1 (Registration).

UK NAC will be required to maintain a log of all patient informed consent forms that have been completed at site (regardless of whether the patient is subsequently registered to the trial). This log will include details of the versions of informed consent form/patient information sheet used, patient completion of the consent form, the name of the person taking consent, etc. A copy of the log must be submitted to LEEDS CTRU at the frequency detailed in the trial monitoring plan or on request. Also refer to section 5 (Informed Consent).

Copies of completed drug accountability logs will be collected at LEEDS CTRU for all trial patients. Sites will be required to submit logs on request. A proportion of these will be monitored centrally, as per the monitoring plan, to ensure completeness and correlation with data captured in the CRF. Also refer to section 9.3 (pharmacy responsibilities).

Participating RHC/sites (and UK NAC in its role as a RHC/site) 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 LEEDS CTRU will be subject to review in accordance with section 12 (Data Management and Data Handling Guidelines).

Where central monitoring of data and/or documentation submitted by sites indicates that a patient may have been placed at risk (e.g. evidence of an overdose having been administered, indication that stopping 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 17 (Incident Reporting and Serious Breaches) and 16.2 ('For cause' on-site monitoring) for further details).

16.2 'For Cause' On-Site Monitoring

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. The letter will include a list of the documents that are to be reviewed, interviews that will be conducted, planned inspections of the facilities, who will be performing the visit and when the visit is likely to occur.

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

LEEDS CTRU 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 17 (Incident Reporting and Serious Breaches) for details.

16.3 Oversight Committees

16.3.1 Trial Management Group (TMG)

The TMG will include the Chief Investigator, clinicians and experts from relevant specialities and CATALYST trial staff from LEEDS CTRU (see Page 3). The TMG will be responsible for overseeing the trial. The group will meet regularly and will send updates to PIs (via newsletters and/or at Investigator meetings) and to the NCRI Myeloma 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 individuals.

Members of the TMG will be asked to sign a TMG charter outlining their duties and responsibilities.

The TMG, comprising the Chief Investigator, CTRU team and co-investigators (see page 3) will be assigned responsibility for the clinical set-up, on-going management, promotion of the trial, and for the interpretation of results. Specifically the TMG will be responsible for (i) protocol completion, (ii) CRF development, (iii) obtaining approval from the main REC and supporting applications for Site Specific Assessments, (iv) submitting a CTA LRECs, (iv) submitting a DDXt to trial participations by responsible individuals from the research staff or from regulatory application and obtaining approval from the MHRA, (v) completing cost estimates and project initiation, (vi) facilitating the Dose Escaltion Review Group, (vii) reporting of serious adverse events, (viii) monitoring of screening, recruitment, treatment and follow-up procedures, (ix) auditing consent procedures, data collection, trial end-point validation and database development. During the dose escalation phase, the TMG along with at least one investigator from each recruiting site (PI or delegate), a company representative (when available) and non-recruiting clinician(s) (where available) will review the safety and ethics of the study by regularly reviewing safety data during the dose escalation phase. The decision about whether to expand the cohort or open up the next level will be based on the frequency of observed toxicity and the definitions of DLT and MTD in section 8. The group will meet or communicate via teleconference approximately monthly.

16.3.2 Safety Review Committee

The Safety Review Committee , comprising the Chief Investigator, at least one investigator from each recruiting site (PI or delegate), CTRU statistician(s), Senior Trial Co-ordinator, a company representative (when available) non-recruiting clinician(s) will regularly review the safety and ethics of the study during the dosae escalaltion phase to provide independent advice on data and safety aspects of the trial. The decision about whether to expand the cohort or open up the next level will be based on the frequency of observed toxicity and the definitions of DLT and MTD in Section 8. The Group will meet or communicate via teleconference approximately monthly.
Additionally, the Group will periodically review safety reports throughout the dose expansion phase of the trial.
Members of the IDMC will be asked to sign a SRC charter outlining their duties and responsibilities.

16.3.3 Role of LEEDS CTRU

The CTRU will provide set-up and monitoring of trial conduct to CTRU SOPs, and the GCP Conditions and Principles as detailed in the UK Medicines for Human Use (Clinical Trials) Regulations including, registration design and service, database development and provision, protocol development, CRF design, trial design, source data verification, monitoring schedule and statistical analysis for the trial. In addition the CTRU will support IRAS and NIHR CSP submissions and clinical set-up, ongoing management including training, monitoring reports and promotion of the trial. The CTRU will be responsible for the day to day running of the trial including trial administration, database administrative functions, data management, safety reporting and all statistical analyses.

17.0 Incident Reporting and Serious Breaches

17.1 Incident Reporting

The trial will be conducted in accordance with the principles of Good Clinical Practice in clinical trials, as applicable under UK regulations, the NHS Research Governance Framework (and Scottish Executive Health Department Research Governance Framework for Health and Social Care 2006 for studies conducted in Scotland), and through adherence to CTRU Standard Operating Procedures (SOPs).

Organisations must notify LEEDS CTRU of all deviations from the protocol or GCP immediately. LEEDS CTRU may require a report on the incident(s) and a form will be provided if the organisation does not have an appropriate document (e.g. Trust Incident Form for UK sites).

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

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

Each site must also report according to their trust incidence reporting policies.

17.2 Serious Breaches

CTRU and Sponsor have systems in place to ensure that serious breaches of GCP or the trial protocol are picked up and reported. Investigators are required to promptly notify the CTRU of a serious breach (as defined by Regulation 29A of the Medicines for Human Use (Clinical Trials) Regulations 2004 [Statutory Instrument 2004/1031], as amended by Statutory Instrument 2006/1928) that they become aware of. A "serious breach" is a breach which is likely to effect to a significant degree –

- the safety or physical or mental integrity of the participants of the trial; or
- the scientific value of the trial.

For further information, the Investigator should contact the CTRU.

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 an actual serious breach has been identified, LEEDS CTRU will inform the MHRA within 7 calendar days of becoming aware of the breach.

Sites must notify the CTRU of serious breaches (MHRA Guidance on the Notification of Serious Breaches). The CTRU will notify the sponsor of all serious breaches.

Leeds CTRU will use an organisation's history of non-compliance to make decisions on future collaborations.

18.0 Endpoints

18.1 Primary endpoints

Dose-Limiting Toxicities (Dose escalation phase), between the time of receiving the first registered dose of Carfilzomib in cycle 1 and day 1 cycle 2, in order to establish the Maximum Tolerated Dose (MTD) and recommended dose (RD) of Carfilzomib in combination with Thalidomide and Dexamethasone.

Proportion of patients treated who experience any grade 3 or 4 CTCAE toxicity throughout all treatment cycles

18.2 Secondary endpoints

- Clonal response rate within 3m, at 3m, within 6m and at 6m
- Amyloidotic organ response rate within 3m and 6m
- Time to amyloidotic organ response
- Number of deaths at 6 months
- Number of patients progression free at 6 months
- Maximum response
- Time to maximum response
- Number of patients withdrawing from treatment
- Number of patients experiencing dose delays, and compliance profile of KTD.
- Relative Dose intensity

Exploratory

Additional exploratory endpoints may be collected; any additional endpoints will be fully detailed in the statistical analysis plan.

18.3 Endpoint definitions

- DLT and MTD are defined in section 8.1.4 and 8.1.5

- The proportion of patients treated who experience any grade 3 or 4 CTCAE toxicity will be calculated as number of patients who experience any grade 3 or 4 CTCAE toxicity throughout their treatment cycle.

- Clonal response rate (based on paraprotein and FLCs) is defined as the proportion of patients who achieve at least a PR within 3 months, at 3 months, within 6 months and at 6 months after trial registration.

- Amyloidotic organ response rate is defined as the proportion of patients who achieve organ response within 3 months and within 6 months of trial registration.

- Time to Amyloidotic organ response is defined as the time from the dose allocation to first achieving organ response.

- The number of patients experiencing dose delays will be defined as the number of patients experiencing delays in treatment with any of the study treatments.

- KTD compliance: Patients will be regarded as compliant to treatment where treatment is received as per protocol until withdrawal from treatment and have no more than 1 dose omission of Carfilzomib, 5 of Thalidomide or 1 of Dexamethasone during each cycle.

- Relative Dose intensity will be calculated as the percentage ratio between the received and planned dose intensities, where dose intensity is the cumulative dose divided by the duration of treatment.

19.0 Statistical considerations

19.1 Sample size

In the dose escalation phase of this study, a minimum of 6 (3 at dose level 0 and 3 at dose level -1) and a maximum of 18 (6 at dose level 0 1 and 2) patients will recruited in a 3+3 design with cohorts of between 3 and 6 patients, in order to determine maximum tolerated dose and recommended dose.

At the recommended dose level identified, a further 20 patients will be recruited to further assess safety and toxicities at the RD.

The secondary objective of assessing activity will be primarily assessed by the clonal response rate.

19.2 General Considerations

Statistical analysis of clinical endpoint data is the responsibility of the CTRU Statistician. A full statistical analysis plan will be written before any analyses are undertaken. The analysis plan will be written in accordance with current CTRU standard operating procedures and will be finalised and agreed by the following people: the trial statistician and supervising statistician, the Chief Investigator, the CTRU Delivery and Scientific Leads and the Senior Trial Manager. Any changes to the finalised analysis plan, and reasons for changes, will be documented.

All patients that receive at least one dose of Carfilzomib and with no protocol deviations with relevant impact on safety will be included in the safety analysis set.

The per protocol set will include all patients with at least one post baseline efficacy assessment who receive at least one dose of Carfilzomib and have no protocol deviations with relevant impact on efficacy.

Determination of the MTD in the dose escalation phase of the trial will be based on those patients who have received at least one cycle KTD and will be evaluated between the time of receiving the first dose of Carfilzomib in cycle 1 and the first dose of treatment in cycle 2. The safety review committee will review each DLT and attribute the DLT to the loading dose or the registered dose; any DLT attributed to the loading dose will be excluded when determining the MTD.

KTD Patients who do not receive one complete cycle due to experiencing a DLT will be included in the analysis; patients who do not receive at least one complete cycle for reasons other than toxicity, without experiencing a DLT, and who miss a dose of Carfilzomib, more than 14 doses Thalidomide or 2 doses of Dexamethasone in the first cycle, will be replaced. Evaluability will be considered by the safety review committee on an individual basis to account for attributing DLTs and missed doses to the loading or the registered dose.

The RD cohort will include all patients who are registered to receive and receive at least one dose of Carfilzomib at the RD. This cohort will include patients from the dose escalation and dose expansion phases of the study. All patients who do not fulfil these criteria will be included in the non-RD cohort.

Statistical analysis will be descriptive for all endpoints, and will be summarised overall and by dose cohort. All safety analyses will be based upon the safety analysis set; safety data from patients not included in this analysis set will be listed separately. All efficacy analyses will be based upon the per protocol set. Patients who do meet the criteria to be included in each of analysis sets will have the reasons for emission listed. A sensitivity analysis on the efficacy endpoints may be considered if the total number of patients in each of the analysis sets differs by more than 3 patients.

19.3 Primary Endpoint Analysis

The number of patients experiencing DLTs within the first cycle of KTD will be presented, with descriptive summaries of the specific DLTs observed. Summaries will be presented for each dose level. This data will be presented for patients registered to the dose escalation phase of the study only.

Further summaries of longer-term tolerability will also be presented for patients registered to the dose escalation phase to include the maximum toxicity grade experienced within the first three cycles of treatment, overall and by cycle. Individual listings of the toxicities, grade and cycle of all toxicities experienced within the first three cycles will be presented.

The number of patients experiencing any grade 3 or 4 CTCAE toxicity within all cycles of treatment will be summarised. This will be presented overall and by dose cohort, across all cycles as well as by each cycle.

19.4 Secondary Endpoint Analysis

Safety and toxicity profiles for each cycle and cohort: data will be summarised descriptively, including the proportion of patients experiencing at least one SAE, the number of SAEs experienced per participant, and the number of SAEs experienced according to seriousness criteria, causality, and body system; Toxicity will be summarised according to CTCAE grades and will be summarised as the maximum grade toxicity experienced within each cycle, and overall.

The proportion of patients achieving at least a PR (clonal response) within 3m, at 3m, within 6m and at 6m and the proportion of patients achieving an amyloidotic organ response within 3m and 6m will be presented in tabulated form. Corresponding 90% and 95% confidence intervals will also be presented. Responses at 3 and 6 months will be broken down by response achieved, and by organ (for organ response).

Time to amyloidotic organ response and time to maximum response will be calculated using the Kaplan Meier method. Median time to amyloidotic organ response and median time to maximum response will be presented, with corresponding 95% confidence intervals.

The proportion and number of patients alive at 6 months and patients progression free at 6months will be presented with corresponding 90% and 95% confidence intervals. If the data warrants Kaplan Meier curves for progression free survival may be explored.

Each patient will be assessed for their maximum clonal response; the number and proportion of participants in each response category within 6 cycles of treatment will be presented with corresponding 95% confidence intervals. Patients who do not achieve a maximum response will be summarised as, "no maximum response".

Feasibility of delivering treatment according to protocol schedule will be summarised descriptively to include the number of patients requiring dose delays and/or reductions, the number of patients withdrawing from treatment, and reasons for dose delays / reductions and withdrawals. Time on treatment and reasons for stopping treatment will also be presented. The number of doses missed will be summarised overall and by cycle.

The following definitions will be used:
% of intended dose = 100*(dose received / planned dose)
To represent delays in cycles and reduced dose:
Dose intensity (DI) = Cumulative Dose / Duration
Relative Dose intensity (RDI) = Actual DI / Planned DI
Summaries will be produced at each cycle, for each treatment and overall.

19.5 Frequency of Analyses

During the Dose Escalation Phase, recruitment will be halted after each group of three patients have completed at least one cycle of KTD, to allow safety data to be assessed. CTRU will produce a summary of DLTs at each dose level, detailed safety listings, and recruitment figures for consideration by the Safety Review Committee.

No formal analyses are planned until after the trial is closed to recruitment and the required number of patients has been recruited. Final analysis will be carried out when the required number of patients has been recruited and all patients have been followed up for at least 6 months from registration.

20.0 Data Monitoring

20.1 Safety Review Committee

The Safety Review Committee (SRC) will review the safety and ethics of the trial by reviewing interim data after each cohort of treatment during recruitment to the Dose Escalation Cohort. The SRC will meet or communicate via teleconference at least after each dose level in the Dose Escalation Cohort has recruited at least 3 patients and they have received their first cycle of treatment, to review safety.

Safety reports will be periodically reviewed for the trial unless otherwise requested to determine patterns and trends of events, or to identify safety issues, which would not be apparent on an individual case basis. Detailed reports containing safety summaries will be prepared by the CTRU for the SRC every 3 months.

20.2 Trial Steering Committee (during the dose expansion phase only):

The Trial Steering Committee will review safety data and liaise with the SRC regarding safety issues, and periodically reviewing efficacy data in the dose expansion phase.

20.3 Data Monitoring

Data will be monitored for quality and completeness by the CTRU. Missing data will be chased until it is received, confirmed as not available or the trial is at analysis. The CTRU will reserve the right to intermittently conduct source data verification exercises on a sample of patients, which will be carried out by staff from the CTRU. Source data verification will involve direct access to participant medical records at the participating centres, and the central collection of copies of consent forms and other relevant investigation reports. A Trial Monitoring Plan will be developed and a Meeting Group Monitoring Schedule including primary endpoint and safety data will be defined and agreed by the Trial Management Group (TMG), if necessary.

20.4 Clinical Governance Issues

To ensure responsibility and accountability for the overall quality of care received by patients during the trial period, clinical governance issues pertaining to all aspects of routine management will be brought to the attention of the SRC, sponsor and, where applicable, to individual NHS Trusts.

21.0 Ethical and Regulatory Approvals

In conducting the trial, the Sponsor, LEEDS CTRU and sites shall comply with all 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
- 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 Research Governance Framework for Health and Social Care, issued by the UK Department of Health (Second Edition 2005) or the Scottish Health Department Research Governance Framework for Health and Community Care (Second Edition 2006)

21.1 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.

LEEDS CTRU will submit an application for favourable ethical opinion and will subsequently submit Annual Progress Reports to the REC, which will commence one year from the date of ethical approval for the trial.

21.2 Regulatory Approval

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.

21.3 Site Approvals

Local governance checks will be undertaken by local CLRNs associated with individual trial sites.

Evidence of approval from the Trust R&D for a trial site must be provided to LEEDS CTRU. Sites will only be activated when all necessary local approvals for the trial have been obtained.

21.4 Protocol Amendments

LEEDS CTRU will be responsible for gaining ethical and regulatory approvals, as appropriate, for amendments made to the protocol and other trial-related documents. Once approved, LEEDS CTRU 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.

21.5 Patient Confidentiality & Data Protection

Patient identifiable data, including date of birth, patient initials and NHS number will be required for the registration process and will be provided to LEEDS CTRU.

LEEDS CTRU 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 LEEDS CTRU trials are registered in accordance with the Data Protection Act 1998 with the Data Protection Officer at UCL.

The CTRU will comply with all aspects of the 1998 Data Protection Act and operationally this will include:

- consent from participants to record personal details including name, date of birth, NHS ID, hospital ID
- appropriate storage, restricted access and disposal arrangements for participant personal and clinical details
- consent from participants for access to their medical records by responsible individuals from the research staff or from regulatory authorities, where it is relevant to trial participation
- consent from participants for the data collected for the trial to be used to evaluate safety and develop new research.
- participant name will be collected on the consent form when a participant is registered into the trial, but all other data collection forms that are transferred to or from the CTRU will be coded with a trial number and will include two participant identifiers, usually the participant's initials and date of birth.
- where central monitoring of source documents by CTRU (or copies of source documents) is required (such as scans or local blood results), the participant's name must be obliterated by site before sending
- where anonymisation of documentation is required, sites are responsible for ensuring only the instructed identifiers are present before sending to CTRU

If a participant withdraws consent from further trial treatment and / or further collection of data, their data and samples will remain on file and will be included in the final trial analysis.

The trial staff at the participating site will be responsible for ensuring that any data / documentation sent to the CTRU is appropriately anonymised as per instructions given by CTRU in accordance with the trial procedures to conform with the 1998 Data Protection Act.

22.0 Sponsorship and Indemnity

22.1 Sponsor Details:

Sponsor Name:	University College London
Address:	Joint Research Office Gower Street London WC1E 6BT
Contact:	Tendai Nelson, Regulatory Advisor 0207 679 6492
Telephone:	
Fax:	020 3108 2312

22.2 Indemnity

University College London holds insurance against claims from patients for injury caused by their participation in the clinical trial. Patients 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.

Patients 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. Patients 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.

23.0 Funding

Carfilzomib is provided free of charge for the trial duration by Amgen .

24.0 Publication Policy

All publications and presentations relating to the trial will be authorised by the Trial Management Group. The TMG will form the basis of the writing committee and advise on the nature of publications. Contributing site investigators in this trial will also be acknowledged. Data from all sites will be analysed together and published as soon as possible. Participating sites may not publish trial results prior to the first publication by the TMG or without prior written consent from the TMG. The trial data is owned by UCL. However, drug companies who have provided grants towards the trial will be permitted to see the draft manuscripts and make comments at least prior to submission for publication as detailed in the trial drug supply agreement. The ISRCTN number allocated to this trial will be quoted in any publications resulting from this trial.

The trial will be registered with an authorised registry, according to ICMJE Guidelines, prior to the start of recruitment.

The success of the trial depends upon the collaboration of all patients. For this reason, credit for the main results will be given to all those who have collaborated in the trial, through authorship and contributor ship. Uniform requirements for authorship for manuscripts submitted to medical journals will guide authorship decisions. These state that authorship credit should be based only on substantial contribution to:

- conception and design, or acquisition of data, or analysis and interpretation of data
- drafting the article or revising it critically for important intellectual content
- and final approval of the version to be published
- and that all these conditions must be met (www.icmje.org).

In light of this the Chief Investigator and relevant senior CTRU staff will be named as authors in any publication. Dependent on the number of participating centres and journal restrictions, wherever possible all Principal Investigators and at least two CTRU staff will be named as authors.

Publication of emerging safety data in the form of abstracts for oral or poster presentation, or journal letters is permitted. However no formal manuscript publication is permitted until the final analysis of the trial data has been completed. All abstracts and letters must be reviewed by at least the Chief Investigator and CTRU trial statistician. The release of any data prior to the end of the trial must be approved by the Safety Review Committee. Amgen will review any resulting publications prior to submission as detailed in the contract.

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APPENDIX 1: ABBREVIATIONS

ABPI	Association of British Pharmaceutical Industry
ADL	Activities of Daily Living
AE	Adverse Event
AL	Refers to the serum free light chain fibrils that are produced in this type of Amyloidosis
ALP	Alkaline phosphatase
ALT	Alanine transaminase
AML	Acute Myeloid Leukaemia
ANC	Absolute Neutrophil Count
APTT	Activate partial thromboplastin time
AR	Adverse Reaction
ASCT	Autologous stem cell transplantation
AST	Aspartate aminotransferase
AUC	Area Under the Curve
Bcl	B-cell lymphoma
BUN	Blood urea nitrogen
CAM	Cell Adhesion Molecule
CD	Cluster of differentation
CEA	Carcinoembryonic Antigen
CI	Chief Investigator
CLRN	Comprehensive local research network
CR	Complete response
CrCl	Creatinine clearance
CRd	A chemotherapy regimen of Carfilzomib, lenalidomide, and Dexamethasone
CRF	Case Report Form
CR UK	Cancer Research UK
CT	Computerised Tomography
CTA	Clinical Trial Authorisation
CTAAC	Clinical Trials Advisory & Awards Committee
CTCAE	see NCI CTCAE
CTD	Chemotherapy regimen containing cyclophosphamide, Thalidomide & Dexamethasone
CTDa	Attenuated CTD
CTRU	Clinical Trials Research Unit
CTSA	Clinical Trial Site Agreement
CVD	Chemotherapy regimen containing Bortezomib, Cyclophosphamide & Dexamethasone
CXR	Chest X-Ray
DFS	Disease Free Survival
DH	Department of Health
DI	Dose intensity
DLT	Dose Limiting Toxicity
DOR	Duration of Response
DPA	Data Protection Act
DSUR	Development Safety Update Report
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDTA	Ethylene Diamine Tetra Acetate
eGFR	Estimated glomerular filtration rate
EudraCT	European Clinical Trials Database
FBC	Full Blood Count
FLC	Free Light Chain
G-CSF	Granulocyte Colony Stimulating Factor
GFR	Glomerular Filtration Rate
GI	Gastro-intestinal
GGT	Gamma glutamyl-transpeptidase/transferase
Hb	Haemoglobin
HIV	Human Immunodeficiency Virus
HL	Hodgkin's lymphoma

HUS	Haemolytic uraemic syndrome
IκBα	Inhibitor protein: I kappa B alpha-assocaited protein kinase
IB	Investigator's Brochure
ICH GCP	International Conference of Harmonisation-Good Clinical Practice
IDMC	Independent Data Monitoring Committee
IDMD	Intermediate dose melphalan and Dexamethasone
IL	Interleukin
ImiD	Immunomodulatory Drug
IMP	Investigational Medicinal Product
IMWG	International Myeloma Working Group
INR	International Normalised Ratio
ISRCTN	International Standard Randomised Controlled Trial Number
IUD	Intrauterine Device
IUS	Intrauterine System
IV	Intravenous
KTD	Chemotherapy regimen containing Carfilzomib, Thalidomide & Dexamethasone
LDH	Lactate Dehydrogenase
LFT	Liver Function Tests
LLN	Lower Limit of Normal
LVEF	Left ventricular ejection fraction
MDS	Myelodysplastic Syndrome
MM	Multiple Myeloma
MP	Melphalan & Prednisolone
MR	Maximum response
MRC	Medical Research Council
MTD	Maximum Tolerated Dose
REC	Research Ethics Committee
MRI	Magnetic Resonance Image
MHRA	Medicines and Healthcare products Regulatory Agency
NAC	See UK NAC
NCI	National Cancer Institute
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
nCR	Near Complete Response
NCRI	National Cancer Research Institute
NCRN	National Cancer Research Network
NHL	Non-Hodgkin's lymphoma
NICE	National Institute of Clinical Excellence
NIHR	National Institute for Health Research
NF-κB	Nuclear Factor-κB
NR	Not meeting Free Light Chain criteria for Complete Response (CR) or Partial Response (PR)
NRES	National Research Ethics Service
NT-proBNP	N-terminal prohormone of brain natriuretic peptide
NYHA	New York Heart Association
ORR	Overall response rates
OS	Overall Survival
PA	Posteroanterior
PAD	Chemotherapy regimen containing Bortexomib, Doxorubicin & Dexamethasone
PD	Progressive Disease
PFS	Progression Free Survival
PI	Principal Investigator
PO	By mouth
PR	Partial Response
PRES	Posterior reversible encephalopathy syndrome
PT	Prothrombin time
RD	Recommended Dose
RDI	Relative dose intensity
REC	Research Ethics Committee
RECIST	Response Evaluation Criteria in Solid Tumours
RHC	Regional Haematology Centre (Site)

RPLS	Reversible posterior leukoencephalopathy syndrome
R/RMM	Relapsed/refractory multiple myeloma
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SAP	Serum Amyloid Protein
SC	Subcutaneous
SCC	Stem cell collection
SD	Stable Disease
SOP	Standard operating procedure
SPC	Summary of Product Characteristics
SRC	Safety Review Committee
SSA	Site Specific Assessment
SUSAR	Suspected Unexpected Serious Adverse Reaction
TLS	Tumour lysis syndrome
TMF	Trial Master File
TMG	Trial Management Group
TRM	Treatment Related Mortality
TSC	Trial Steering Committee
TTP	Time to progression
UCL	University College London
U&E	Urea and Electrolyte
UK NAC	UK National Amyloidosis Centre (Royal Free Hospital)
ULN	Upper Limit of Normal
VAD	Chemotherapy regimen containing vincristine, doxorubicin and Dexamethasone
VGPR	Very Good Partial Response
WBC	White Blood Cells

APPENDIX 2: DEFINITION OF AMYLOIDOSIS, MYELOMA AND RELATED DISEASES

Amyloid

- Tissue biopsy showing red-green birefringence in cross polarised light when stained with Congo red by Puchtler's method

Overt Non-Amyloid manifestations of Multiple Myeloma

- Lytic bony lesions (>4 if limited to skull only)
- Hypercalcaemia, hyperviscosity or plasmacytomata

Amyloid-related organ involvement causing organ dysfunction

For details please refer to Gertz et al. Definition of organ involvement and treatment response in immunoglobulin light chain amyloidosis (AL): a consensus opinion from the 10th International Symposium on Amyloid and Amyloidosis. **Am J Hematol.** 2005 Aug;79(4):319-28.

Defining organ involvement	
Kidney	24-hour urine protein >0.5 g per day, predominantly albumin
Heart	Echo: mean left ventricular wall thickness >12 mm, no other cardiac cause or severe diastolic dysfunction in presence of NT-ProBNP >150 pMol/L and low voltage complexes on ECG without any other cause for these anormalities
Liver	Total liver span >15 cm in the absence of heart failure or alkaline phosphatase >1.5 times institutional upper limit of normal
Gastrointestinal tract	Symptomatic GI disturbance with or without direct biopsy verification with
Nerve	Peripheral: clinical; symmetric lower extremity sensorimotor peripheral neuropathy Autonomic: gastric-emptying disorder, pseudo-obstruction, voiding dysfunction not related to direct organ infiltration, postural hypotension
Soft tissue	Tongue enlargement, clinical Arthropathy Myopathy by biopsy or pseudohypertrophy Lymph node enlargement

Number of organs involved by amyloid

One to 5 of the following organ systems could be involved by amyloid;

- Renal
- Gastro-intestinal (including liver)
- Cardiac
- Nerves (peripheral and/or autonomic)
- Miscellaneous (e.g. significant soft tissue, factor X deficiency, adrenal insufficiency)

APPENDIX 3: ECOG GRADES OF PERFORMANCE STATUS AND NYHA CLASS

Grade	Summary	Description
0	Normal	Able to carry out all normal activity without restriction
1	With effort	Restricted in physically strenuous activity; ambulatory, can do light work
2	Restricted	Ambulatory and capable of all self-care but unable to carry out any work; up and about more than 50% of waking hours
3	Dependent	Capable of only limited self-care; confined to bed or chair for more than 50% of waking hours
4	Immobile	Completely disabled; cannot carry out any self-care; totally confined to bed or chair

NYHA CLASS

Class I	Patients with no limitation of activities; they suffer no symptoms from ordinary activities.
Class II	Patients with slight, mild limitation of activity; they are comfortable with rest or with mild exertion.
Class III	Patients with marked limitation of activity; they are comfortable only at rest.
Class IV	Patients who should be at complete rest, confined to bed or chair; any physical activity brings on discomfort and symptoms occur at rest.

APPENDIX 4: DEFINITIONS OF RESPONSE

(based on IMWG criteria 2006 and amyloidosis consensus criteria 2005)

Haematological Response:

CR	Negative immunofixation of serum and urine (serum alone in anuric patients) AND Normal FLC concentration and kappa/lambda FLC ratio (FLC ratio alone in renal failure) AND ≤5% plasma cells in bone marrow[a] without clonality by immunohistochemistry or immunofluorescence[a]
VGPR[b]	>90% reduction in serum paraprotein or abnormal component of FLC or dFLC over the starting value or dFLC <40mg/L
PR	≥50% decrease in aberrant FLC concentration or dFLC (or ≥50% decrease in dFLC if renal failure) or serum paraprotein but not fulfilling criteria for CR or VGPR
MR	>25% but <50% decrease in aberrant FLC or dFLC or paraprotein
NR	Not meeting FLC criteria for CR, PR or MR

Abbreviations: CR, complete response; FLC, free light chain; PR, partial response; NR, no response.

Plateau	2 consecutive FLC samples or serum paraprotein (at least 2 weeks apart) showing the aberrant (monoclonal) light chain concentration to be abnormal but stable (within 20% of each other). In the context of progressive renal impairment, the κ/λ ratio or dFLC rather than absolute FLC concentration should remain stable (i.e. within 20%).

[a] Confirmation with repeat bone marrow biopsy only if done, not mandatory. Presence/absence of clonal cells is based upon the *k*/λ ratio. An abnormal *k*/λ ratio by immunohistochemistry and/or immunofluorescence requires a minimum of 100 plasma cells for analysis. An abnormal ratio reflecting presence of an abnormal clone is *k*/λ of >4:1 or <1:2. Alternatively, the absence of clonal plasma cells can be defined based on the investigation of phenotypically aberrant PC. The sensitivity level is 10^{-3} (less than one phenotypically aberrant PC within a total of 1000 PC). Examples of aberrant phenotypes include (1) $CD38^{+dim}$ and $CD56^{+\ strong}$ and $CD19^{-}$ and $CD45^{-}$; (2) $CD38^{+dim}$ and $CD138^{+}$ and $CD56^{++}$ and $CD28^{+}$; (3) $CD138^{+}$, $CD19^{-}$ $CD56^{++}$, $CD117^{+}$.

APPENDIX 4 CONTINUED OVERLEAF.....

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Haematological Relapse:

From CR	Increase in the aberrant serum free light chain concentration to outside the normal range and by a factor of ≥2 from that at the time of CR or re-appearance of the original paraprotein
From PR or VGPR:	Increase in the aberrant free light chain concentration by a factor of ≥2 from that at the time of PR (≥50% change in ratio away from normal in patients with renal failure) or doubling of the serum paraprotein level (if starting >5g/L) or doubling and increase of serum paraprotein to >5g/L (if starting <5g/L)

Organ Response:

Heart	Interventricular septal thickness decreased by 2 mm or 10% improvement in ejection fraction or a 30% and 35 pMol/L reduction in NT-ProBNP (only applicable if there is no change or <25% improvement in renal function) or significant improvement in lateral wall TDI S wave and E/E' ratio
Kidney	50% decrease (at least 0.5 g/day) in 24-hr urinary protein loss (urine protein must be>0.5 g/day pretreatment) without fall in creatinine clearance of ≥25% from baseline
Liver	50% decrease in abnormal alkaline phosphatase value or a decrease in liver size radiographically by at least 2 cm
Nerve	Improvement in electromyogram nerve conduction velocity (rare)
Soft tissue	Definite clinical and/or radiographic improvement with associated functional improvement in affected tissue

Organ Progression:

Heart	Interventricular septal thickness increased by >2 mm compared with baseline or 20% decline in ejection fraction
Kidney	50% increase (at least 1 g/day) in 24-hr urinary protein loss to >1 g/day OR Sustained fall in creatinine clearance of ≥25% from baseline
Liver	50% increase of alkaline phosphatase from the lowest value
Nerve	Progressive neuropathy by electromyography or nerve conduction velocity
Soft tissue	Definite clinical and/or radiographic deterioration with associated functional deterioration in affected tissue

APPENDIX 5: TOXICITY CRITERIA

NCI CTCAE Toxicity Criteria (V4.03). For full list see:
http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf

Toxicity	1	2	3	4
CONSTIPATION	Occasional or intermittent symptoms; occasional use of stool softeners, laxatives, dietary modification, or enema	Persistent symptoms with regular use of laxatives or enemas; limiting instrumental ADL	Obstipation with manual evacuation indicated; limiting self care ADL	Life-threatening consequences; urgent intervention indicated
DIARRHOEA (patients without colostomy)	Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline	Increase of 4 - 6 stools per day over baseline; moderate increase in ostomy output compared to baseline	Increase of ≥7 stools per day over baseline; incontinence; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self care ADL	Life-threatening consequences; urgent intervention indicated
FATIGUE	Fatigue relieved by rest	Fatigue not relieved by rest; limiting instrumental ADL	Fatigue not relieved by rest, limiting self care ADL	-
HYPOTENSION	Asymptomatic, intervention not indicated	Non-urgent medical intervention indicated	Medical intervention or hospitalization indicated	Life-threatening and urgent intervention indicated
INFECTION WITH NORMAL ANC	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting ageappropriate instrumental ADL	Severe or medically significant but not immediately lifethreatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL	Life-threatening consequences; urgent intervention indicated
LETHARGY	Mild symptoms; reduced alertness and awareness	Moderate symptoms; limiting instrumental ADL	-	-
MUCOSITIS:				
ANAL MUCOSITIS	Asymptomatic or mild symptoms; intervention not indicated	Symptomatic; medical intervention indicated; limiting instrumental ADL	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated
ORAL MUCOSITIS	Asymptomatic or mild symptoms; intervention not indicated	Moderate pain; not interfering with oral intake; modified diet indicated	Severe pain; interfering with oral intake	Life-threatening consequences; urgent intervention indicated
SMALL INTESTINAL MUCOSITIS	Asymptomatic or mild symptoms; intervention not indicated	Moderate pain; not interfering with oral intake; modified diet indicated	Severe pain; interfering with oral intake; tube feeding, TPN or hospitalization indicated; limiting self care ADL	Life-threatening consequences; urgent intervention indicated
LARYNGEAL MUCOSITIS	Endoscopic findings only; mild discomfort with normal intake	Moderate discomfort; altered oral intake	Severe pain; severely altered eating/swallowing; medical intervention indicated	Life-threatening airway compromise; urgent intervention indicated (e.g., tracheotomy or intubation)
PHARYNGEAL MUCOSTIS	Endoscopic findings only; minimal symptoms with normal oral intake; mild pain but analgesics not indicated	Moderate pain and analgesics indicated; altered oral intake; limiting instrumental ADL	Severe pain; unable to adequately aliment or hydrate orally; limiting self care ADL	Life-threatening consequences; urgent intervention indicated
TRACHEAL MUCOSITIS	Endoscopic findings only; minimal hemoptysis, pain, or respiratory symptoms	Moderate symptoms; medical intervention indicated; limiting instrumental ADL	Severe pain; hemorrhage or respiratory symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated
PERIPHERAL MOTOR NEUROPATHY	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL; assistive device indicated	Life-threatening consequences; urgent intervention indicated
PERIPHERAL SENSORY NEUROPATHY	Asymptomatic; loss of deep tendon reflexes or paresthesia	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated
RASH MACULO-PAPULAR	Macules/papules covering <10% BSA with or without symptoms (e.g., pruritus, burning, tightness)	Macules/papules covering 10 - 30% BSA with or without symptoms (e.g., pruritus, burning, tightness); limiting instrumental ADL	Macules/papules covering >30% BSA with or without associated symptoms; limiting self care ADL	
NEUTROPHILS COUNT DECREASED	<LLN - 1500/mm3; <LLN - 1.5 x 10e9 /L	<1500 - 1000/mm3; <1.5 - 1.0 x 10e9 /L	<1000 - 500/mm3; <1.0 - 0.5 x 10e9 /L	<500/mm3; <0.5 x 10e9 /L
SOMNOLENCE	Mild but more than usual drowsiness or sleepiness	Moderate sedation; limiting instrumental ADL	Obtundation or stupor	Life-threatening consequences; urgent intervention indicated
THROMBOEMBOLIC EVENT	Venous thrombosis (e.g., superficial thrombosis)	Venous thrombosis (e.g., uncomplicated deep vein thrombosis), medical intervention indicated	Thrombosis (e.g., uncomplicated pulmonary embolism [venous], nonembolic cardiac mural [arterial] thrombus), medical intervention indicated	Life-threatening (e.g., pulmonary embolism, cerebrovascular event, arterial insufficiency); hemodynamic or neurologic instability; urgent intervention indicated
RESTRICTIVE CARDIOMYOPATHY	-	-	Symptomatic heart failure or other cardiac symptoms, responsive to intervention	Refractory heart failure or other poorly controlled cardiac symptoms
HAEMORRHAGE (GI)	Mild; intervention not indicated	Moderate symptoms; medical intervention or minor cauterization indicated	Transfusion, radiologic, endoscopic, or elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated
HAEMORRHAGE (OTHER)	Mild; intervention not indicated	Symptomatic; medical intervention indicated	Transfusion indicated	Life-threatening consequences; urgent intervention indicated
PAIN	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-

APPENDIX 6: DETAILS OF INVESTIGATIONS AND THEIR TIMINGS

PLEASE ALSO SEE PROTOCOL SECTION 11

PLEASE NOTE – prior to starting each treatment cycle at RHC a 5ml serum sample must be collected and sent to UK NAC (see protocol section 1 for contacts).

Clinical Assessments to be performed at the following timepoints:

- Baseline at UK NAC
- Re-confirmation of Eligibility at RHC
- Prior to each cycle at RHC
- UK NAC visit following 3rd cycle of study treatment
- UK NAC visit 7.5 months after start of treatment or 1 month after the end of study treatment if 6 cycles given.

- Medical History at baseline
- Weight
- 5 minute standing blood pressure
- Physical examination
- Lying blood pressure
- ECOG Performance Status
- NYHA heart failure class

Haematology to be performed at the following timepoints:

- Baseline at UK NAC
- Re-confirmation of Eligibility at RHC
- Prior to each cycle at RHC and at day 8 and 15
- UK NAC visit following 3rd cycle of study treatment
- UK NAC visit 7.5 months after start of treatment or 1 month after the end of study treatment if 6 cycles given.

- Haemoglobin
- Platelets
- APTT
- White blood count (including differential)
- PT
- Factor X (if indicated)

Biochemistry to be performed at the following timepoints:

- Baseline at UK NAC
- Re-confirmation of Eligibility at RHC
- Prior to each cycle at RHC
- UK NAC visit following 3rd cycle of study treatment
- UK NAC visit 7.5 months after start of treatment or 1 month after the end of study treatment if 6 cycles given.

- Urea
- eGFR (to be calculated as per local biochemistry laboratory standard protocol)
- Phosphate
- ALP
- AST
- Bilirubin
- Potassium
- Creatinine (to be checked at day 8 & day 15 of each cycle)
- Calcium
- CRP
- GGT
- ALT
- Albumin
- Sodium

APPENDIX 6 CONTINUED OVERLEAF.....

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Other investigations to be performed at UK NAC at the following timepoints:

- PLEASE NOTE – prior to starting each cycle at RHC a 5ml serum sample must be collected and sent to UK NAC

- * Baseline at UK NAC, at UK NAC visit following 3rd cycle of study treatment, at UK NAC visit 6 months after registration or 1 month after the end of study treatment if 6 cycles given and on posted serum samples and on each posted sample sent by RHC as defined in protocol
- ** Baseline visit to UK NAC and at UK NAC visit 6 months after registration or 1 month after the end of study treatment if 6 cycles given. Bone marrow tests will be done at these time points only if clinically indicated.
- *** Baseline at UK NAC, at UK NAC visit following 3rd cycle of study treatment, at UK NAC visit 6 months after start of treatment or 1 month after the end of study treatment if 6 cycles given. At RHC ECHO will be done at end of cycle 2 only. Echocardiogram to be repeated at any cycle if clinically indicated for unexpected worsening of cardiac function.
- **** Baseline at UK NAC, 1st cycle of treatment at day 1, 8 & 15 at RHC, day 1 of every subsequent cycle at RHC, at UK NAC visit following 3rd cycle of study treatment, at RHC at end of treatment, visit, at UK NAC visit 6 months after registration or or 1 month after the end of study treatment if 6 cycles given.

- Serum Free Light Chains*
- NT-ProBNP****
- Echocardiography ***
- Bone marrow aspirate & trephine plasmacytosis**
- 24 hour urinary light chain type and quantification**
- Serum monoclonal protein*

APPENDIX 7: AMYLOID STAGE

The amyloid stage definition will be based on the report published by Dispenzieri et al 2004. The stages will be classified as follows:

Stage I: Both NT-proBNP and cardiac troponin-T normal defined as NT-proBNP ≤36 pMol/L and cardiac troponin T ≤0.03 ng/ml (or cardiac high sensitivity troponin T ≤ 0.05 μg/L)

Stage II: Either one of NT-proBNP or cardiac troponin T abnormal defined as: NT-proBNP>36 pMol/L ***or*** cardiac troponin T >0.03 ng/ml (or cardiac high sensitivity troponin T >0.05 μg/L)

Stage III: Both NT-proBNP **and** cardiac troponin T abnormal defined as: NT-proBNP >36 pMol/L ***and*** cardiac troponin T >0.03 ng/ml (or cardiac high sensitivity troponin T >0.05 μg/L)

APPENDIX 8: POSSIBLE RISKS AND DISCOMFORTS WITH CARFILZOMIB

Carfilzomib Risks

Carfilzomib (KyprolisTM) is approved by the U.S. Food and Drug Administration (FDA) to be used only in certain U.S. patients with relapsed and refractory multiple myeloma that have tried and failed other therapies. It has not been approved to be used for any other disease or condition. In this study, Carfilzomib is an investigational study drug because it is not approved for use in all patients in the United States, and it is not approved by some regulatory authorities (the agencies that are responsible for approving the use of a medicine in a country such as the European Medicines Agency and Health Canada). You will be told about the known risks, which are the side effects reported previously by others who took Carfilzomib. However, your doctors do not know all the side effects that you may experience. As with all investigational drugs, all risks may not have been identified at this time. There may be serious unexpected or unforeseen risks while taking Carfilzomib, including death. It is known that nearly everyone who takes Carfilzomib will have some side effects while on the drug. Many of these side effects may be mild but some side effects can be serious and even fatal.

Everyone taking part in the study will be watched carefully for any side effects. You should talk to your study doctor about any side effects that you have while taking part in the study.

If side effects occur, your health care team may give you medicines to help lessen side effects. Your doctor may have you stop taking Carfilzomib or take a lower dose of Carfilzomib because of the side effects, or the side effects may go away on their own even if you continue to take Carfilzomib.

Information provided below is based on data from approximately 800 patients who took Carfilzomib while taking part in clinical studies over the past 6 years. During this time period the following side effects have been observed and may be due to Carfilzomib.

Likely Side Effects: those occurring in more than 20% of patients (or more than 20 out of 100 persons) who received Carfilzomib:

- Fatigue (tiredness)
- Fever
- Headache
- Cough
- Shortness of breath (at rest or with exertion) which in rare cases may be life-threatening or resulting in death
- Nausea
- Vomiting
- Diarrhea
- Constipation
- Decreased red blood cell count which may lead to feeling tired
- Decreased platelet counts which may lead to increase bleeding or bruising
- Decreased white blood cell count which may decrease your ability to fight infection
- Upper respiratory tract infection
- Mild decreases in kidney function which are generally reversible
- Swelling of the arms or legs
- Back pain

Less Likely Side Effects: those occurring in 5-20% of patients (or 5 to 20 out of 100 persons) who received Carfilzomib:

- Flu-like symptoms such as fever, chills, or shaking that may occur at any time but are more likely to occur on the day of or the day after Carfilzomib infusion.
- Loss of or decreased appetite which may lead to weight loss
- Insomnia (difficulty sleeping)
- Anxiety
- Dizziness
- Confusion or changes in mental state
- Blurred or double vision
- Numbness, tingling, or decreased sensation in hands and/or feet
- Blood chemistry and electrolyte alterations

APPENDIX 8 CONTINUED OVERLEAF.....

- Rash and/or itching, or dry skin
- Pain, burning, or irritation at the infusion site
- Generalized pain
- Pain in the bones or joint pain
- Muscle spasm, pain, or weakness
- General weakness, or lack of energy or strength
- Abdominal pain, discomfort, or swelling
- Indigestion (upset stomach)
- Inflammation of the liver (mild, reversible changes in liver function tests)
- Increase or decrease in blood pressure
- Pneumonia or other lower respiratory tract infections
- Urinary tract infection
- Nosebleeds
- Dehydration
- Sore throat, inflammation of the nose and throat, runny nose or nasal congestion

Rare and/or Potentially Serious Side Effects: those occurring in less than 5% of patients (or in less than 5 out of 100 persons) who received Carfilzomib; side effects can be serious enough to be life-threatening or even fatal in rare cases:

- Infusion reactions (which can occur during or shortly after Carfilzomib infusion) including flushing or feeling hot, fever, shakes, nausea, vomiting, weakness, shortness of breath, swelling of the face, pain in the muscles or joints, tightness or pain in the chest, and low blood pressure
- Allergic reaction including total body rash, hives, and difficulty breathing
- Inflammation of the pancreas (pancreatitis)
- Kidney failure which can lead to dialysis
- Worsening liver function up to and including liver failure
- Decreased or worsening of heart function including chest pain, abnormal heart rhythm, heart attack, and heart failure
- Increase in the blood pressure in the arteries of the lungs
- Blood clots in the leg or lungs
- Infections in the blood
- Tumor lysis syndrome (TLS)
- Tumor lysis syndrome is caused by rapid killing of tumor cells during treatment. When the tumor cells die, they release their contents into the bloodstream. If cell killing is very rapid, this can affect blood chemistries and the kidneys. In severe cases, this can lead to shutdown of kidney function requiring dialysis.
- Myelodysplastic syndromes (MDS)/ Acute Myeloid Leukemia (AML)
- Myelodysplastic syndromes refers to disorders that develops when the cells in the bone marrow (the soft inner part of the bones, where new blood cells are made) do not work properly and have problems making new blood cells. A person with MDS may experience no symptoms or may experience fatigue, infection, easy bruising or bleeding. MDS can turn into a cancer of bone marrow cells called acute myeloid leukemia (AML).
- Posterior reversible encephalopathy syndrome (PRES)
- Posterior reversible encephalopathy syndrome (PRES) is a rare condition that causes swelling of the brain and affects how it functions. A person with PRES may experience headaches, confusion, loss or decreased level of consciousness, blurred vision or blindness, seizures, and possibly death. If caught early and treated, PRES may be reversed.

You should seek medical care immediately if you develop any of the following symptoms: severe shortness of breath, chest pain, fevers, chills, shaking with fever, vomiting, muscle weakness or cramping, seizures, confusion, severe headaches, fainting, blurred vision or blindness, and/or significantly decreased urine output.
Carfilzomib may impair ability to operate a car, other motorized vehicle, or machinery because of tiredness, dizziness, changes in blood pressure, or fainting.
Hydration Risks (Prevention of TLS)

There may be risks associated with over hydrating (having too much fluid in your body) so it is important to follow your doctor's instructions regarding how much water or other fluids you should drink. Over hydration may negatively affect the heart, lungs, and kidneys.