Phase I/II study to determine the maximum tolerated dose and activity of the combination of romidepsin and carfilzomib in relapsed or refractory peripheral T-cell lymphoma

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Chief Investigator: Dr Graham Collins
Sponsor: University of Birmingham
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SIGNATURE PAGE

RomiCar Trial Protocol V3.0_04-Dec-2015

This protocol has been approved by:

<table>
<thead>
<tr>
<th>Name:</th>
<th>Dr Graham Collins</th>
<th>Trial Role:</th>
<th>Chief Investigator</th>
</tr>
</thead>
</table>

Signature: [Signature]

Date: 08/Dec/2015

This protocol describes the RomiCar trial and provides information about procedures for patients taking part in the RomiCar trial. The protocol should not be used as a guide for treatment of patients not taking part in the RomiCar trial.
AMENDMENTS

The following amendments and/or administrative changes have been made to this protocol since the implementation of the first approved version:

<table>
<thead>
<tr>
<th>Amendment number</th>
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<td>1</td>
<td>03-Feb-2015</td>
<td>2.0</td>
<td>Substantial</td>
<td>Statistical change – correction of typological error of sample size from 57 to 58</td>
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<td>Addition of hydration to IMP administration</td>
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<td>Change to procedure – allowing patients in phase I to receive MTD once defined</td>
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<td>Clarification of ‘Treatment Details’ section</td>
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<td>Clarification of adverse event reporting</td>
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<td>Change to procedure – removal of the requirement to stop treatment following a DLT</td>
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<td>Addition of pulmonary toxicities as per IB update.</td>
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<td>Addition of sub study information; Circulating DNA and 100,000 Genomes Project.</td>
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<td>Change to inclusion and exclusion criteria</td>
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<td>Addition of optional MUGA</td>
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TRIAL SYNOPSIS

Title
Phase I/II study to determine the maximum tolerated dose and activity of the combination of romidepsin and carfilzomib in relapsed or refractory peripheral T-cell lymphoma.

Trial Design
This is a prospective, single arm, multicentre phase I/II clinical trial utilising the following design in each phase:
Phase I: Continual Reassessment Method (CRM) to determine the Maximum Tolerated Dose (MTD) of the combination of romidepsin and carfilzomib.
Phase II: A’Hern’s single stage design to assess the activity of the combination of romidepsin and carfilzomib

Objectives
- Determine the MTD of the combination of romidepsin and carfilzomib based on a CRM with target Dose Limiting Toxicity (DLT) set at 25%
- Assess the activity of the combination at the MTD in terms of overall response
- An exploratory objective is to determine whether the expression of the protein HR23B can be used as a predictive biomarker of response to this combination

Outcome Measures

Primary Outcome Measures

Phase I
- MTD of the combination of romidepsin and carfilzomib as determined by the CRM with a predefined target Dose Limiting Toxicity (DLT) probability of 25%.

Phase II
- Best overall response rate (PR + CR) during the first 8 cycles of treatment at the MTD using International response criteria [1]

Secondary Outcome Measures

Phase I
- Toxicity of the combination of romidepsin and carfilzomib using Common Terminology Criteria for Adverse Events (CTCAE) v4
- Best overall response during the first 8 cycles of treatment at the MTD
- Maximum % change in the radiological sum of the product of the diameters from baseline (see Appendix 1 for selection of suitable target and non-target lesions)
- Duration of response from time of first documented response until relapse or progression

Phase II
- Best overall response rate post 8 cycles of treatment until the end of the trial, assessed using International response criteria [1]
- Toxicity of the combination of romidepsin and carfilzomib using CTCAE v4
- Maximum % change in the radiological sum of the product of the diameters from baseline
- Duration of response from time of first documented response until relapse or progression
- Progression free survival
- Overall survival

Patient Population
This trial will recruit patients with relapsed or refractory peripheral T-cell lymphoma.

Sample Size
The phase I part will recruit up to 27 patients, plus the possibility of an additional 3 patients at the MTD.
A further recruitment of up to 28 patients will be required for the phase II component (including at least 6 patients treated at the MTD from the phase I).
Therefore, a maximum of 58 patients are required for both phase I and II.

Main Inclusion and Exclusion Criteria

Inclusion criteria
- Age ≥ 16 years of age
- Life expectancy > 12 weeks
- ECOG performance status ≤ 2 (Appendix 5)
- Relapsed or refractory* peripheral T-cell lymphoma including the following histologies: peripheral T-cell lymphoma not otherwise specified, angioimmunoblastic T-cell lymphoma,
anaplastic large cell lymphoma, enteropathy associated T-cell lymphoma, extranodal NK/T-cell lymphoma, transformed mycosis fungoides, hepatosplenic T-cell lymphoma

- Failed at least 1 prior therapy (but no upper limit of prior regimens)
- Patients MAY have had a prior allogeneic stem cell transplant but must not require systemic immunosuppression for graft-versus-host disease (local treatments are permitted)
- Adequate haematopoietic reserve (Hb ≥ 9g/dl, neutrophils ≥ 1.0x10^9/l and platelets ≥ 100x10^9/l or ≥ 75x10^9/l if marrow involvement documented)
- Adequate liver function (bilirubin ≤ 1.5 x upper limit of normal (ULN) (unless due to Gilbert's syndrome), AST / ALT ≤ 2x ULN)
- Adequate renal function (creatinine clearance ≥ 20ml/min as assessed by Cockcroft and Gault calculation)
- Serum potassium ≥ 3.8 mmol/l, calcium ≥ 2.2 mmol/l and magnesium ≥ 0.85 mmol/l prior to trial entry (supplements permitted – see Appendix 7)
- CT measurable disease with at least 1 lesion having short axis > 1.5cm or splenomegaly > 14cm in cranio-caudal length attributable to relapsed lymphoma
- Ability to give informed consent

* For all relapsed patients, relapse must be confirmed by tissue biopsy (or bone marrow trephine if no other tissue available). For refractory patients, a biopsy must have been obtained within the last 6 months and preferably to confirm refractory disease.

**Exclusion Criteria**

- Persistent treatment related toxicities of CTCAE v4.0 grade ≥ 2
- Previous treatment with histone deactylase inhibitor or proteasome inhibitor
- Need for any other concurrent anti-cancer drug (apart from corticosteroids at a dose equivalent to prednisolone ≤ 7.5mg daily). A steroid prephase may be used but should be stopped by the first day of cycle 1.
- Concurrent medical illness deemed by the investigator as uncontrolled and/or clinically significant
- Previous systemic malignancy within the last 3 years unless treated with curative intent with no sign of recurrence. Other exceptions include non-melanotic skin cancer or carcinoma in-situ of the uterine cervix
- Co-existing active infection requiring parenteral antibiotics
- Patients unable to swallow oral medication
- Active infection with HIV, hepatitis B or hepatitis C
- Radiotherapy* (except for palliative reasons), endocrine therapy, immunotherapy or use of other investigational agents within 28 days prior to trial entry (or a longer period depending on the defined characteristics of the agents used, please contact the trials office for confirmation).
  *Limited field radiotherapy to an isolated lesion in bone or soft tissue must be completed 2 weeks prior to trial entry
- Major surgery within 4 weeks of trial entry
- Patients with proven CNS involvement
- QTc interval of ≥ 480ms or patients taking medications that significantly prolong the QT interval (Appendix 6)
- Clinically significant cardiac disease ≥ NYHA Class III (see Appendix 8), symptomatic ischaemia, conduction abnormalities uncontrolled by conventional intervention or myocardial infarction within 6 months of trial entry
- Pregnant and lactating patients (patients of childbearing potential must have a negative pregnancy test prior to study entry and within 7 days prior to the start of treatment. Postmenopausal females (> 45 years old and without menstruation for > 1 year) and surgically sterilised females are exempt from a pregnancy test)
- Patients and partners of childbearing potential not willing to use effective contraception during and for 3 months after therapy
- Concurrent Pulmonary Hypertension
- Left Ventricular Ejection Fraction (LVEF) of≤40%

**Trial Duration**

Patients will be recruited over 36 months from the 13 Trials Acceleration Programme (TAP) centres with the potential to expand to further non-TAP centres.
Following registration, patients will receive a minimum of 8 cycles (each of 28 days duration) of the combination of romidepsin and carfilzomib. At the end of 8 cycles, cycles of either the combination or romidepsin alone (at the investigators discretion) will be delivered until disease progression, unacceptable toxicity or patient choice. The patient will have an end of treatment visit 30 days after the last day of treatment (+/- 5 days).

Patients will continue to be followed up for progression and survival until the end of trial or a minimum of 12 months.

**Trials Office Contact Details**

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Trial Schema

- **Screening**
  - Bone marrow biopsy within 6 weeks of trial entry
  - Diagnostic tissue biopsy*
    - *performed at relapse for relapsed patients. Refractory disease should be confirmed via biopsy within 6 months of trial entry.

- **Registration**

- **8 cycles (of 28 days) of romidepsin in combination with carfilzomib at allocated dose level**
  - Perform ECG within an hour before and an hour after romidepsin treatment on days 1, 8 and 15 of cycles 1 and 2 in phase I.
  - Perform ECG within an hour before on day 1 of each subsequent cycle and phase II.

- **End of treatment visit once patient discontinues due to Progressive Disease (PD), unacceptable toxicity or patient choice**
  - (visit 30 days after last day of treatment)

- **Continue cycles of romidepsin with/without carfilzomib until PD, unacceptable toxicity or patient choice**

- **Where no PD continue follow-up every 3 months until PD or 1 year**

- **Contrast enhanced CT scan of neck, chest, abdomen and pelvis within 6 weeks of trial entry**

- **End of treatment visit once patient discontinues due to Progressive Disease (PD), unacceptable toxicity or patient choice**
  - (visit 30 days after last day of treatment)

- **Continue cycles of romidepsin with/without carfilzomib until PD, unacceptable toxicity or patient choice**

- **Contrast enhanced CT scan of neck, chest, abdomen and pelvis at suspicion of PD or 1 year following end of treatment**
### Schedule of Events

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<th>Screening (within 6 weeks)</th>
<th>Cycles 1-8 (28 day cycles)</th>
<th>Continuation period&lt;sup&gt;5&lt;/sup&gt;</th>
<th>End of treatment visit</th>
<th>Follow up where no disease progression&lt;sup&gt;6&lt;/sup&gt;</th>
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<td>Concomitant medications</td>
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1. Must be within 7 days of start of treatment
2. To be done at baseline and to be repeated only for CR confirmation.
3. CT performed every 2 cycles during the first 8 cycles. Following 8 cycles, CT performed every 4 cycles or if PD suspected
4. Anytime from day 21, if after 4 cycles, or if PD suspected
5. After 8 cycles, cycles will be delivered until PD, unacceptable toxicity or patient choice. Addition/frequency of carfilzomib to monthly romidepsin is at investigator discretion and patient choice
6. Until PD or end of study
7. Re-calculate dose if weight change is >10%
8. An ECG to be performed within 1 hour before and after administration of romidepsin on day 1, 8 and 15 of cycles 1 & 2 (phase I only). In subsequent cycles and phase II, perform on day 1 only before administration unless patient is at risk of cardiac arrhythmia (perform on day 1, 8 and 15 prior to romidepsin infusion).
9. At suspicion of PD or 1 year
10. Preferred (but optional) at PD
11. To be taken in order for results to be available prior to treatment administration. Bloods may be taken up to 2 days before treatment administration to allow for timely results.
12. Sample collection for this sub study at screening, cycle 3, cycle 6 and cycle 10 (or at equivalent time point if patient is off treatment).
13. Blood sample(s) to be taken for study explicitly with patient consent via 100000 Genomes study specific consent form if this study is approved locally.
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1. BACKGROUND AND RATIONALE

1.1 Background

Peripheral T-cell lymphoma (PTCL) is an uncommon form of non-Hodgkin Lymphoma (NHL), accounting for 10% of NHL cases i.e. approximately 1200 new cases per year in the UK [2]. The term PTCL encompasses a heterogeneous group of conditions, all derived from mature post-thymic T-cells. The most common subtypes are PTCL not otherwise specified (PTCL-NOS) and angioimmunoblastic T-cell lymphoma (AITL) which account for 26% and 19% respectively as reported by the International T-cell Lymphoma Project group. Before the routine use of immunohistochemistry, T and B-cell high grade NHLs were treated in an identical way with combination chemotherapy, often in the form of cyclophosphamide, doxorubicin, vincristine and prednisolone (CHOP). Although B-cell lymphoma outcomes were generally good (especially with the addition of rituximab), patients with T-cell lymphoma fared much less well with typical 3 year progression free survival rates of 20-40% [3-5]. In younger patients without significant comorbidities, many centres perform an autologous stem cell transplant in first or subsequent remission. Although no randomised studies have been performed, prospective studies suggest a long term progression free survival rate of approximately 50% using this approach [6, 7]. As many patients aren’t suitable for high dose therapy, approximately 700-800 patients per year in the UK relapse with PTCL and their prognosis is extremely poor with a median survival of 6-18 months [8, 9].

Recently, a number of novel agents have been tested in the setting of relapsed PTCL. The agent with most impressive activity is brentuximab vedotin, an antibody drug conjugate whereby an anti-CD30 monoclonal mediates cellular entry of the potent tubulin toxin monomethyl auristatin E. In relapsed / refractory CD30 positive anaplastic large cell lymphoma (ALCL), an Overall Response Rate (ORR) of 86% was observed with 57% Complete Remission (CR) rate [10]. However this agent is only expected to work in CD30 positive disease, which represents the majority of cases of ALCL but the minority of other subtypes. Other new agents with proven activity include the anti-folate agent pralatrexate [8], the anti-CD52 monoclonal antibody alemtuzumab [11], the alkylating agent bendamustine [12] and the IL2 – diphtheria toxin fusion protein denileukin diftitox [13]. Overall Response Rates (ORR) as single agents range between 29-50% and some of the agents are being combined with CHOP first line.

Romidepsin is a histone deacetylase (HDAC) inhibitor, which has been approved by the US Food and Drugs Administration (FDA) for use in relapsed PTCL and cutaneous T-cell lymphoma (CTCL). This was based on phase II studies showing response rates of 25-38% as a single agent, with an acceptable toxicity profile [9, 14]. Of particular note in the Coiffier study, 89% of patients achieving a complete remission (CR) / complete remission undetermined (CRu) had not progressed after a median follow up of 13.4 months suggesting that the best responses were durable. On the whole the drug was well tolerated with the main toxicities of grade 3 or more being thrombocytopenia, leucopenia, infection and fatigue. During pre-clinical animal and subsequent phase I studies, romidepsin was observed to cause electrocardiogram (ECG) changes. This led to intensive cardiac monitoring in a phase II efficacy study [15]. Over 2000 ECGs were evaluated, with a roughly even division between pre-treatment ECGs, 1 hour post and 24 hour post infusion. 159 evaluations of left ventricular function were also performed, with most patients having completed at least 2 cycles of treatment. Romidepsin was observed to result in ST-segment depression and T-wave flattening in > 50% of post-treatment ECGs but these were not associated with troponin rises, or impairment of LV function. Post-treatment ECGs were also noted to show an average QT interval prolongation (heart-rate corrected) of 14.4ms compared with baseline. However these changes were transient and no patient had treatment-related sustained or symptomatic arrhythmia.

Proteasome inhibition is also a relatively novel strategy in anti-cancer therapeutics. Bortezomib is the most widely used proteasome inhibitor with established activity in myeloma and mantle cell lymphoma [16]. A phase II study by Zinzani et al also demonstrated activity in CTCL with an impressive response rate of 67% [17]. 2 patients in this study had PCTL with 1 of these showing a response. Newer proteasome inhibitors include the agent carfilzomib which, in contrast to bortezomib is an irreversible inhibitor of the proteasome and which, unlike Bortezomib does not appear to cause clinically significant peripheral neuropathy [18].
In vitro and in vivo pre-clinical studies demonstrate significant synergy when HDAC inhibitors and proteasome inhibitors are combined, in a number of cancer types including myeloma, mantle cell lymphoma, Hodgkin lymphoma, diffuse large B-cell lymphoma and renal cell carcinoma [19-23]. This makes biological sense as recent work has shown that HDAC inhibitors partly work through up-regulation of the protein HR23B which shuttles ubiquitinated proteins to the proteasome. Up-regulation appears to inhibit proteasome function, presumably through a saturation mechanism [24]. One way therefore to improve outcome in relapsed PTCL is to combine novel agents which have previously demonstrated single agent activity but show synergy when combined. Another way to improve treatments is to use predictive biomarkers to target potentially toxic treatments to those patients most likely to respond.

The above mentioned protein HR23B was shown in a global loss of function screen, to be necessary for HDAC inhibitor action [24]. Subsequent studies demonstrated a correlation between high HR23B expression and response to HDAC inhibitor therapy in CTCL [25]. A more recent study has confirmed a similar association in hepatocellular carcinoma [26]. Unpublished data also suggests HR23B maybe be predictive of proteasome inhibitor action in vitro. It may therefore be hypothesised to be more valuable as a predictive biomarker in combination therapy than for single agents. Validation of such potential biomarkers is necessary in order to use as part of routine treatment decision making.

1.2 Trial Rationale

1.2.1 Justification for patient population

The outcome for patients with relapsed / refractory PTCL is extremely poor, with a median survival of just 6-18 months and very few patients cured of their disease. Therefore although these patients are uncommon, there is a significant unmet need to develop rational drug combinations with validated predictive biomarkers.

1.2.2 Justification for design

The phase I component of the study will determine the MTD via a Continual Reassessment Method (CRM). A CRM offers several advantages over a standard 3+3 design, including more accurate determination of the MTD, ability to expose fewer patients to potentially toxic doses and allocating more patients to the MTD. The MTD cohort (i.e. patients who have received the MTD of the combination) will be expanded into the Phase II component.

Relapsed PTCL is uncommon, and patients with this condition are sometimes not well enough to enter a study. Therefore, it is not thought feasible to perform a randomised phase II study. A single arm, single stage, A'hern design utilised in phase II will generate robust evidence of activity for the regimen to be tested in an upfront trial. The recent validation of HR23B as a potential biomarker for response in CTCL and hepatocellular carcinoma makes it an obvious choice for evaluation as a predictive biomarker for HDAC / proteasome inhibitor therapy in PTCL.

1.2.3 Choice of treatment

With numerous novel agents showing some activity in this condition it is imperative that rational combinations are trialled in an effort to maximise efficacy. The combination of HDAC inhibitor (romidepsin) and proteasome inhibitor (carfilzomib) therapy is rational, based on extensive preclinical data showing synergy in a number of different cell lines. Combinations of these agents have also been tested in patients with other diseases and encouraging responses have been seen [27]. Further trials are on-going.

1.2.4 Rationale for Doses

A dose finding study by Harrison et al [27] defined the MTD of romidepsin in a combination of romidepsin and bortezomib, as 10mg/m² on days 1, 8 and 15 of a 28 day cycle. Potential to increase this dose is justified in this study as the usual single agent dose in relapsed / refractory PTCL is 14mg/m².
In the first phase I study of carfilzomib, O’Connor et al [28] established an MTD of 15mg/m² although the drug was administered on 5 consecutive days with 9 days rest. A subsequent phase I trial assessed carfilzomib given on days 1, 2, 8, 9, 15 and 16 of a 28d cycle. An MTD was not reached although the maximum dose tried was 27mg/m² [29]. A recently presented phase I study of single agent carfilzomib in relapsed / refractory myeloma reported an MTD of 56mg/m². Higher doses were achieved by maintaining 20mg/m² dosing for the first few doses, increasing the infusion time to 30 minutes and using a premedication dose of dexamethasone of 4mg (for ≤ 45mg/m² and 8mg for > 45mg/m² [30]). A phase I study of carfilzomib as a single agent in lymphoma has found an MTD of 70mg/m² although the 56mg/m² dose was better tolerated. In the study by O’Connor et al [28], a dose of ≥11mg/m² was associated with > 75% inhibition of the 20S chymotrypsin-like activity of the proteasome in whole blood and peripheral blood mononuclear cells after the first dose.

2. AIMS, OBJECTIVES AND OUTCOME MEASURES

2.1 Aims and Objectives

- Determine the MTD of the combination of romidepsin and carfilzomib based on a CRM with target Dose Limiting Toxicity (DLT) set at 25%
- Assess the activity of the combination at the MTD in terms of overall response
- An exploratory objective is to determine whether the expression of the protein HR23B can be used as a predictive biomarker of response to this combination

2.2 Outcome Measures

Primary Outcome Measures
Phase I
- MTD of the combination of romidepsin and carfilzomib as determined by the CRM with a predefined target Dose Limiting Toxicity (DLT) probability of 25%.

Phase II
- Best overall response rate (PR + CR) during the first 8 cycles of treatment at the MTD using International response criteria [1]

Secondary Outcome Measures
Phase I
- Toxicity of the combination of romidepsin and carfilzomib using CTCAE v4
- Best overall response during the first 8 cycles of treatment at the MTD
- Maximum % change in the radiological sum of the product of the diameters from baseline (see Appendix 1 for selection of suitable target and non-target lesions)
- Duration of response from time of first documented response until relapse or progression

Phase II
- Best overall response rate post 8 cycles of treatment until the end of the trial, assessed using International response criteria [1]
- Toxicity of the combination of romidepsin and carfilzomib using CTCAE v4
- Maximum % change in the radiological sum of the product of the diameters from baseline (see Appendix 1 for selection of suitable target and non-target lesions)
- Duration of response from time of first documented response until relapse or progression
- Progression free survival
- Overall survival

Definition of a Dose Limiting Toxicity (DLT)

DLTs are defined as severe haematological and non-haematological toxicities assessed using CTCAE v4.0 occurring within 4 weeks of treatment (1 cycle) defined as the following:

- Grade 4 neutropenia not responding to normal supportive therapy with G-CSF within 7 days
• Grade 4 thrombocytopenia
  a) for > 7 days or
  b) associated with active bleeding or
  c) requiring platelet transfusion (defined as treatment of a bleeding event, platelets < 20x10^9/l with concomitant infection or platelets < 10x10^9/l in asymptomatic patients)

• Grade 3 or 4 toxicity with at least a possible causal relationship to romidepsin or carfilzomib and in organs other than the bone marrow
  o EXCLUDING: Grade 3 nausea; alopecia, Grade 3 or 4 vomiting in patients who have not received optimal treatment with anti-emetics or Grade 3 or 4 diarrhoea in patients who have not received optimal treatment with anti-diarrhoeals.

• Grade 3 and 4 biochemical adverse events with at least a possible causal relationship to romidepsin or carfilzomib and are considered clinically significant the treating clinician and/or Chief Investigator

• Treatment related death

Following a DLT, the patient may continue on treatment at the next lower dose level so long as the following criteria are met:

a) The toxicity resolves to grade 2 or less within 7 days
b) The investigator deems it is in the patients best interest to stay on the trial
c) It is agreed by the trial management group

The dose of both romidepsin AND carfilzomib should be reduced 1 dose level. If either drug is on the lowest dose level specified in the protocol (i.e. romidepsin 8mg/m^2 and carfilzomib 20/36mg/m^2) then there is an option to continue on romidepsin 8mg/m^2 alone (with no carfilzomib). This decision should be discussed with the chief investigator.

A patient in Phase I of the trial (the dose-finding phase) is inevaluable if they fail to complete treatment cycle 1 and withdraw or die for reasons that are not related to treatment. Such patients can be replaced.

3. TRIAL DESIGN

This is a prospective, single arm, phase I/II, multicentre, dose finding study of romidepsin in combination with carfilzomib.

The aim of the phase I is to establish the MTD of the combination using a restricted two-stage CRM. The MTD is defined as the dose level that is closest to the level at which 25% of patients experience a DLT over the first cycle of treatment.

Patients will be assigned to the dose levels in groups of 3. The initial guess of MTD is at dose combination level 4, however to exercise caution, dose level 2 is defined as the starting dose level.

In the first stage, the first cohort of 3 patients will be enrolled at dose level 2. If none experiences a DLT, the next cohort of 3 patients will be recruited at the next level, i.e. dose level 3. This process continues until the first DLT is observed in a cohort. Once there is a DLT, the second stage which comprises of the model based CRM begins. The recommended dose for the next cohort will be made using the CRM, taking into account all the previous data observed in the first stage. This would be the dose with estimated DLT probability closest to the target of 25%. Subsequent cohorts will be assigned a dose level in the same way using all previous data observed until maximum sample size is reached or if the trial is stopped early if there is a high chance that the lowest dose is too toxic.

Once the MTD is defined, patients recruited at a lower dose may receive the MTD for any subsequent cycles of treatment at the discretion of the treating Investigator and the Chief Investigator.

Table 1: Dose levels
## Dose Level

<table>
<thead>
<tr>
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<tr>
<td>1</td>
<td>8mg/m²</td>
<td>20/36mg/m²</td>
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<tr>
<td>2</td>
<td>10mg/m²</td>
<td>20/36mg/m²</td>
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<tr>
<td>3</td>
<td>10mg/m²</td>
<td>20/45mg/m²</td>
</tr>
<tr>
<td>4</td>
<td>12mg/m²</td>
<td>20/45mg/m²</td>
</tr>
<tr>
<td>5</td>
<td>12mg/m²</td>
<td>20/56mg/m²</td>
</tr>
<tr>
<td>6</td>
<td>14mg/m²</td>
<td>20/56mg/m²</td>
</tr>
</tbody>
</table>

* For all dose levels, the carfilzomib dose will be 20mg/m² for the first 2 doses (i.e. day 1 and 2 of cycle 1), rising to the target dose for subsequent doses and cycles.

The phase II component will aim to provide a preliminary estimate of activity in 28 patients at the MTD combination established in phase I. The phase II component is based on A’Hern’s single arm, single stage design and would utilise patients allocated to the MTD in phase I. Patients will be recruited over a 36-month period and will receive a minimum of 8 cycles of treatment. Patients will continue to be followed up for progression and survival until the end of the trial.

### 4. ELIGIBILITY

#### 4.1 Inclusion Criteria
- Age ≥ 16 years of age
- Life expectancy > 12 weeks
- ECOG performance status ≤ 2 (Appendix 5)
- Relapsed or refractory* peripheral T-cell lymphoma including the following histologies: peripheral T-cell lymphoma not otherwise specified, angioimmunoblastic T-cell lymphoma, anaplastic large cell lymphoma, enteropathy associated T-cell lymphoma, extranodal NK/T-cell lymphoma, transformed mycosis fungoides, hepatosplenic T-cell lymphoma
- Failed at least 1 prior therapy (but no upper limit of prior regimens)
- Patients MAY have had a prior allogeneic stem cell transplant but must not require systemic immunosuppression for graft-versus-host disease (local treatments are permitted)
- Adequate haematopoietic reserve (Hb ≥ 9g/dl, neutrophils ≥ 1.0x10⁹/l and platelets ≥ 100x10⁹/l or ≥ 75x10⁹/l if marrow involvement documented)
- Adequate liver function (bilirubin ≤ 1.5 x upper limit of normal (ULN) (unless due to Gilbert’s syndrome), AST / ALT ≤ 2x ULN)
- Adequate renal function (creatinine clearance ≥ 20ml/min as assessed by Cockcroft and Gault calculation)
- Serum potassium ≥ 3.8 mmol/l, calcium ≥ 2.2 mmol/l and magnesium ≥ 0.85 mmol/l prior to trial entry (supplements permitted – see Appendix 7)
- CT measurable disease with at least 1 lesion having short axis > 1.5cm or splenomegaly > 14cm in cranio-caudal length attributable to relapsed lymphoma
- Ability to give informed consent
* For all relapsed patients, relapse must be confirmed by tissue biopsy (or bone marrow trephine if no other tissue available). For refractory patients, a biopsy must have been obtained within the last 6 months and preferably to confirm refractory disease.

#### 4.2 Exclusion Criteria
- Persistent treatment related toxicities of CTCAE v4.0 grade ≥ 2
- Previous treatment with histone deactylase inhibitor or proteasome inhibitor
- Need for any other concurrent anti-cancer drug (apart from corticosteroids at a dose equivalent to prednisolone ≤ 7.5mg daily). A steroid prephase may be used but should be stopped by the first day of cycle 1.
- Concurrent medical illness deemed by the investigator as uncontrolled and/or clinically significant
- Previous systemic malignancy within the last 3 years unless treated with curative intent with no sign of recurrence. Other exceptions include non-melanotic skin cancer or carcinoma in situ of the uterine cervix
- Co-existing active infection requiring parenteral antibiotics
- Patients unable to swallow oral medication
- Active infection with HIV, hepatitis B or hepatitis C
- Radiotherapy* (except for palliative reasons), endocrine therapy, immunotherapy or use of other investigational agents within 28 days prior to trial entry (or a longer period depending on the defined characteristics of the agents used, please contact the trials office for confirmation). *Limited field radiotherapy to an isolated lesion in bone or soft tissue must be completed 2 weeks prior to trial entry
- Major surgery within 4 weeks of trial entry
- Patients with proven CNS involvement
- QTc interval of ≥ 480ms or patients taking medications that significantly prolong the QT interval (Appendix 6)
- Clinically significant cardiac disease ≥ NYHA Class III (see Appendix 8), symptomatic ischaemia, conduction abnormalities uncontrolled by conventional intervention or myocardial infarction within 6 months of trial entry
- Pregnant and lactating patients (patients of childbearing potential must have a negative pregnancy test prior to study entry and within 7 days prior to the start of treatment. Postmenopausal females (> 45 years old and without menstruation for > 1 year) and surgically sterilised females are exempt from a pregnancy test)
- Patients and partners of childbearing potential not willing to use effective contraception during and for 3 months after therapy
- Concurrent Pulmonary Hypertension
- Left Ventricular Ejection Fraction (LVEF) of ≤40%

5. SCREENING AND CONSENT

5.1 Screening

Investigators will be expected to maintain a Screening Log of all potential study candidates. This Log will include limited information about the potential candidate (e.g. date of birth and gender), the date and outcome of the screening process (e.g. enrolled into study, reason for ineligibility, or refused to participate).

For patients who appear to meet the criteria for participation in the study, the Investigator will provide information to allow them to make an informed decision regarding their participation. If informed consent is given (see section 5.2), the Investigator will conduct a full screening evaluation to ensure that the patient satisfies all inclusion and exclusion criteria. A patient who gives written informed consent and who satisfies all the inclusion and exclusion criteria may be registered onto the study. Note that assessments conducted as standard of care do not require informed consent and may be provided as screening data if conducted within the stipulated number of weeks prior to registration. Assessments required in screening are listed in the flowchart of assessments and detailed in section 5.1.1.

5.1.1 Screening Assessments

All patients will be screened prior to trial enrolment. The following screening assessments will be performed within 6 weeks prior to commencing treatment unless stated otherwise:
- Medical history (including prior diagnosis and treatment, and baseline conditions) and demographic data
- Vital signs
- ECOG performance status
- Full blood count (including haemoglobin, mean cell volume, platelets, white cell count, neutrophils (ANC) and lymphocytes) and biochemistry (including LDH, AST/ALT, ALP, Bilirubin, Calcium, Creatinine, Potassium, Magnesium, Sodium, Uric acid, Urea and eGFR)
- Blood for virology. Patients must have negative virology for HIV and hepatitis C prior to trial entry. Patients with an isolated anti-hepatitis B sAg antibody may be entered as this indicates previous vaccination. Patients with hepatitis B anti-core antibody alone (with a negative HBsAg and HBV DNA) may also be entered as these patients are at low risk of hepatitis B reactivation.
- Electrocardiogram (ECG)
- ECHO or MUGA
- Bone marrow trephine biopsy
- Diagnostic tissue biopsy (within 6 months for refractory disease or at point of relapse)
- CT scan (with IV contrast) of neck, chest, abdomen and pelvis (within 6 weeks)

The following screening assessments must be performed within 7 days prior to starting treatment:
- Height, weight, body surface area
- Pregnancy test for patients of child bearing potential (must be performed prior to randomisation. If start of treatment is delayed, this may need to be repeated).
- Clinical disease assessment (by evaluation of CT scan results, bone marrow/ diagnostic tissue biopsies if applicable, assessment of B symptoms)
- Physical exam

5.2 Informed Consent
It is the responsibility of the Investigator or delegate to obtain written informed consent for each patient prior to performing any trial related procedure. A Patient Information Sheet is provided to facilitate this process. Investigators must ensure that they adequately explain the aim, trial treatment, anticipated benefits and potential hazards of taking part in the trial to the patient. The Investigator should also stress that the patient is completely free to refuse to take part or withdraw from the trial at any time. The patient should be given ample time (e.g. 24 hours) to read the Patient Information Sheet and to discuss their participation with others outside of the site research team. The patient must be given an opportunity to ask questions which should be answered to their satisfaction. The right of the patient to refuse to participate in the trial without giving a reason must be respected. If the patient expresses an interest in participating in the trial they should be asked to sign and date the latest version of the Informed Consent Form. The Investigator must then sign and date the form. A copy of the Informed Consent Form should be given to the patient, a copy should be filed in the hospital notes, and the original placed in the Investigator Site File (ISF). Once the patient is entered into the trial the patient's trial number should be entered on the Informed Consent Form maintained in the ISF. In addition, if the patient has given explicit consent a copy of the signed Informed Consent Form must be sent in the post to the Trials Office for review. Details of the informed consent discussions should be recorded in the patient's medical notes, this should include date of, and information regarding, the initial discussion, the date consent was given, with the name of the trial and the version number of the Patient Information Sheet and Informed Consent Form. Throughout the trial the patient should have the opportunity to ask questions about the trial and any new information that may be relevant to the patient's continued participation should be shared with them in a timely manner. On occasion it may be necessary to re-consent the patient in which case the process above should be followed and the patient’s right to withdraw from the trial respected. The patient should be given ample time to read changes made to the patient information sheet, which may vary depending on the nature of the updated information. Patients are permitted to re-consent at the same visit that the new information is provided if the patient wishes to do so.

Electronic copies of the Patient Information Sheet and Informed Consent Form are available from the Trials Office and should be printed or photocopied onto the headed paper of the local institution. Details of all patients approached about the trial should be recorded on the Patient Screening/Enrolment Log and with the patient’s prior consent their General Practitioner (GP) should also be informed that they are taking part in the trial. A GP Letter is provided electronically for this purpose.
6. **TRIAL ENTRY**
Patients will be registered to the trial via the Cancer Research UK Clinical Trials Unit (CRCTU).

☎:0121 414 7673

9am-5pm Monday to Friday

An eligibility checklist and registration form (found in the ISF) should be completed prior to registration by the Investigator.
The patient trial number and dose allocation will be given over the telephone, followed by a fax confirmation.

7. **TREATMENT DETAILS**
All patients will be treated with the combination of romidepsin and carfilzomib. Both romidepsin and carfilzomib are considered IMPs for the purposes of the trial and will be supplied free of charge for the trial by the manufacturers Celgene and Onyx respectively.

Romidepsin will be supplied as a lyophilised powder in a single-use vial containing 10 mg of romidepsin and 20mg of the bulking agent, povidone. In addition, each kit contains 1 sterile vial containing 2ml (deliverable volume) of diluents composed of 80% propylene glycerol and 20% dehydrated alcohol. The product should be stored between 20-25°C (although excursions between 15-30°C are permitted).

Carfilzomib will be supplied as a lyophilised powder for injection in a single-dose vial. Each single-dose vial provides 60mg of carfilzomib in a 50 cc labelled glass vial with an elastomeric stopper and a flip-off lid. The lyophilised product is reconstituted with water for injection. The concentration of reconstituted carfilzomib for injection is 2 mg/ml. The product is supplied containing four single-use vials per carton and is shipped and stored between 2°C - 8°C.

The IMPs will be packaged and labelled in accordance with local regulations and Good Manufacturing Practice (GMP), stating that the drug is for clinical trial use only and to keep it out of the reach of children.

For further details, instructions and ordering details, please refer to the pharmacy manual.

**Method of romidepsin infusion:** Diluted romidepsin should be administered by intravenous infusion over a 4 hour period. Once diluted the product is stable for up to 24 hours, however, it should be administered as soon as possible after dilution. Prior to administration it is advisable to visually inspect the diluted product for particulate matter.

**Method of carfilzomib infusion:** Carfilzomib will be given as an intravenous infusion over approximately 30 minutes. Prior to administration it is advisable to visually inspect the diluted product for particulate matter.

A pre-medication with dexamethasone 4mg (for carfilzomib doses ≤ 36 mg/m²) or 8mg (for carfilzomib doses > 36 mg/m²) should be administered either orally or intravenously to reduce infusion related reactions. Dexamethasone is to be administered for all cycles but may be omitted after cycle 1 if causing significant side effects.

**Hydration**
Patients should aim to maintain good oral hydration for 24 hours prior to each dose and for 24 hours afterwards. Satisfactory oral hydration would be 30 ml/kg/day which is approximately 6-8 cups of liquid per day.

During Cycle 1, on days when Carfilzomib ALONE is being administered, patients should receive pre-hydration with 250-500ml normal saline (or other appropriate intravenous formulation) over 60 minutes. In cases where <500ml pre-hydration is administered post treatment hydration must be given (over 60
minutes, after the administration of Carfilzomib to equate to a total of 500ml hydration (i.e., patients must receive a minimum of 500ml hydration and this can therefore be made up by giving post hydration). On days where both drugs are given, romidepsin should be administered before the Carfilzomib as the Romidepsin infusion will serve as the pre-carfilzomib hydration. The Romidepsin should be administered in 500ml normal saline (or other appropriate intravenous formulation).

Post treatment hydration (for all patients and in particular, patients at increased risk of tumour lysis syndrome e.g., including but not limited to those with high LDH, high uric acid or impaired renal function at baseline) of up to 500ml normal saline (or other appropriate intravenous formulation) over 60 minutes can be given to patients on days where they receive combination treatment with both romidepsin and carfilzomib and also on days where they receive stand-alone treatment with carfilzomib. Post treatment hydration is to be administered at the Investigator’s discretion in all cases.

Cycle 2 onwards: Pre and post hydration can be given at the treating Investigators discretion and would generally be confined to those patients deemed at continuing increased risk of tumour lysis syndrome.

There is a risk of fluid overload during cycle 1 (and cycle 2 onwards if pre- and post-hydration regimen continued). Patients should be monitored for clinical evidence of fluid overload at study visits during this time and given diuretics if clinically indicated.

7.1 Treatment Schedule

The combination treatment will be given as 28 day cycles. Romidepsin is given intravenously on days 1, 8 and 15 and carfilzomib is given intravenously on days 1, 2, 8, 9, 15 and 16 of a 28 day cycle.

Every effort should be made to attend on the scheduled visit days, however if not possible, visits may be arranged for +/- 2 days. If rescheduling occurs, subsequent visits may be rescheduled in line with the protocol or in line with the rescheduled arrangements at the treating Investigators discretion.

Patients will receive 8 cycles of combination therapy. At the end of 8 cycles, further cycles will be delivered until disease progression, unacceptable toxicity or patient choice. Continuation of the combination is preferred although carfilzomib may be omitted or given on days 1, 8 and 15 only.

Reasons for omitting or reducing the frequency of the carfilzomib administration may include:

- toxicity which, although not resulting in a DLT or dose reduction still impairs patient quality of life - please refer to the relevant Investigator Brochure for expected adverse events for both IMPs
- practical difficulties experienced by the patient in attending for treatment 6 days in the 28 day cycle

The starting dose for the first cohort of 3 patients is 10mg/m$^2$ of romidepsin and 36mg/m$^2$ of carfilzomib (dose level 2). However, in all cohorts, the carfilzomib dose will be 20mg/m$^2$ for the first 2 doses of the first cycle, rising to the target dose for all subsequent doses and cycles.

The recommended dose for the second cohort will be made using the CRM after observing the occurrence of DLT in the first cohort. If no DLTs are observed in the first cohort patients will be recruited into the next dose level, this will continue until a DLT is observed. Once a DLT has occurred CRM will be used to determine dose level for the next cohort, and this will continue for subsequent cohorts until the maximum sample size for phase I is reached.

The dose levels for the study are:

<table>
<thead>
<tr>
<th>Dose Level</th>
<th>Romidepsin dose (days 1,8,15)</th>
<th>Carfilzomib dose (days 1,2,8,9,15,16)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>8mg/m$^2$</td>
<td>20/36mg/m$^2$</td>
</tr>
<tr>
<td>2 Starting dose</td>
<td>10mg/m$^2$</td>
<td>20/36mg/m$^2$</td>
</tr>
<tr>
<td>3</td>
<td>10mg/m$^2$</td>
<td>20/45mg/m$^2$</td>
</tr>
</tbody>
</table>
Phase II patients will be allocated the MTD identified from phase I. Any phase I patients still receiving treatment at this time may also receive the MTD at the treating Investigators discretion.

BSA should be calculated according to the Mosteller or Du Bois formula if this is not possible due to local prescribing systems, this should be discussed with the trials office.

BSA will be calculated prior to each cycle of therapy. The dose should only be amended if weight change is >10%.

Patients with a BSA of >2.2 m² will receive a dose of carfilzomib based on 2.2 m² BSA.

Each cycle of therapy may begin on day 1 providing the following conditions are met:

- Patients must have had a serum potassium level ≥ 3.8 mmol/L and a serum magnesium level ≥ 0.85 mmol/L prior to treatment as hypokalemia and hypomagnesaemia can be associated with ECG abnormalities. Low levels can be corrected with supplementation (see Appendix 7).
- Non-haematological toxicities of grade 3 or 4 have resolved to grade 1 or less*
- Neutrophil count ≥ 1.0x10⁹/l and platelet count ≥ 75x10⁹/l**

*If these conditions are not met on day 1 of a new cycle, the patient will be re-evaluated weekly.
**If counts are below these levels then delay treatment and re-evaluate weekly, re-commencing at the same dose when the counts have recovered. If counts are below these levels for 2 consecutive cycles, once counts recovered, re-commence with dose of BOTH drugs reduced by one dose level.

The maximum treatment delay is 4 weeks. If grade 3 or 4 toxicities have failed to resolve to grade 1 or less after this time, drug administration should be discontinued.

Further management is described under 7.4 ‘Dose Modification and Delays’.

### Assessments

#### 7.2.1 Full blood count and biochemistry

Full blood count (including haemoglobin, mean cell volume, platelets, white cell count, neutrophils (ANC) and lymphocytes) and serum biochemistry (including LDH, AST/ALT, ALP, Bilirubin, Calcium, Creatinine, Potassium, Magnesium, Sodium, Uric acid, Urea and eGFR) will be performed on day 1, 8, and 15 of each 28 day cycle and at the end of treatment visit and also every 3 months during follow up where no disease progression (as per schedule of events table). Full blood count and biochemistry will also be performed at any point between day 22 and 28 in order to assess participants before their next cycle. Full blood count and biochemistry may be performed up to 2 days prior to treatment administration in order to have results available before the administration of drug.

#### 7.2.2 Physical Assessment

Patients will receive a physical exam, including vital signs, and assessment of ECOG performance status on day 1 of each cycle and at the end of treatment visit. The physical exam should also include investigation of skin lymphoma deposits and rashes, liver and spleen assessment and assessment of lymph node measurements.

#### 7.2.2.1 Electrocardiograms (ECG)

In the Phase I component, patients must receive an ECG within an hour before the infusion of romidepsin and within an hour following the infusion on days 1, 8 and 15 of cycles 1 and 2.

In the phase II component, and cycle 3 onwards in the phase I, patients must receive an ECG within an hour before romidepsin infusion on day 1 of each cycle. In patients at risk of cardiac arrhythmia (e.g. those taking antiarrhythmic drugs), an ECG will continue to be performed on days 8 and 15 of each cycle, within 1 hour of the romidepsin infusion.

<p>| | | |</p>
<table>
<thead>
<tr>
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<tbody>
<tr>
<td>4</td>
<td>12mg/m²</td>
<td>20/45mg/m²</td>
</tr>
<tr>
<td>5</td>
<td>12mg/m²</td>
<td>20/56mg/m²</td>
</tr>
<tr>
<td>6</td>
<td>14mg/m²</td>
<td>20/56mg/m²</td>
</tr>
</tbody>
</table>
7.2.3 Disease assessment

A contrast enhanced CT scan of the neck, chest, abdomen and pelvis will be performed after every 2 cycles of treatment during the first 8 cycles to assess response.

Patients who continue to receive treatment with romidepsin and/or carfilzomib beyond the initial 8 cycles will receive a CT scan after every 4 cycles or sooner (anytime from day 21 of the last treatment cycle) if the investigator is concerned there may be disease progression or the patient discontinues treatment. If the patient has not progressed at the end of treatment visit, the patient will continue to be followed up every 3 months for 1 year and a CT scan will be performed if there is clinical suspicion of progression or at the end of the 1 year follow-up period.

Response will be assessed according to the Revised Response Criteria [1].

A bone marrow trephine biopsy will be performed at screening. If this shows involvement, the patient should receive a further bone marrow trephine biopsy at radiological CR to confirm CR. Further bone marrow biopsy should also be performed if progression within the marrow is suspected and the CT does not show progression.

7.3 Sample Collection

7.3.1 Tumour paraffin blocks

An important exploratory component of this study is to evaluate the utility of HR23B expression as a predictive biomarker of response to the romidepsin/carfilzomib combination. Formalin fixed, paraffin embedded diagnostic tissue blocks will be collected. For relapsed patients, this should be taken at relapse; for refractory patients it is recommended to be taken to confirm refractory disease (but is not essential). If tissue to confirm refractory disease is not available, the initial diagnostic biopsy should be sent and should have been taken within 6 months of study entry.

Nodal or soft tissue biopsies are always preferred but if the only diagnostic material available is from a trephine biopsy, this is sufficient.

Samples should be sent to:

Sample handling laboratory,
Early Phase Trials Unit,
Level 1 Oxford Cancer and Haematology Centre,
Churchill Hospital
Oxford OX3 7EJ

The samples will be stored until the last patient has been enrolled. The samples will then be processed as one or more batches. Immunohistochemistry will be performed in the ECMC GCP laboratory for one or more of the following:

- CD2
- CD3
- CD5
- CD30
- HR23B

Formal central review of diagnosis will not be performed. The T-cell markers are being used to ensure that any observed HR23B staining is indeed localised to the malignant T-cells. HR23B staining will be scored independently by an experienced haematopathologist using the system reported by Khan et al or a modified system if felt more appropriate at the time of analysis [25].

In addition to the slides required for the above study, tissue microarrays will be constructed and 3 10µm sections will be stored. These samples may be used in other ethically approved research projects deemed of scientific merit by an advisory panel. The remaining tissue will be returned to the referring institution.
At progression, an optional tissue biopsy is encouraged and should be sent to the same address. This may be used to assess for changes in HR23B (and possibly other associated molecules) which may indicate a mechanism of tumour escape.

7.3.2 Sub Studies
This trial incorporates two optional sub studies, as detailed below:

Circulating DNA Study
As part of an optional sub-study, patients will be asked to provide blood samples (prior to treatment) at screening, cycle 3, cycle 6 and cycle 10 (or at equivalent time point if patient is off treatment). Samples will be collected, processed and stored at site, prior to shipment to the University of Leicester at specified time points. For further details please refer to the RomiCar Sub Study Manual.

100,000 Genomes Project
Patients participation in RomiCar will be eligible to take part in the 100, 000 Genome Project. This is a separate project with a separate consent form. For this sub-study, patients will be asked to provide a blood sample(s) and saliva. Approximately 50mls of blood will be collected and possibly some saliva if needed. Patients will also be asked to donate a piece of their existing tissue biopsy which would have been collected as part of their standard care procedure (this may be the initial diagnostic biopsy or the biopsy taken at relapse). For further details please contact the 100,000 Genomes Project (http://www.genomicsengland.co.uk/the-100000-genomes-project/).

7.4 Dose Modifications and delays

The following applies to patients on both the phase I (from cycle 2 onwards) and phase II component of the study.

Any treatment delay and dose reduction always applies to BOTH romidepsin and carfilzomib.

For all modifications:
- Maximum treatment delay is 4 weeks. If grade 3 or 4 toxicities have failed to resolve to grade 1 or less after this time, drug administration should be discontinued.
- Once a reduction in dose level has occurred, the dose should NOT be increased again throughout the treatment course.

**Non-Haematological toxicities**

<table>
<thead>
<tr>
<th>Non-haematological toxicity</th>
<th>EXCLUDING grade 3 nausea, grade 3 alopecia, grade 3 or 4 vomiting (in the absence of optimal anti-emetic treatment), grade 3 or 4 diarrhoea (in the absence of optimal anti-diarrhoeal treatment). Applies to any point within the 28 day cycle.</th>
</tr>
</thead>
</table>
| First episode of any grade 3 | • Delay treatment  
|                              | • Evaluate weekly  
|                              | • Restart both drugs at same dose when toxicity ≤ grade 1 |
| Second episode of any grade 3 | • Delay treatment  
| in consecutive cycle OR     | • Evaluate weekly  
| First episode of any grade 4 | • Restart both drugs at next lower dose level when toxicity ≤ grade 1 |
**Haematological toxicities**

Grade 4 neutropenia should always be treated with GCSF according to local policy (see section 7.6).

<table>
<thead>
<tr>
<th>Haematological toxicity on day 1 of cycle</th>
<th></th>
</tr>
</thead>
</table>
| • Neutrophils <1.0x10^9/l and/or Platelets <75x10^9/l | • Delay treatment  
• Evaluate weekly  
• Restart both drugs at same dose if counts recovered to neutrophils ≥ 1.0x10^9/l and platelets ≥ 75x10^9/l |

<table>
<thead>
<tr>
<th>Consecutive cycle occurrence of:</th>
<th></th>
</tr>
</thead>
</table>
| • Neutrophils <1.0x10^9/l and/or Platelets <75x10^9/l | • Delay treatment  
• Evaluate weekly  
• Restart both drugs at next lower dose level if counts recovered to neutrophils ≥ 1.0x10^9/l and platelets ≥ 75x10^9/l |

<table>
<thead>
<tr>
<th>Haematological toxicity on day 8 or 15 of cycle</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Neutrophils 0.5-1.0x10^9/l and/or Platelets 50-75x10^9/l</td>
<td>• Administer both drugs at next lower dose level</td>
</tr>
</tbody>
</table>

| • Neutrophils <0.5x10^9/l and/or Platelets <50x10^9/l | • Delay treatment  
• Evaluate weekly  
• Restart both drugs at next lower dose level if counts recovered to neutrophils ≥ 1.0x10^9/l and platelets ≥ 75x10^9/l |

**Electrolyte Imbalance**

The following applies to patients on both the phase I (from cycle 2 onwards) and phase II component of the study.

Romidepsin should not be given if:
- Potassium<3.8mmol/L
- Magnesium<0.85mmol/L

Treatment with both romidepsin and carfilzomib should be delayed until potassium or magnesium has been replaced (see appendix 7). Maximum treatment delay is 4 weeks. Drug administration should be discontinued if the potassium or magnesium cannot be corrected to within the specified range during a delay in treatment of up to 4 weeks. Romidepsin and Carfilzomib may be administered as soon as the levels are within range (Potassium ≥3.8mmol/L; Mg ≥0.85mmol/L).

**7.5 Treatment Compliance**

Non-compliance is not likely to be an issue as patients must attend hospital to receive infusions of romidepsin and carfilzomib. Pharmacy departments will be required to maintain accurate records of drug accountability.
7.6 Supportive Treatment

7.6.1.1 Febrile Neutropenia
Primary prophylaxis with GCSF is not recommended routinely but may be considered in cases at high risk of febrile neutropenia (e.g. elderly or in those who had multiple infections with prior chemotherapy). For patients who experienced grade 3 neutropenia in a previous cycle, consider prophylaxis with GCSF for subsequent cycles. Secondary prophylaxis (i.e. after an episode of febrile neutropenia) is recommended. Specific GCSF and regimen should be according to local policy. However, please note the following guidance from the American Society of Clinical Oncology guidelines (2006 update) [31]:

- Colony Stimulating Factors (CSFs) should be administered within 24-72 hours after administration of myelotoxic medication
- CSFs should be continued until neutrophil count is ≥2x10⁹/l
- In adults the recommended CSF dose is 5 µg/kg/d
- For pegfilgrastim, 6mg should be administered subcutaneously, 24h after chemotherapy

7.6.1.2 Tumour Lysis Syndrome (TLS)

7.6.1.3 Patients with rapidly proliferating tumour and high tumour burden are at risk of TLS. These patients should be monitored closely and managed according to best medical practice. Management of TLS may include aggressive hydration, monitoring of renal function, correction of electrolyte abnormalities, anti-hyperuricaemic therapy, and supportive care.

Hypertension including Hypertensive Crises

All patients should be routinely evaluated for hypertension and treated as needed. If the hypertension cannot be controlled, the Carfilzomib dose should be reduced, per protocol. In case of hypertensive crisis, stop Carfilzomib until resolved or returned to baseline and consider whether to restart Carfilzomib based on a benefit/risk assessment.

7.6.1.4 Pulmonary Toxicity
Evaluate and stop Carfilzomib until resolved and consider whether to restart Carfilzomib based on a benefit/risk assessment.

7.6.1.5 Pulmonary Hypertension
Stop Carfilzomib until pulmonary hypertension has resolved or returned to baseline, and consider whether to restart a Carfilzomib based on a benefit/risk assessment.

7.7 Concomitant Medication
Prophylaxis is recommended for:

- Nausea and vomiting have been reported with romidepsin and therefore the use of anti-emetics is recommended
- Oral Candida according to local guidelines (may include mouthwashes and oral fluconazole)
- Herpes simplex and zoster reactivation according to local guidelines e.g. aciclovir 200mg oral (po), three times a day (tds)
  Ranitidine 150mg po, twice daily (bd) or a proton pump inhibitor are permitted.
- Pneumocystis pneumonia (PCP) prophylaxis according to local guidelines

N.B. Pentamidine should NOT be used for this indication due to its cardiac effects.

Concomitant use of any other anticancer therapy, drugs that could significantly prolong the QTc interval (Appendix 6), moderate-to-significant inhibitors of CYP3A4 (Appendix 6), or therapeutic warfarin is prohibited.
7.8 Patient Follow Up

All patients will need to be followed up until disease progression and for survival until the end of the trial (minimum of 12 months follow-up from the date of commencing treatment for the last patient).

If the patient stops trial treatment but has not progressed, they will be reviewed in clinic every 3 months for a year with a CT scan of neck, chest, abdomen and pelvis on clinical suspicion of progression or at 1 year (whichever is sooner). If there is no evidence of progression after 1 year, patients will have no specific trial follow up, but the Investigator will be contacted every 6 months to determine progression and survival data. At progression, patients will then be followed up annually for survival data for a minimum of 12 months.

7.9 Treatment Discontinuation and Patient Withdrawal

In the event of discontinuation of study treatment, e.g. unacceptable toxicity or patient choice, full details of the reason/s for discontinuation should be recorded on the appropriate pages on the CRF. All patients, including non-compliant subjects, should be followed up according to the protocol unless they withdraw specific consent.

In the event of a patient’s decision to withdraw from the trial, the Investigator should ascertain from which aspects of the trial the patient wishes to withdraw and record the details on the appropriate CRF. All information and blood/tissue samples collected up until point of retraction will be retained and analysed. If a patient chooses to withdraw from treatment only, the patient should discontinue treatment and continue to be assessed in accordance with the protocol. If a patient wishes to withdraw from the trial (i.e. including trial specific assessments), but is willing for further data to be supplied to the Trials Office, then further routine “follow-up” data (e.g. disease status and survival) will continue to be supplied by the Investigator to the Trials Office.

Patients who stop treatment due to adverse experiences (clinical or laboratory) will be treated and followed according to accepted medical practice. All pertinent information concerning the outcome of such treatment must be recorded in the CRF.

The following are justifiable reasons for the Investigator to stop study treatment:

- unforeseen events: any event which in the judgement of the Investigator makes further treatment inadvisable
- serious violation of the study protocol (including persistent patient non-attendance and persistent non-compliance)
- stopping by the Investigator for clinical reasons not related to the study drug treatment

Patients must stop study treatment in the event of:

- unacceptable toxicity
- SAE requiring permanent discontinuation of treatment
- the patient becoming pregnant

8. ADVERSE EVENT REPORTING

The collection and reporting of Adverse Events (AEs) will be in accordance with the Medicines for Human Use Clinical Trials Regulations 2004 and its subsequent amendments. Definitions of different types of AE are listed in Appendix 3. The Investigator should assess the seriousness and causality (relatedness) of all AEs experienced by the patient (this should be documented in the source data) with reference to the Investigator Brochure.
8.1 Reporting Requirements

8.1.1 Adverse Events
All medical occurrences which meet the definition of an AE (see Appendix 3 for definition) should be reported. Please note this includes the following abnormal laboratory findings that meet the definition of CTCAE criteria and are clinically significant:

- ALP
- AST/ALT
- Bilirubin
- Calcium
- Creatinine
- LDH
- Potassium
- Magnesium
- Sodium
- Uric acid
- Urea
- eGFR
- Haemoglobin
- Platelets
- White Cell Count
- Neutrophils (ANC)
- Lymphocytes

8.1.2 Serious Adverse Events
Investigators should report AEs that meet the definition of an SAE (see Appendix 3 for definition) and are not excluded from the reporting process as described below.

8.1.2.1 Events that do not require reporting on a Serious Adverse Event Form
The following events should not be reported on an SAE Form:

- Hospitalisations for:
  - Protocol defined treatment
  - Pre-planned elective procedures unless the condition worsens
  - Treatment for progression of the patient’s cancer
- Progression as a result of the patient’s cancer, as this information is captured elsewhere on the Case Report Form

8.1.2.2 Monitoring pregnancies for potential Serious Adverse Events
It is important to monitor the outcome of pregnancies of patients in order to provide SAE data on congenital anomalies or birth defects.

In the event that a patient or their partner becomes pregnant during the SAE reporting period please complete a Pregnancy Notification Form (providing the patient’s details) and return to the Trials Office as soon as possible. If it is the patient who is pregnant provide outcome data on a follow-up Pregnancy Notification Form. Where the patient’s partner is pregnant consent must first be obtained and the patient should be given a Release of Medical Information Form to give to their partner. If the partner is happy to provide information on the outcome of their pregnancy they should sign the Release of Medical Information Form. Once consent has been obtained provide details of the outcome of the pregnancy on a follow-up Pregnancy Notification Form. If appropriate also complete an SAE Form as detailed below.
8.1.3 Reporting period
Details of all AEs (except those listed above) will be documented and reported from the date of commencement of protocol defined treatment until 30 days after the administration of the last treatment. Pre-existing symptoms will only be reported as AEs if they increase in grade after commencing trial therapy.

8.1.4 Post study SUSARs
SAEs that are judged to be at least possibly related to the IMP(s) and are unexpected must still be reported in an expedited manner irrespective of how long after IMP administration the reaction occurred.

8.2 Reporting Procedure

8.2.1 Site

8.2.1.1 Adverse Events
AEs should be reported on an AE Form (and where applicable on an SAE Form). A running AE Form should be continuously maintained and faxed to the trials office after every treatment cycle whilst on treatment. The original should be returned to the Trials Office when complete.

AEs will be reviewed using the Common Terminology Criteria for Adverse Events (CTCAE), version 4.0 (see Appendix 4). Any AEs experienced by the patient but not included in the CTCAE should be graded by an Investigator and recorded on the AE Form using a scale of (1) mild, (2) moderate or (3) severe. For each sign/symptom, the highest grade observed since the last visit should be recorded.

8.2.1.2 Serious Adverse Events
For more detailed instructions on SAE reporting refer to the Guidelines contained in the Investigator Site File (ISF).

AEs defined as serious and which require reporting as an SAE (excluding events listed in Section 8.1 above) should be reported on an SAE Form. When completing the form, the Investigator will be asked to define the causality and the severity of the AE which should be documented using the CTCAE version 4.0.

On becoming aware that a patient has experienced an SAE, the Investigator (or delegate) must complete, date and sign an SAE Form. The form should be faxed together with a SAE Fax Cover Sheet to the Trials Office using one of the numbers listed below as soon as possible and no later than 24 hours after first becoming aware of the event:

To report an SAE, fax the SAE Form with an SAE Fax Cover Sheet to:

0121 414 6061 or 0121 414 3700

On receipt the Trials Office will allocate each SAE a unique reference number. This number will be transcribed onto the SAE Fax Cover Sheet which will then be faxed back to the site as proof of receipt. If confirmation of receipt is not received within 1 working day please contact the Trials Office. The SAE reference number should be quoted on all correspondence and follow-up reports regarding the SAE. The SAE Fax Cover Sheet completed by the Trials Office should be filed with the SAE Form in the ISF.

For SAE Forms completed by someone other than the Investigator the Investigator will be required to countersign the original SAE Form to confirm agreement with the causality and severity assessments. The form should then be returned to the Trials Office in the post and a copy kept in the ISF.

Investigators should also report SAEs to their own Trust in accordance with local practice.
8.2.1.3 Provision of follow-up information
Patients should be followed up until resolution or stabilisation of the event. Follow-up information should be provided on a new SAE Form (refer to the Trial Guidelines for further information).

8.2.2 Trials Office
On receipt of an SAE Form seriousness and causality will be determined independently by a Clinical Coordinator. An SAE judged by the Investigator or Clinical Coordinator to have a reasonable causal relationship with the trial medication will be regarded as a Serious Adverse Reaction (SAR). The Clinical Coordinator will also assess all SARs for expectedness. If the event meets the definition of a SAR that is unexpected (i.e. is not defined in the Reference Safety Information (RSI)) it will be classified as a Suspected Unexpected Serious Adverse Reaction (SUSAR).

8.2.3 Reporting to the Competent Authority and main Research Ethics Committee

8.2.3.1 Suspected Unexpected Serious Adverse Reactions
The Trials Office will report a minimal data set of all individual events categorised as a fatal or life threatening SUSAR to the Medicines and Healthcare products Regulatory Agency (MHRA) and main Research Ethics Committee (REC) within 7 days. Detailed follow-up information will be provided within an additional 8 days.
All other events categorised as SUSARs will be reported within 15 days

8.2.3.2 Serious Adverse Reactions
The Trials Office will report details of all SARs (including SUSARs) to the MHRA and main REC annually from the date of the Clinical Trial Authorisation, in the form of a Development Safety Update Report (DSUR).

8.2.3.3 Adverse Events
Details of all AEs will be reported to the MHRA on request.

8.2.3.4 Other safety issues identified during the course of the trial
The MHRA and main REC will be notified immediately if a significant safety issue is identified during the course of the trial.

8.2.4 Investigators
Details of all SUSARs and any other safety issue which arises during the course of the trial will be reported to Principal Investigators. A copy of any such correspondence should be filed in the ISF.

8.2.5 Trial Steering Committee
The Trial Steering Committee (TSC) will oversee all toxicity data. The TSC will have the power to recommend discontinuation of the study on the basis of the data they receive.

8.2.6 Manufacturer of Investigational Medicinal Product
All SAEs will be reported to the manufacturers of the Investigational Medicinal Products as defined in the agreement between Sponsor and manufacturer.

9. DATA HANDLING AND RECORD KEEPING

9.1 Data Collection
The Case Report Form (CRF) will contain the following forms:

<table>
<thead>
<tr>
<th>Form</th>
<th>Summary of data recorded</th>
<th>Schedule for submission</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eligibility Checklist</td>
<td>Confirmation of eligibility</td>
<td>Faxed at point of registration</td>
</tr>
<tr>
<td>Registration</td>
<td>Patient details; optional consent issues</td>
<td>As soon as possible after</td>
</tr>
<tr>
<td>Form Type</td>
<td>Description</td>
<td>Timeframe</td>
</tr>
<tr>
<td>-----------------------------------</td>
<td>-----------------------------------------------------------------------------</td>
<td>------------------------------------------------</td>
</tr>
<tr>
<td>Screening</td>
<td>Baseline characteristics</td>
<td>Within 1 month of registration</td>
</tr>
<tr>
<td>Treatment Form</td>
<td>Details of trial treatment and blood and biochemistry parameters</td>
<td>Within 1 month of protocol scheduled visit</td>
</tr>
<tr>
<td>Treatment Continuation Form</td>
<td>Details of trial treatment and blood and biochemistry parameters</td>
<td>Within 1 month of protocol scheduled visit</td>
</tr>
<tr>
<td>End of Treatment Form</td>
<td>Details of trial treatment and blood and biochemistry parameters</td>
<td>Within 1 month of protocol scheduled visit</td>
</tr>
<tr>
<td>Follow-up Form</td>
<td>Patient disease status</td>
<td>Within 1 month of protocol scheduled visit</td>
</tr>
<tr>
<td>Deviation Form</td>
<td>Completed in the event of a deviation from the protocol</td>
<td>Immediately upon discovering deviation</td>
</tr>
<tr>
<td>Withdrawal Form</td>
<td>Used to notify the Trials Office of patient withdrawal from the trial</td>
<td>Immediately upon patient withdrawal</td>
</tr>
<tr>
<td>Treatment Discontinuation Form</td>
<td>Used to notify the Trials Office of discontinuation of trial treatment</td>
<td>Immediately upon discontinuation of treatment</td>
</tr>
<tr>
<td>Adverse Event Form</td>
<td>Record all adverse events experienced by patient throughout the trial</td>
<td>To be faxed to the Trials Unit after every treatment cycle</td>
</tr>
<tr>
<td>Concomitant Medication Form</td>
<td>Used to record all concomitant medication taken by the patient throughout the trial.</td>
<td>To be sent at the end of treatment</td>
</tr>
</tbody>
</table>

**Ad hoc forms**
- Serious Adverse Event Form
- Death Form
- Pregnancy Notification Form
- Progression Form
- Sample Collection Forms

The CRF must be completed, signed/dated and returned to the Trials Office by the Investigator or an authorised member of the site research team (as delegated on the Site Signature and Delegation Log) within the timeframe listed above. The exceptions to this are the SAE Form and Withdrawal Form which must be co-signed by the Investigator.

Entries on the CRF should be made in ballpoint pen, in blue or black ink, and must be legible. Any errors should be crossed out with a single stroke, the correction inserted and the change initialled and dated. If it is not obvious why a change has been made, an explanation should be written next to the change.

Data reported on each form should be consistent with the source data or the discrepancies should be explained. If information is not known, this must be clearly indicated on the form. All missing and ambiguous data will be queried. All sections are to be completed before returning.

In all cases it remains the responsibility of the Investigator to ensure that the CRF has been completed correctly and that the data are accurate.

The completed originals should be sent to the Trials Office and a copy filed in the Investigator Site File.

Trial forms may be amended by the Trials Office, as appropriate, throughout the duration of the trial. Whilst this will not constitute a protocol amendment, new versions of the form must be implemented by participating sites immediately on receipt.

### 9.2 Archiving

It is the responsibility of the Principal Investigator to ensure all essential trial documentation and source records (e.g. signed Informed Consent Forms, Investigator Site Files, Pharmacy Files, patients’ hospital notes, copies of CRFs etc.) at their site are securely retained for at least 10 years after the
end of the trial. Do not destroy any documents without prior approval from the CRCTU Document Storage Manager.

10. QUALITY MANAGEMENT

10.1 Site Set-up and Initiation

All sites will be required to sign a clinical trial agreement prior to participation. In addition all participating Investigators will be asked to sign the necessary agreements, registration forms and supply a current CV to the Trials Office. All members of the site research team will also be required to sign the Site Signature and Delegation Log, which should be returned to the Trials Office. Prior to commencing recruitment all sites will undergo a process of initiation. Key members of the site research team will be required to attend either a meeting or a teleconference covering aspects of the trial design, protocol procedures, Adverse Event reporting, collection and reporting of data and record keeping. Sites will be provided with an Investigator Site File and a Pharmacy File containing essential documentation, instructions, and other documentation required for the conduct of the trial. The Trials Office must be informed immediately of any change in the site research team.

10.2 On-site Monitoring

Monitoring will be carried out as required following a risk assessment and as documented in the CRCTU Quality Management Plan. Additional on-site monitoring visits may be triggered for example by poor CRF return, poor data quality, low SAE reporting rates, excessive number of patient withdrawals or deviations. If a monitoring visit is required the Trials Office will contact the site to arrange a date for the proposed visit and will provide the site with written confirmation. Investigators will allow the RomiCar trial staff access to source documents as requested.

10.3 Central Monitoring

Where a patient has given explicit consent sites are requested to send in copies of signed Informed Consent Forms for in-house review. Trials staff will be in regular contact with the site research team to check on progress and address any queries that they may have. Trials staff will check incoming Case Report Forms for compliance with the protocol, data consistency, missing data and timing. Sites will be sent Data Clarification Forms requesting missing data or clarification of inconsistencies or discrepancies.

Sites may be suspended from further recruitment in the event of serious and persistent non-compliance with the protocol and/or GCP, and/or poor recruitment. Any major problems identified during monitoring may be reported to Trial Management Group and Data Monitoring Committee and the relevant regulatory bodies. This includes reporting serious breaches of GCP and/or the trial protocol to the main Research Ethics Committee (REC) and the Medicines for Healthcare products Regulatory Agency (MHRA).

10.4 Audit and Inspection

The Investigator will permit trial-related monitoring, audits, ethical review, and regulatory inspection(s) at their site, providing direct access to source data/documents. Sites are also requested to notify the Trials Office of any MHRA inspections.

10.5 Notification of Serious Breaches

In accordance with Regulation 29A of the Medicines for Human Use (Clinical Trials) Regulations 2004 and its amendments the Sponsor of the trial is responsible for notifying the licensing authority in writing of any serious breach of:

- The conditions and principles of GCP in connection with that trial or;
- The protocol relating to that trial, within 7 days of becoming aware of that breach

For the purposes of this regulation, a “serious breach” is a breach which is likely to effect to a significant degree:

- The safety or physical or mental integrity of the subjects of the trial; or
- The scientific value of the trial
Sites are therefore requested to notify the Trials Office of a suspected trial-related serious breach of GCP and/or the trial protocol. Where the Trials Office is investigating whether or not a serious breach has occurred sites are also requested to cooperate with the Trials Office in providing sufficient information to report the breach to the MHRA where required and in undertaking any corrective and/or preventive action.

11. END OF TRIAL DEFINITION
The end of trial will be 6 months the last data capture. This will allow sufficient time for the completion of protocol procedures, data collection and data input. The Trials Office will notify the MHRA and main REC that the trial has ended and will provide them with a summary of the clinical trial report within 12 months of the end of trial.

12. STATISTICAL CONSIDERATIONS
12.1 Implementation of CRM in Phase I
The aim of the phase I is to establish the MTD of romidepsin in combination with carfilzomib using a restricted two-stage CRM. The target DLT (as defined in section 2) probability for the combination drug treatment is 25%. This decision was reached based on a rough estimate of 5% and 20% event rate in the study population with 10mg/m$^2$ and 12mg/m$^2$ of romidepsin alone respectively. A target event rate higher than the rate of romidepsin alone was deemed acceptable after taking into account that the combined regimen might be more effective than romidepsin alone.

As romidepsin has proven activity in PTCL, the starting dose will be 10mg/m$^2$. Current phase I combination studies with carfilzomib are on-going. However, the MTD in combination with panobinostat (another HDAC inhibitor) has not yet been reached and the dose currently being tested in 45mg/m$^2$ (verbal communication with Onyx). The prior guess of MTD is at dose combination level 4, but to exercise caution, the doses will start at level 2, 10mg/m$^2$ of romidepsin and 20/36mg/m$^2$ of carfilzomib. In case of excess toxicity at the initial dose, we would de-escalate to level 1 of 8mg/m$^2$ of romidepsin and 20/36mg/m$^2$ of carfilzomib. Escalation of carfilzomib and romidepsin dose will alternate up to the maximum dose of carfilzomib 56mg/m$^2$ and romidepsin 14mg/m$^2$ which represent the MTD of each drug as a single agent.

The dose escalation/de-escalation decision is made using a restricted two-stage CRM [32-34]. Patients will be assigned to dose-combinations in groups of 3. In the first stage, the first cohort of 3 patients will be enrolled at dose level 2. If none experiences a DLT, the next cohort of 3 patients will be recruited at the next higher level, i.e. dose level 3. This process continues until the first DLT is observed in a cohort.

Once there is a DLT, the second stage which comprises of the model based CRM begins. We will utilise an empiric dose-toxicity model, $F(x, \beta)$ given as

$F(x, \beta) = x^{\exp(\beta)}$ for $0 < x < 1$,

where the model parameter $\beta$ is estimated using Bayesian analysis and $x$ comprises of the initial guesses of probability of DLT at each dose level.

The recommended dose for the next cohort will be made using the CRM, taking into account all the previous data observed in the first stage. This would be the dose with estimated DLT probability closest to the target of 25%. Subsequent cohorts will be assigned a dose level in the same way using all previous data observed until maximum sample size is reached.

<table>
<thead>
<tr>
<th>Dose Level</th>
<th>Romidepsin dose (days 1, 8, 15)</th>
<th>Carfilzomib dose (days 1, 2, 8, 9, 15, 16)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>8mg/m$^2$</td>
<td>20/36mg/m$^2$</td>
</tr>
<tr>
<td>Starting Dose</td>
<td>10mg/m$^2$</td>
<td>20/36mg/m$^2$</td>
</tr>
<tr>
<td>3</td>
<td>10mg/m$^2$</td>
<td>20/45mg/m$^2$</td>
</tr>
</tbody>
</table>
Restrictions will apply to avoid skipping doses in escalation, as well as to ensure no escalation immediately if observed toxicity at the current dose level is greater than the target toxicity level. A “look ahead” strategy will be implemented if the next recommended dose level by the CRM model is the same regardless of the outcome of the remaining patient(s) in the current cohort (DLT or no DLT). If that occurs, the next cohort will be opened. By implementing this strategy, the next cohort of patients can be recruited immediately before observing all the patients’ outcomes in the current cohort (whenever such a scenario occurs). This has the advantage of reducing waiting time between cohorts.

We plan to accrue 27 patients for Phase I. However, to ensure that MTD is adequately assigned, an extension criterion could be considered by the data monitoring committee. This would extend enrolment of the CRM beyond the fixed sample size by 3 patients if the number of subjects at the recommended MTD (after 9 cohorts) is less than 6. The MTD is then determined as the combination dose with estimated DLT closest to target DLT of 25%.

Criteria for Termination of the Trial
A further modification to the CRM to allow for early termination of the trial is if there is a high probability that the posterior probability of DLT at the lowest dose is much greater than the target DLT rate, indicating that the lowest dose is too toxic. If the model recommends early stopping due to this safety criteria, the Trial Management Group and Trial Steering Committee will be alerted and the latter, with support of any external evidence, will recommend if the trial should be stopped.

Details of the operating characteristics for the proposed CRM design described above will be made available in the RomiCar Statistical Analysis Plan.

### 12.2 Definition of Outcome Measures

#### Primary Outcome Measures

**Phase I**
- The MTD will be determined by the doses at which 25% of patients are expected to experience a dose limiting toxicity (as defined in section 2) over the first cycle of treatment

**Phase II**
- Best overall response rate during the first 8 cycles of treatment at the MTD will be assessed using contrast-enhanced CT scans of the neck, chest, abdomen and pelvis, using the Revised Response Criteria for Malignant Lymphoma (Cheson, 2007 [1])

#### Secondary Outcome Measures

**Phase I and II**
- Toxicity will be assessed using CTCAE v4.0
- Best Overall Response post 8 cycles of treatment until the end of trial assessed using the Revised Response Criteria for Malignant Lymphoma [1]
- Maximum % change in the radiological Sum of the Product of the Diameters (SPD) will be assessed using the Revised Response Criteria for Malignant Lymphoma [1]
- Duration of response is defined as the time from first documented response until relapse/progression, as determined by the Revised Response Criteria [1], or date of last follow up if relapse/progression free. Patients who die before a relapse/progression will be censored at their date of death.
Progression free survival is defined as the time from date of registration to the date of disease progression or date of death from any cause. Patients not reaching progression or death at the time of analysis will be censored at the last date they were known to be alive and progression free. Patients will be followed up for a minimum of 12 months.

Overall survival time is defined as the time from date of registration to the date of death from any cause. Patients discontinuing the study, lost to follow-up or still alive at the end of the study will be censored at the date of last follow-up. Patients will be followed up for a minimum of 12 months.

12.3 Analysis of Outcome Measures
Descriptive statistics will be reported for each dose level as described below.

Phase I
- The MTD, which is the dose level that is closest to the level at which 25% of patients experience a dose limiting toxicity, will be reported with its associated probability of DLT and 90% probability interval.

Phase II
- Best response will be reported as the number and proportion of patients in each response category, and overall, during the first 8 cycles of treatment. In addition, best response observed after 8 cycles until the end of the trial will be reported by category and overall.
- The mean maximum % change during the first 8 cycles of treatment and overall will be reported with 95% confidence intervals.
- The number and proportion of patients experiencing toxicity, including haematological and non-haematological toxicity, will be reported with 95% confidence intervals.
- Time to event outcomes will be assessed using the method of Kaplan and Meier with point estimates presented at 6, 12, 24 and 36 months with 95% confidence intervals along with median survival time and confidence intervals.

The biomarker study at present is exploratory. There is little data on the expression of HR23B in PTCL so the aim is to define expression in biopsy samples taken at relapse using a previously validated scoring system. We will then seek to determine a cut off which best predicts response to the drug combination. The intention is to take this forward in a subsequent phase II/III study. Appropriate statistical models (e.g. area under the curve, logistic regression) will be used to determine the cut off as detailed in the Statistical Analysis Plan.

12.4 Planned Sub Group Analyses
Toxicity and overall response outcomes will be compared in the top 3 most common PCTL subtypes: PTCL-NOS, AITL and ALCL. This analysis would be conducted at the end of phase II and would be considered exploratory due to the lack of statistical power for subgroup analyses in this early phase trial.

12.5 Planned Interim Analysis
For the phase II component, accumulating data and analyses will be monitored regularly by the TSC with an independent chair (see section 13.4).

12.6 Planned Final Analyses
For the phase I component, final analysis will be performed to determine the MTD and 90% probability interval when the maximum sample size is reached.

For the phase II component, the first main analysis of the primary outcome measure will be performed after all patients have been treated and followed up for 8 months (8 cycles). Subsequent analyses of all outcome measures will be performed after a minimum of 12 months follow up of all patients.
12.7 Power Calculations

Phase I
Up to 27 + possible 3 additional patients at the MTD for phase I to ensure sufficient patients are treated at the determined MTD

Phase II
Total sample size: 28
Patients allocated to the MTD in phase I will be included in the phase II component hence further recruitment to reach the target sample size in phase II will depend on the number of patients treated at the MTD in phase I.

The sample size calculation is based on A’Hern’s single stage phase II design [35]. Complete clinical response to romidepsin alone in this patient group is in the region of 30%. An overall response rate of 50% on the combination therapy of romidepsin and carfilzomib is defined as the minimum clinically acceptable level to warrant further evaluation of this combined therapy. Thus, with exact type I and II error rates of α=0.103, β=0.172, and π₀=0.3, π₁=0.5, we would need to observe at least 12 patients who achieve at least a PR out of a total of 28 patients in order to conclude the treatment is effective and worthy of further evaluation.

A maximum of 58 patients are required for both phase I and II.
PASS 2008 was used for the phase II power calculation above.

13. TRIAL ORGANISATIONAL STRUCTURE

13.1 Sponsor
The trial is sponsored by the University of Birmingham.

13.2 Coordinating Centre
The trial is being conducted under the auspices of the Cancer Research UK Clinical Trials Unit (CRCTU), University of Birmingham according to their local procedures.

13.3 Trial Management Group
A Trial Management Group (TMG) will be established and will include the Chief Investigator, Co-Investigators, Statisticians and Coordinators. Key trial personnel will be invited to join the TMG as appropriate to ensure representation from a range of professional groups.
Notwithstanding the legal obligations of the Sponsor and Chief Investigator, the TMG will be responsible for the day-to-day running and management of the trial and will meet by teleconference or in-person as required.

13.4 Trial Steering Committee
A Trial Steering Committee (TSC), with an independent chair, will provide overall supervision for the trial and provide advice through its independent chair. The ultimate decision for the continuation of the trial lies with the TSC. The TSC will meet at the end of each treatment cohort if there is at least 1 occurrence of suspected DLT, to assess DLTs, or more often if required. If the trial continues to phase II, the TSC will meet 6 months after the phase II component has opened and annually thereafter to monitor all safety and primary activity data.

13.5 Finance
This is a clinician-initiated and clinician-led trial funded by the Leukaemia and Lymphoma Research Trials Acceleration Programme (TAP). Romidepsin is being provided free of charge by Celgene in addition to an educational grant. Carfilzomib is being provided free of charge by Onyx in addition to an educational grant.
No individual per patient payment will be made to NHS Trusts, Investigators or patients.
This trial is also included in the NIHR CRN portfolio, reference 136755.
This project is supported by the facilities funded through Birmingham Science City: Translational Medicine Clinical Research Infrastructure and Trials Platform, an Advantage West Midlands (AWM) funded project which forms part of the Science City University of Warwick and University of Birmingham Research Alliance.
14. ETHICAL CONSIDERATIONS

The trial will be performed in accordance with the recommendations guiding physicians in biomedical research involving human subjects, adopted by the 18th World Medical Association General Assembly, Helsinki, Finland, June 1964, amended at the 48th World Medical Association General Assembly, Somerset West, Republic of South Africa, October 1996 (website: http://www.wma.net/en/30publications/10policies/b3/index.html).

The trial will be conducted in accordance with the Research Governance Framework for Health and Social Care, the applicable UK Statutory Instruments, (which include the Medicines for Human Use Clinical Trials 2004 and subsequent amendments and the Data Protection Act 1998 and Human Tissue Act 2008) and the Guidelines for Good Clinical Practice (GCP). This trial will be carried out under a Clinical Trial Authorisation in accordance with the Medicines for Human Use Clinical Trials regulations. The protocol will be submitted to and approved by the main Research Ethics Committee (REC) prior to circulation.

Before any patients are enrolled into the trial, the Principal Investigator at each site is required to obtain local R&D approval. Sites will not be permitted to enrol patients until written confirmation of R&D approval is received by the Trials Office.

It is the responsibility of the Principal Investigator to ensure that all subsequent amendments gain the necessary local approval. This does not affect the individual clinicians’ responsibility to take immediate action if thought necessary to protect the health and interest of individual patients.

15. CONFIDENTIALITY AND DATA PROTECTION

Personal data recorded on all documents will be regarded as strictly confidential and will be handled and stored in accordance with the Data Protection Act 1998. Patients will be identified using only their unique trial number, initials and date of birth on the Case Report Form and correspondence between the Trials Office and the participating site. However patients are asked to give permission for the Trials Office to be sent a copy of their signed Informed Consent Form which will not be anonymised. This will be used to perform in-house monitoring of the consent process.

The Investigator must maintain documents not for submission to the Trials Office (e.g. Patient Identification Logs) in strict confidence. In the case of specific issues and/or queries from the regulatory authorities, it will be necessary to have access to the complete trial records, provided that patient confidentiality is protected.

The Trials Office will maintain the confidentiality of all patient’s data and will not disclose information by which patients may be identified to any third party other than those directly involved in the treatment of the patient and organisations for which the patient has given explicit consent for data transfer. Representatives of the RomiCar trial team may be required to have access to patient’s notes for quality assurance purposes but patients should be reassured that their confidentiality will be respected at all times.

16. INSURANCE AND INDEMNITY

University of Birmingham employees are indemnified by the University insurers for negligent harm caused by the design or co-ordination of the clinical trials they undertake whilst in the University’s employment.

In terms of liability at a site, NHS Trust and non-Trust hospitals have a duty to care for patients treated, whether or not the patient is taking part in a clinical trial. Compensation is therefore available via NHS indemnity in the event of clinical negligence having been proven.

The University of Birmingham cannot offer indemnity for non-negligent harm. The University of Birmingham is independent of any pharmaceutical company, and as such it is not covered by the Association of the British Pharmaceutical Industry (ABPI) guidelines for patient compensation.

17. PUBLICATION POLICY

Results of this trial will be submitted for publication in a peer reviewed journal. The manuscript will be prepared by the Trial Management Group (TMG) and authorship will be determined by mutual agreement.

Any secondary publications and presentations prepared by Investigators must be reviewed by the TMG. Manuscripts must be submitted to the TMG in a timely fashion and in advance of being submitted for publication, to allow time for review and resolution of any outstanding issues. Authors
must acknowledge that the trial was performed with the support of University of Birmingham. Intellectual property rights will be addressed in the clinical trial agreement between Sponsor and site.
18. REFERENCE LIST


30. Papadopoulos, K.P., et al., A Phase 1b/2 Study of Prolonged Infusion Carfilzomib in Patients with Relapsed and/or Refractory (R/R) Multiple Myeloma: Updated Efficacy and Tolerability From the Completed 20/56mg/m2 Expansion Cohort of PX-171-007. ASH Annual Meeting Abstracts, 2011. 118(21): p. 2930-.


APPENDIX 1 – REVISED RESPONSE CRITERIA FOR MALIGNANT LYMPHOMA [1]

<table>
<thead>
<tr>
<th>Response Category</th>
<th>Lymph Node Masses</th>
<th>Spleen and Liver</th>
<th>Bone Marrow</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>Normal*</td>
<td>Not palpable, nodules disappeared</td>
<td>Normal or if indeterminate** by morphology, negative on immunohistochemistry</td>
</tr>
<tr>
<td>PR</td>
<td>Normal*</td>
<td></td>
<td>Persistent morphological bone marrow involvement</td>
</tr>
<tr>
<td></td>
<td>≥ 50% decrease in SPD of up to 6 largest dominant masses***, no increase in other lesions</td>
<td>No increase in size of liver or spleen; ≥ 50% decrease in SPD of nodules</td>
<td>Irrelevant</td>
</tr>
<tr>
<td>SD</td>
<td>No change in size of previous lesions on CT</td>
<td>No increase in liver / spleen</td>
<td></td>
</tr>
<tr>
<td>Relapse/progression</td>
<td>New or increased****</td>
<td>&gt; 50% increase from nadir in SPD of any previous lesions</td>
<td>New or recurrent involvement</td>
</tr>
</tbody>
</table>

* ≤ 1.5 cm in their greatest transverse diameter for nodes >1.5 cm before therapy. Previously involved nodes that were 1.1 to 1.5 cm in their greatest transverse diameter and > 1.0 cm in the short axis before treatment must have decreased to ≤1 cm in their short axis after treatment.

**Indeterminate bone marrow (increased number or size of aggregates without cytologic or architectural atypia).

***Select diameters of up to six of the largest dominant nodes or nodal masses. These nodes or masses should be selected according to all of the following: they should be clearly measurable in at least 2 perpendicular dimensions; if possible they should be from disparate regions of the body; and they should include mediastinal and retroperitoneal areas of disease whenever these sites are involved.

****Appearance of a new lesion(s) > 1.5 cm in any axis; ≥ 50% increase in SPD of more than one node, or ≥ 50% increase in longest diameter of a previously identified node > 1 cm in short axis.
APPENDIX 2 - WMA DECLARATION OF HELSINKI

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI

Recommendations guiding physicians in biomedical research involving human subjects
Adopted by the 18th World Medical Assembly
Helsinki, Finland, June 1964
and amended by the
29th World Medical Assembly, Tokyo, Japan, October 1975
35th World Medical Assembly, Venice, Italy, October 1983
41st World Medical Assembly, Hong Kong, September 1989
and the
48th General Assembly, Somerset West, Republic of South Africa, October 1996

INTRODUCTION

It is the mission of the physician to safeguard the health of the people. His or her knowledge and conscience are dedicated to the fulfillment of this mission.
The Declaration of Geneva of the World Medical Association binds the physician with the words, "The Health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."
The purpose of biomedical research involving human subjects must be to improve diagnostic, therapeutic and prophylactic procedures and the understanding of the aetiology and pathogenesis of disease.
In current medical practice most diagnostic, therapeutic or prophylactic procedures involve hazards. This applies especially to biomedical research.
Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.
In the field of biomedical research a fundamental distinction must be recognized between medical research in which the aim is essentially diagnostic or therapeutic for a patient, and medical research, the essential object of which is purely scientific and without implying direct diagnostic or therapeutic value to the person subjected to the research.
Special caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.
Because it is essential that the results of laboratory experiments be applied to human beings to further scientific knowledge and to help suffering humanity, the World Medical Association has prepared the following recommendations as a guide to every physician in biomedical research involving human subjects. They should be kept under review in the future. It must be stressed that the standards as drafted are only a guide to physicians all over the world. Physicians are not relieved from criminal, civil and ethical responsibilities under the laws of their own countries.

I. BASIC PRINCIPLES

Biomedical research involving human subjects must conform to generally accepted scientific principles and should be based on adequately performed laboratory and animal experimentation and on a thorough knowledge of the scientific literature.

1. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol which should be transmitted for consideration, comment and guidance to a specially appointed committee independent of the investigator and the
sponsoring party provided that this independent committee is in conformity with the laws and regulations of the country in which the research experiment is performed.

1. Biomedical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given his or her consent.

2. Biomedical research involving human subjects cannot legitimately be carried out unless the importance of the objective is in proportion to the inherent risk to the subject.

3. Every biomedical research project involving human subjects should be preceded by careful assessment of predictable risks in comparison with foreseeable benefits to the subject or to others. Concern for the interests of the subject must always prevail over the interests of science and society.

4. The right of the research subject to safeguard his or her integrity must always be respected. Every precaution should be taken to respect the privacy of the subject and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.

5. Physicians should abstain from engaging in research projects involving human subjects unless they are satisfied that the hazards involved are believed to be predictable. Physicians should cease any investigation if the hazards are found to outweigh the potential benefits.

6. In publication of the results of his or her research, the physician is obliged to preserve the accuracy of the results. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

7. In any research on human beings, each potential subject must be adequately informed of the aims, methods, anticipated benefits and potential hazards of the study and the discomfort it may entail. He or she should be informed that he or she is at liberty to abstain from participation in the study and that he or she is free to withdraw his or her consent to participation at any time. The physician should then obtain the subject's freely-given informed consent, preferably in writing.

8. When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship to him or her or may consent under duress. In that case the informed consent should be obtained by a physician who is not engaged in the investigation and who is completely independent of this official relationship.

9. In case of legal incompetence, informed consent should be obtained from the legal guardian in accordance with national legislation. Where physical or mental incapacity makes it impossible to obtain informed consent, or when the subject is a minor, permission from the responsible relative replaces that of the subject in accordance with national legislation. Whenever the minor child is in fact able to give a consent, the minor's consent must be obtained in addition to the consent of the minor's legal guardian.

10. The research protocol should always contain a statement of the ethical considerations involved and should indicate that the principles enunciated in the present Declaration are complied with.

II. MEDICAL RESEARCH COMBINED WITH PROFESSIONAL CARE

(Clinical Research)

1. In the treatment of the sick person, the physician must be free to use a new diagnostic and therapeutic measure, if in his or her judgement it offers hope of saving life, reestablishing health or alleviating suffering.
2. The potential benefits, hazards and discomfort of a new method should be weighed against the advantages of the best current diagnostic and therapeutic methods.

3. In any medical study, every patient - including those of a control group, if any - should be assured of the best proven diagnostic and therapeutic method. This does not exclude the use of inert placebo in studies where no proven diagnostic or therapeutic method exists.

4. The refusal of the patient to participate in a study must never interfere with the physician-patient relationship.

5. If the physician considers it essential not to obtain informed consent, the specific reasons for this proposal should be stated in the experimental protocol for transmission to the independent committee (I, 2).

6. The physician can combine medical research with professional care, the objective being the acquisition of new medical knowledge, only to the extent that medical research is justified by its potential diagnostic or therapeutic value for the patient.

III. NON-THERAPEUTIC BIOMEDICAL RESEARCH INVOLVING HUMAN SUBJECTS (Non-Clinical Biomedical Research)

7. In the purely scientific application of medical research carried out on a human being, it is the duty of the physician to remain the protector of the life and health of that person on whom biomedical research is being carried out.

8. The subject should be volunteers - either healthy persons or patients for whom the experimental design is not related to the patient's illness.

9. The investigator or the investigating team should discontinue the research if in his/her or their judgement it may, if continued, be harmful to the individual.

10. In research on man, the interest of science and society should never take precedence over considerations related to the wellbeing of the subject.
APPENDIX 3 - DEFINITION OF ADVERSE EVENTS

Adverse Event
Any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment.

Comment:
An AE can therefore be any unfavourable and unintended sign (including clinically significant abnormal laboratory findings of full blood count and LFTs, ALP, eGFR, urea, uric acid, creatinine, potassium, sodium, magnesium and calcium), symptom or disease temporally associated with the use of an investigational medicinal product, whether or not related to the investigational medicinal product.

Adverse Reaction
All untoward and unintended responses to an IMP related to any dose administered.

Comment:
An AE judged by either the reporting Investigator or Sponsor as having causal relationship to the IMP qualifies as an AR. The expression reasonable causal relationship means to convey in general that there is evidence or argument to suggest a causal relationship.

Serious Adverse Event
Any untoward medical occurrence or effect that at any dose:
- Results in death unrelated to original cancer
- Is life-threatening*
- Requires hospitalisation** or prolongation of existing inpatients' hospitalisation
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly/birth defect
- Or is otherwise considered medically significant by the Investigator***

Comments:
The term severe is often used to describe the intensity (severity) of a specific event. This is not the same as serious, which is based on patients/event outcome or action criteria.
* Life threatening in the definition of an SAE refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.
**Hospitalisation is defined as an unplanned, formal inpatient admission, even if the hospitalisation is a precautionary measure for continued observation. Thus hospitalisation for protocol treatment (e.g. line insertion), elective procedures (unless brought forward because of worsening symptoms) or for social reasons (e.g. respite care) are not regarded as an SAE.
*** Medical judgment should be exercised in deciding whether an AE is serious in other situations. Important AEs that are not immediately life threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above, should be considered serious.

Serious Adverse Reaction
An Adverse Reaction which also meets the definition of a Serious Adverse Event.

Suspected Unexpected Serious Adverse Reaction
A SAR that is unexpected i.e. the nature, or severity of the event is not consistent with the applicable product information.
A SUSAR should meet the definition of an AR, UAR and SAR.
Unexpected Adverse Reaction

An AR, the nature or severity of which is not consistent with the applicable product information (e.g. Investigator Brochure for an unapproved IMP or (compendium of) Summary of Product Characteristics (SPC) for a licensed product).

When the outcome of an AR is not consistent with the applicable product information the AR should be considered unexpected.
APPENDIX 4 - COMMON TOXICITY CRITERIA GRADINGS

Toxicities will be recorded according to the Common Terminology Criteria for Adverse Events (CTCAE), version 4.0. The full CTCAE document is available on the National Cancer Institute (NCI) website, the following address was correct when this version of the protocol was approved:

## APPENDIX 5 – ECOG PERFORMANCE STATUS SCALE

<table>
<thead>
<tr>
<th>ECOG Status</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Asymptomatic, fully active and able to carry on all predisease performance without restrictions.</td>
</tr>
<tr>
<td>1</td>
<td>Symptomatic, fully ambulatory but restricted in physically strenuous activity and able to carry out performance of a light or sedentary nature, e.g., light housework, office work.</td>
</tr>
<tr>
<td>2</td>
<td>Symptomatic, ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours: in bed less than 50% of day.</td>
</tr>
<tr>
<td>3</td>
<td>Symptomatic, capable of only limited self-care, confined to bed or chair more than 50% of waking hours but not bedridden.</td>
</tr>
<tr>
<td>4</td>
<td>Completely disabled. Cannot carry on any self-care. Totally bedridden.</td>
</tr>
<tr>
<td>5</td>
<td>Dead</td>
</tr>
</tbody>
</table>

References:
APPENDIX 6 - PROHIBITED CONCOMITANT MEDICATION

Therapies that significantly prolong the QTc interval

An exhaustive list can be found at [https://www.crediblemeds.org](https://www.crediblemeds.org)

Commonly used drugs which should be avoided are:

- Clarithromycin
- Erythromycin
- Chloroquine
- Pentamidine
- Domperidone
- Haloperidol
- Chlorpromazine
- methadone

Moderate/significant inhibitors of CYP3A4

An exhaustive list can be obtained at [http://medicine.iupui.edu/flockhart/](http://medicine.iupui.edu/flockhart/) (at the time of writing this protocol)

- Clarithromycin
- Itraconazole
- Ketoconazole
- Nefazodone
- Telithromycin
- Atazanavir
- Indinavir
- Ritonavir
- Cobicistat
- Troleandomycin
- Saquinavir
- Voriconazole
- Mibefradil
- Lopinavir
- Elvitegravir
- Posaconazole
- Nelfinavir
- Nelfazodone
- Grapefruit juice (240ml double-strength administered TID for 3 days)
Monitoring for, and correcting hypokalaemia and hypomagnesaemia is important as low levels may increase the risk of arrhythmias when romidepsin is administered.

Romidepsin should NOT be given if:

- Potassium < 3.8 mmol/L
- Magnesium < 0.85 mmol/L

1. Potassium. Supplementation should be in accordance with local policies. There are 2 main ways to correct low potassium levels:

- Parenteral. This is recommended if a patient has had their treatment delayed due to low levels.
  a. 40mmol of potassium in 1000ml normal saline is suggested, over 2-4 hours. This can be via a peripheral cannula. Pre-mixed potassium-containing solutions are preferred, for safety reasons.
  b. In patients in whom less fluid is required, higher concentrations maybe used although some trusts require specific prescriptions before dispensing this (ECG monitoring may be required in some patients and administration through a large peripheral vein is recommended for higher concentrations).
  c. To prevent this from happening again, consider treating the underlying cause (e.g. stopping, or changing, a potassium-wasting drug) and / or starting the patient on regular oral supplements.

- Enteral. This is recommended if a patient has potassium of < 4.0 mmol/L and is therefore nearing the level at which romidepsin would have to be delayed. It should also be considered in patients who have needed prior parenteral replacement.
  a. Consider potassium effervescent tablets (Sando-K®) or potassium chloride solution (K-Cee-L®). These should be given with a full glass of water, preferably with or after food. Administration may be 1-2 times per day.
  b. For patients intolerant of the above, consideration maybe given to potassium chloride MR (slow-K®). This may however cause oesophageal erosion or GI ulceration and should be swallowed whole with a whole glass of water in the sitting or standing position.

2. Magnesium. Supplementation should be in accordance with local policies. Again, replacement can be enteral or parenteral.

- Parenteral. This is recommended if a patient has had their treatment delayed due to low levels.
  a) 10-20 mmol (2.5-5g) magnesium sulphate in 500ml of 5% glucose or normal saline intravenous. The rate should not exceed 4mmol per hour as renal excretion increases above this.
  b) Note – care must be taken in patients with renal impairment, and doses should be reduced.

- Enteral. This is recommended if a patient has magnesium of < 1.0 mmol/L and is therefore nearing the level at which romidepsin would have to be delayed. It should also be considered in patients who have needed prior parenteral replacement.
  a) A dose of 8 mmol magnesium sulphate, three times per day (24 mmol per day) is suggested.
  b) Alternatively, magnesium glycerophosphate tablets (2 tablets three times per day = 24mmol per day) maybe used although this is unlicensed.
  c) Note – care must be taken in patients with renal impairment.
In addition to the required measurements of potassium and magnesium, centres may wish to monitor levels more closely (for example 1-2 times weekly) in patients who are requiring replacement.

Romidepsin may be administered as soon as the levels are within the range specified i.e.

Potassium: ≥ 3.8 mmol/L
Magnesium: ≥ 0.85 mmol/L
APPENDIX 8 – NYHA FUNCTIONAL CLASSIFICATION

Doctors usually classify patients' heart failure according to the severity of their symptoms. The table below describes the most commonly used classification system, the New York Heart Association (NYHA) Functional Classification. It places patients in one of four categories based on how much they are limited during physical activity.

<table>
<thead>
<tr>
<th>Class</th>
<th>Functional Capacity: How a patient with cardiac disease feels during physical activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Patients with cardiac disease but resulting in no limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea or anginal pain.</td>
</tr>
<tr>
<td>II</td>
<td>Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea or anginal pain.</td>
</tr>
<tr>
<td>III</td>
<td>Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea or anginal pain.</td>
</tr>
<tr>
<td>IV</td>
<td>Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort increases.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Class</th>
<th>Objective Assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>No objective evidence of cardiovascular disease. No symptoms and no limitation in ordinary physical activity.</td>
</tr>
<tr>
<td>C</td>
<td>Objective evidence of moderately severe cardiovascular disease. Marked limitation in activity due to symptoms, even during less-than-ordinary activity. Comfortable only at rest.</td>
</tr>
<tr>
<td>D</td>
<td>Objective evidence of severe cardiovascular disease. Severe limitations. Experiences symptoms even while at rest.</td>
</tr>
</tbody>
</table>