*(Form to be on hospital/institution headed paper)*

**PATIENT INFORMATION SHEET**

**CARDAMON: Carfilzomib/Cyclophosphamide/Dexamethasone with maintenance carfilzomib in untreated transplant-eligible patients with symptomatic MM to evaluate the benefit of upfront ASCT**

We would like to invite you to take part in a trial. Before you decide whether or not to take part, one of your trial doctor’s team will go through this patient information sheet with you and answer any questions you may have so that you fully understand why we are running the trial and what it would involve for you.

Please take the time to read the information carefully and talk to others about the trial if you wish. Ask us if there is anything you don’t understand or if you would like more information and take your time to decide whether or not you wish to take part.

This patient information sheet has 2 parts:

PART 1 will explain the purpose of the trial and what will happen to you if you decide to take part.

PART 2 gives you more detailed information about how the trial will be run.

# PART 1

## **What is the purpose of the trial?**

Multiple Myeloma is a cancer of the bone marrow that is treatable, but not usually curable. In routine practice, patients who are young and fit enough are treated with chemotherapy (sometimes called induction chemotherapy) for around 6 months. Patients who respond to induction chemotherapy with at least a partial response (defined as 50% reduction in the myeloma protein, called a paraprotein), may proceed to a stem cell transplant using the patient’s own stem cells (Autologous Stem Cell Transplant). This is the treatment you would receive if you were not in this clinical trial.

Autologous Stem Cell Transplant (or stem cell transplant) is used after initial chemotherapy treatment because it was shown in studies carried out 15-20 years ago to increase remission time, and overall survival. Those studies were all done using induction treatment combinations, known as regimens, which are no longer used today, because we have new and more effective regimens containing new drugs to treat patients with newly diagnosed myeloma. Patients treated with these new regimens are able to achieve better responses than was previously possible with older traditional regimens, and many also achieve a complete response (complete disappearance of the myeloma paraprotein).

The purpose of this clinical trial is to find out if patients who are treated on these new regimens will benefit from proceeding straight onto a stem cell transplant. It is possible that patients who respond to a new drug containing regimen will obtain most benefit from their stem cells if these stem cells are frozen and stored, so that they can be used at a later date when their disease relapses.

## **How will patients be treated on the trial?**

Patients will be treated with a new induction regimen containing Carfilzomib, combined with 2 standard drugs, Cyclophosphamide and Dexamethasone. After completing induction chemotherapy, provided they have responded, patients will have their stem cells harvested. Patients will then be randomly allocated to receive either a stem cell transplant, using their own cells, or consolidation therapy (4 more cycles of chemotherapy similar to the induction regimen). We will compare the outcome of patients who receive a transplant versus those patients who instead receive consolidation therapy.

After patients have completed either the consolidation treatment or stem cell transplant they will also be given maintenance treatment for 18 months. The aim of maintenance treatment is to prolong the period of remission, and delay the time to relapse.

## **What is Carfilzomib?**

Carfilzomib is a drug that is licensed in the UK for patients with advanced multiple myeloma, and is approved by the National Institute for Health and Care Excellence (NICE) in these patients only. It is not currently available to newly diagnosed patients in the UK, other than to those participating in a clinical trial. In a clinical trials setting, carfilzomib has been used to treat more than 9000 myeloma patients world-wide with both relapsed and newly diagnosed myeloma. Carfilzomib is similar to another drug called bortezomib which is used frequently to treat myeloma. If you do not take part in this clinical trial, you are likely to receive treatment with a bortezomib regimen. Both bortezomib and carfilzomib work by preventing breakdown of abnormal proteins in cancer cells, causing the cells to die. Carfilzomib is structurally different from bortezomib and it has only rarely been reported to be associated with the side effect of peripheral neuropathy (pins & needles/numbness in extremities) which patients have experienced during bortezomib treatment, and which can be uncomfortable and painful.

Several studies using Carfilzomib in relapsed patients have shown that it is an effective treatment, and more patients achieve better and longer responses than with current available treatments. Carfilzomib has also been used to treat newly diagnosed patients, where it has been reported to be well tolerated, and with no associated neuropathy. In the UK, Carfilzomib has recently been included as a treatment arm on the national Myeloma XI trial for newly diagnosed myeloma patients, and Carfilzomib is also being used in clinical trials in patients with relapsed myeloma.

## **What else is new in this trial?**

When patients have recovered from their stem cell transplant, or have completed consolidation with chemotherapy, they will receive maintenance therapy with Carfilzomib, given on its own. Maintenance therapy has been studied in clinical trials, but is not licensed in the UK and hence not available outside a clinical trial.

In summary, the purpose of the CARDAMON trial is:

* to confirm the benefit and safety of a new treatment regimen that includes Carfilzomib plus two standard chemotherapy drugs used for the treatment of Multiple Myeloma,
* to investigate whether patients responding to this new Carfilzomib-containing induction regimen are able to maintain a long remission period without having an Autologous Stem Cell Transplant ‘up-front’, and
* to find out how maintenance therapy with Carfilzomib can improve disease response

## **Why have I been invited?**

You have been diagnosed with Multiple Myeloma and your trial doctor thinks you may be suitable for an Autologous Stem Cell Transplant but you have not yet had any treatment for this disease.

As in all clinical trials you can participate only if your illness makes you suitable for inclusion in this trial, if so, your trial doctor will discuss this with you. Your trial doctor will take into account your disease and general health in deciding whether you will be able to take part.

Patients from hospitals all over the UK will take part in the trial. We expect about 280 patients will be included in the trial.

## **Do I have to take part?**

No. It is up to you to decide whether or not to take part in the trial. We will describe what would be involved and go through this patient information sheet with you, which is yours to take away so that you have the opportunity to read it carefully and discuss the trial with others if you wish.

## **What will happen to me if I take part?**

### A description of what will happen and a flowchart of the trial visits is given below.

#### Consent & Eligibility Tests

If you decide you would like to take part in the CARDAMON trial, we will ask you to sign a consent form. You are free to withdraw at any time, without giving a reason. If you decide not to take part, or later to withdraw, this will not affect the standard of care you receive.

You will undergo some medical tests to see if you are suitable for the trial treatment. Most of these will be the same as the tests you would undergo at this stage of your disease whether or not you were thinking about entering a trial. You will also be asked to complete a Quality of Life questionnaire, which will ask you about your health and wellbeing. This will take around 15 minutes to complete. Please complete the questionnaire as honestly as possible and hand them to your research nurse or trial doctor.

If the tests show you are eligible for the trial your details will be registered with the trials centre who are coordinating the trial, “Cancer Research UK & UCL Cancer Trials Centre” (hereafter referred to as UCL CTC).

#### Treatment with Carfilzomib, Cyclophosphamide and Dexamethasone (CarCyDex)

You will then start induction treatment with CarCyDex, which is given in cycles that are repeated every 28 days (or 4 weeks). You will receive 4 cycles of CarCyDex, according to the schedule below.

* Carfilzomib given as a 30 minute infusion into your vein (intravenous infusion) on days 1, 2, 8, 9, 15 and 16 of each cycle
* Cyclophosphamide as oral (by mouth) tablets once a week on days 1, 8 and 15
* Dexamethasone as oral tablets on days 1, 8, 15 and 22.

You will be given dexamethasone tablets to take at home on Day 22; these are for the next cycle. You may be given cyclophosphamide tablets to take while in clinic or to take at home. This will depend on what hospital you are treated at.

Sometimes your blood test results may show that taking a drug would not be in your best interests. If your trial doctor or nurse contacts you and tells you not to take a particular dose please do as instructed and return the drug at your next visit.

#### Response assessment & Stem Cell Collection

Following completion of 4 cycles of CarCyDex, all patients will have a response assessment. This will involve a number of medical tests to assess how well you have responded to the treatment.

If you have not responded well enough to the first 4 cycles of treatment you will not receive any more trial treatment. Your trial doctor will discuss further treatment with you but this treatment will not be part of the trial. You may be able to have a stem cell transplant after further treatment. We would like to continue to collect information about how you are doing and any subsequent treatment following your involvement in the trial, and this information will be collected every 2-3 months for the first year and then every 6 months until 10 years after the end of your induction treatment. This follow up will not include any additional visits or tests to those you would have as part of your routine care outside the trial.

If you have responded well enough to the first 4 cycles of CarCyDex you will undergo stem cell collection (usually within 4 – 8 weeks after your induction treatment).

Stem cell collection will involve being given a standard chemotherapy drug called cyclophosphamide. Cyclophosphamide makes the bone marrow produce stem cells. Cyclophosphamide is given through a Hickman line (a fine silicone tube (catheter), which is inserted under local anaesthetic into a vein in the neck or chest using ultrasound and x-ray as guidance) or a PICC line (a long, thin, flexible tube inserted into one of the large veins of the arm near the bend of the elbow under local anaesthetic; using x-ray and ultrasound as guidance).

After this, you may be kept in hospital overnight to be given extra fluids via a drip (i.e. through a needle into a vein).

To prepare for the collection of stem cells, you will have daily injections of a growth factor (G-CSF) under the skin (in the arm, leg or stomach), for about a week to 10 days. G-CSF makes the bone marrow produce stem cells and will increase the number of stem cells circulating in the blood. One of the site effects of G-CSF injections is bone and joint pain. We will give you advice about what to do if these pains become severe. You may take paracetamol for the pain but if the pain gets worse please go to your nearest A&E or call your research nurse. After the 10 days or so of daily G-CSF injections, the stem cell collection will begin.

The stem cell collection will be done as a day care procedure and will last several hours each day. You may need to go to the hospital for collections on 2 or 3 successive days. A major vein will be connected by a special tube to a machine that will take stem cells out of the blood and return the blood back to you. If enough stem cells cannot be collected, this procedure may be repeated using different drugs as recommended by your trial doctor. Approximately 10% of patients will fail to generate enough cells for transplant. If this happens you will not receive any more trial treatment and your trial doctor will advise you of the alternatives.

After your stem cell harvest you will also be asked to complete a Quality of Life questionnaire.

#### Randomisation to Transplant or Non-transplant Consolidation therapy

This trial is a ‘randomised trial’. We do randomised trials when there is more than one treatment option available for patients with a disease and we don’t know which one is best. In order to find out, we need to compare the different treatments. So we put people into groups and give each group a different treatment. The results from the different treatment groups are compared to see if one treatment is better. To try to make sure the groups are the same to start with, each patient is put into a group by chance (randomly). Therefore in this trial we will randomly allocate you to either the transplant or non-transplant (consolidation) arm. This allocation will be done by a computer, and neither you nor your trial doctor can choose which treatment you will receive.

All patients who have successfully collected stem cells will be randomised to proceed to a Stem Cell transplant, or to receive a further 4 cycles of CarCyDex.

##### Transplant arm

If you are allocated to the transplant arm, there will be two stages to the transplant.

First you will receive high dose chemotherapy. This will be a high dose of a chemotherapy drug called melphalan on a single day. You will also receive fluids and other drugs before, during and after the high dose chemotherapy, to lessen potential side effects of the melphalan. The high dose chemotherapy aims to kill the remaining myeloma cells in your body, but many of your normal bone marrow cells will also be killed. Once you have had this chemotherapy you will need to receive your previously collected stem cells in order to replenish your bone marrow and enable it to make new blood cells.

The second stage is the stem cell transplant.

The day after you receive the melphalan, you will be given your stem cells back into a vein, in a similar way to receiving a blood transfusion. This will take about 1-4 hours. The stem cells will find their way back into your bone marrow.

Following the transplant, you will be required to stay in hospital in ‘isolation’ for about 2 weeks, and then for a further 1-2 weeks for recovery. This is because your immune system will be weakened following the high dose chemotherapy, and it takes time for the stem cells to start making new blood cells. You may receive injections of a growth factor, G-CSF, to help this process if necessary. You will be monitored closely while in hospital, for infections and you may receive antibiotics to treat infections. You may receive blood and platelet transfusions.

Around three months (100 days) after your transplant, you will be asked to complete a Quality of Life questionnaire.

##### Non-Transplant Consolidation arm

If you are allocated to the consolidation (non-transplant) arm, you will receive 4 further cycles of CarCyDex. The schedule will be very similar to your first four cycles, but the dose of Dexamethasone will be lower.

* Carfilzomib given as a 30 minute infusion into your vein (intravenous infusion) on days 1, 2, 8, 9, 15 and 16 of each cycle
* Cyclophosphamide as oral (by mouth) tablets once a week on days 1, 8 and 15
* Dexamethasone as oral tablets on days 1, 8, 15 and 22.

After you finish consolidation chemotherapy, you will be asked to complete a Quality of Life questionnaire.

#### Disease Assessment and Maintenance therapy

All patients who successfully complete a Stem Cell Transplant, or the Non-Transplant Consolidation therapy will undergo a full disease assessment.

If the tests done as part of your disease assessment show you have responded well enough, within about 4 weeks of the consolidation treatment, or 3 – 4 months after the stem cell transplant, you will receive maintenance treatment. This is treatment to keep the myeloma under control following all other therapy.

The maintenance treatment will be one single drug, Carfilzomib, given on Days 1, 8 and 15 every 28 days for up to 18 months. You may stop your maintenance therapy before 18 months if you experience side effects, your trial doctor considers that it is not in your interest to continue, your disease relapses in the meantime, or if you decide to withdraw from the trial.

After you have completed 6 months of maintenance treatment you will be asked to complete a Quality of Life questionnaire.

##### Follow up assessments

After you complete treatment, you will be asked to attend for regular check-ups to monitor your progress and we will continue to collect information about your disease and any subsequent treatment. These visits will be every 2-3 months for the first year and then at every 6 months for up to 10 years (after completion of your induction treatment). This follow up will not include any additional visits or tests to those you are having as part of your ongoing care outside the trial.

## **Flowchart of the trial**

Informed consent

Registration

Start treatment

Receive 4 cycles of CarCyDex treatment

Test to determine disease response

Stem cell collection

Bone marrow test for Minimal Residual Disease (MRD)

If you have responded then you will be randomised to receive either:

4 more cycles of CarCyDex

Stem Cell Transplant

Test to determine your disease response

Maintenance treatment with Carfilzomib

Screening tests to confirm your eligibility

*Stage 1*

*About 2 weeks*

*Stage 2*

*About 4 months*

*Stage 3*

*4-6 weeks*

*Stage 4*

*4 months*

*Stage 5*

*18 months*

## **What tests will be done?**

During the diagnosis and treatment of your disease, your trial doctors will sometimes need to collect a sample of your bone marrow, your blood or your urine. Most of these samples of bone marrow, blood or urine would need to be collected whether you took part in the trial or not, however we will be collecting one extra bone marrow sample as part of this trial at 6 months after the start of your maintenance treatment.

We will carry out tests on your blood, urine and bone marrow for safety checks and to monitor your disease status. Most of these are routine tests that would be done whether or not you were part of the trial.

You will also have imaging such as an X-ray, MRI, CT scan or a PET-CT scan performed to see if your bones are affected by myeloma. The type of imaging performed will depend on which hospital you are being treated at, and you may need to have more than one scan. You may have another imaging scan after induction chemotherapy if your trial doctor feels it is necessary.

The tables below shows the assessments we will do and at which visits.

*During your treatment:*

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Assessment** | **Eligibility**  **Screening Tests** | **Induction and Consolidation Treatment** | | **End of Induction** | **After stem cell collection** |
| **Day 1 of each cycle** | **Days 2, 8, 9, 15 & 16** |
| Medical history and examination | X |  |  |  |  |
| Pregnancy testing | X | X |  |  |  |
| Blood sampling | X | X | X | X | X |
| 24 hr urine collection | X | X |  | X | X |
| Echocardiogram (or MUGA scan) | X |  |  | X |  |
| ECG | X |  |  | X |  |
| Bone marrow sampling | X |  |  |  | X |
| Imaging (X-ray/MRI/CT or PET-CT scan) | X |  |  | X |  |
| Quality of Life questionnaire | X |  |  |  | X |

*After you complete consolidation treatment or your stem cell transplant:*

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Assessment** | **Day 100 after transplant or at end of consolidation** | **Maintenance Treatment Cycles** | | **After 6 months of maintenance treatment** | **At time of relapse** |
| **Day 1** | **Days 8 & 15** |
| Pregnancy testing |  | X |  |  |  |
| Blood sampling | X | X | X |  |  |
| 24 hr urine collection | X | X |  |  |  |
| Bone marrow sampling | X |  |  | X | X |
| Quality of Life questionnaire | X |  |  | X |  |

## **What do these tests involve?**

Physical examination and medical history (before you start treatment): Your trial doctor will carry out a full physical examination to check for signs of myeloma, and to assess your general fitness to receive chemotherapy. They will also take a medical history for information about your general health, any relevant history including history of other cancers.

Blood sampling: we will take a small sample of your blood for a full blood count (FBC) and blood chemistries (including kidney and liver function tests) along with an assessment of the level of myeloma proteins in the blood. Before you start treatment, we will test your blood for the viruses HIV and Hepatitis B and C. If these tests are positive you won’t be able to take part in the trial. You will be referred to a specialist trial doctor to discuss your results and will be offered counselling.

Urine samples: we will ask you to collect your urine for 24 hours. You will be given a container to take home and asked to collect your urine over the following 24 hours. We will use this sample to assess the level of myeloma proteins in your urine.

Pregnancy test: this will only be done if you are a woman of child bearing potential and we will test for this in your blood and/or urine samples just before you start treatment in each cycle.

ECG (electrocardiogram) and Echocardiogram: these are to assess your heart function. A MUGA scan may be performed in place of an echocardiogram if routine at your hospital.

Imaging (X-ray/MRI/CT or PET-CT): this is to assess if your bones have been affected by myeloma. You will have the standard scans for a myeloma patient treated at your hospital.

Bone marrow sampling: A bone marrow biopsy is done to assess the myeloma cells in your bone marrow and also to carry out genetic tests for known genetic changes in the myeloma cells themselves. This procedure will be explained to you in detail by the trial doctor or nurse. An injection is given into the back of your hip to numb the area. Then a needle is used to remove some liquid bone marrow, and a tiny piece of bone. This may cause discomfort, and there is some soreness in the biopsy area when the numbing medicine wears off. Most patients can go home soon after the test. Some of the bone marrow will be sent away to central laboratories for additional testing, described below.

For this trial, three additional tests will also be carried out on some of the samples collected. These tests will be done on samples that will be collected as part of your routine care:

1. The first is a test called ‘Minimal Residual Disease' (MRD). This is a test on your bone marrow that can detect very low levels of disease, and so will enable the trial doctors to assess how much of a patient’s disease remains after treatment.
2. The second test is to find out the levels of certain proteins which may be abnormal in myeloma cells in your bone marrow. The results from this test will help the trial doctors assess if there is a link between the levels found in the samples and the way patients respond.
3. Finally, a third test will look at some genetic properties of your myeloma cells in your bone marrow, so that we can understand if certain genes are associated with how patients respond. We will compare the results from your bone marrow samples to results obtained on your blood samples to see which changes are specific to the tumour.

## **What extra visits will I have, and what extra procedures will be required?**

Most of your visits and assessments will be as you would have in routine care if you weren’t taking part in a trial. However if you were diagnosed with myeloma more than 3 months ago we may ask you to have a repeat bone marrow before starting the trial. We need to do this to confirm you are suitable for the trial.

We will take one extra bone marrow sample at 6 months after the start of your maintenance treatment.

Also, during the maintenance treatment, you will need to make extra visits to your hospital for treatment; there will be 2 extra visits for every cycle of treatment (so, 2 extra visits every month whilst you are receiving maintenance treatment). We will also take a sample of your blood at these visits for safety tests and, if you are a woman of child bearing potential, you will have a pregnancy test at the start of each cycle of treatment.

## **What will I have to do?**

If you agree to take part in this trial, you will have to take your trial medication regularly as directed by your trial doctor. It is very important that you take all the drugs as they are prescribed for you. You will be given a diary card to record that you have taken your drugs correctly. Please remember to complete this, and to bring it with you to clinic at the end of each treatment cycle.

Please tell your trial doctor if you are taking any other medication for your myeloma or any other health complaint. Let your trial doctor know if there are any changes to the medication you are taking. You will be required to attend clinic for trial visits during the treatment phase and after your treatment has finished. These visits will coincide with your routine visits and will usually be no more frequent than the visits you would have if you were not taking part in the trial. It is very important that you attend all the visits that your trial doctors arrange for you.

Over the course of the trial, you will be asked to complete up to 4 Quality of Life questionnaires. Please complete questionnaires as fully and honestly as you can. Place the questionnaire in the envelope provided and give it to your trial doctor or research nurse.

During your first four cycles of chemotherapy, and before your stem cell harvest, holidays abroad are not recommended, but short breaks in the UK will be possible – discuss this with your trial doctor. For patients who go onto receive a stem cell transplant, it would also be advisable not to travel abroad for 2-3 months after the transplant, due to the increased risk of infection.

## **What are the alternatives for treatment?**

If you decide not to take part in this trial, you will be offered an alternative chemotherapy, considered best for you by your consultant. You may also have a stem cell transplant as part of your treatment. Your consultant will discuss the options with you. You also have the option of not receiving any treatment at all although this is not recommended.

## **What are the possible disadvantages and risks of taking part?**

Being involved in a clinical trial requires a degree of commitment such as regular hospital visits, as described above. The risks and side effects of the trial treatment are described below.

The procedures below are the same as you would have if you didn’t take part in the trial:

Bone marrow sampling

When you have a bone marrow sample taken, you may feel pain and experience slight bruising around the biopsy site. The pain is usually short-lasting, but the biopsy site may ache for a couple of days. Complications are very unusual but they may include bleeding, infection and pain. Your trial doctor will give you instructions on how to look after the biopsy site.

Blood sampling

Having blood taken may cause some discomfort, bleeding, or bruising where the needle enters the body and, in rare cases, light-headedness and fainting.

Central venous catheter

Because you may have a central venous catheter (Hickman or PICC catheter) in place, there is the possibility of infections and/or blood clots forming next to the catheter. Both of these can be treated, but sometimes the catheter has to be replaced before the chemotherapy has been completed.

Intravenous drug administration

One of the drugs we will give you as part of the trial (carfilzomib) will be given through a cannula (a thin, hollow, flexible tube) into a vein in your arm. This can cause complications such as swelling, redness and pain around the injection site, and rarely severe allergic reactions. Your hospital will have procedures in place to manage such complications.

Stem cell transplant

If you are randomised to have a stem cell transplant you will receive a high dose of a chemotherapy drug called melphalan. This will have an effect on bone marrow function and for a time your blood cell counts will be very low, which means you will be more at risk of infection, abnormal bleeding (e.g. bleeding gums) and anaemia (which can make you feel tired and breathless). The stem cells are given back to you to make healthy blood cells, but there will be a period of 3-4 weeks after you receive your cells, when you will need to be in hospital, mainly due to the risk of infection, and the need for regular transfusions. You are likely to feel very tired, to lose your appetite and experience soreness in the mouth that may prevent you eating. As with all chemotherapy treatment, there is a risk of serious infection requiring intravenous antibiotics and a stem cell transplant is also associated with a small risk of death (3-5%). You will be given detailed information about the stem cell transplant and counseled about the risks in the same way as if you were not in the clinical trial, and were receiving it as part of routine care.

In the few weeks after you are discharged from hospital following your transplant, your appetite may still be poor and you may find that you tire easily, and suffer with dry skin, and poor sleep. You may develop fevers, an indication of infection, and you may have to be re-admitted to hospital for antibiotics.

It can take weeks or months to recover from the high dose melphalan and stem cell transplant and so, if you normally work, you may need to take this time off work.

All treatments for myeloma carry some risk. Although the treatments used in this trial have a relatively good safety profile, there are potential risks and side-effects. These will be explained to you by your trial doctor. There is a risk that you may become sterile or infertile as a result of treatment received in this trial. If required, counselling and a referral for fertility assessment and preservation of sperm will be available where appropriate.

Before participating you should consider if taking part in the trial will affect any insurance you have and seek advice if necessary.

## **What are the side effects of any treatment received when taking part?**

Common side effects of chemotherapy

## As with all types of cancer treatment, you may experience some side effects with this treatment. Chemotherapy damages cancer cells but can also affect normal tissues such as the skin, hair and nails, the mouth and the lining of the digestive system, and the bone marrow. This gives rise to many of the side effects of chemotherapy. The side effects vary considerably from patient to patient, and they may be mild or more serious. The commoner side effects are nausea, loss of appetite, hair loss, dry or itchy skin and blisters, discolouration of the skin and nails, increased sweating, muscle pain and weakness, joint pain, general discomfort (or malaise), chills, abnormal blood pressure, abnormal blood counts (which may be severe), worsening liver function (which may be severe), risk of infection and fever (which may be related to an infection). Almost all of the side effects are temporary, and almost all can be treated or managed. You will be monitored regularly for side effects and will be given a diary card to record them. Your trial doctor and clinical team are experienced in dealing with, and minimising these side effects, and it is important that you tell your trial doctor or medical team promptly about any side-effects you have. You will not be taken off the trial unless your trial doctor feels the side effects are too severe for you to continue, and alternative treatments will be discussed with you.

Below are the common potential side effects of the treatment in this trial:

**Carfilzomib** - The most common side effects reported with carfilzomib are tiredness, anaemia (low red blood cell count), feeling sick, low blood counts that can increase your risk of infection or bleeding, diarrhoea, and mild reduction in kidney function. Your blood counts will be monitored closely and regularly throughout your treatment to prevent these counts getting too low. You may also experience shortness of breath with everyday activities or at rest, irregular heartbeat, racing pulse, dizziness, and fainting spells, which can be signs of a condition known as pulmonary hypertension. The doses of carfilzomib will be adjusted if necessary.

Other common side effects include vomiting, muscle spasms, joint pains, back pain and generalised pain, chest infection, pneumonia, fluid in and around the lungs, nose bleed, change in voice, flushing, ringing in the ears, cataract, indigestion, toothache, sore throat, bronchitis, urinary tract infection (UTI), inflammation of nose and throat, flu-like symptoms, viral infection, dehydration, numbness, tingling or decreased sensation of hands and feet, headache, constipation, reduced appetite, anxiety, difficulty sleeping, swelling of arms or legs, cough, changes in blood chemistry, yellowing of skin or eyes (jaundice), blurred vision, abdominal pain or swelling, pain or irritation at the injection site, unusual bruising, blood clots forming in your blood vessels (including in the lungs), chest pain, heart attack, heart failure (the risk of which is higher for those aged over 75 and for participants who are Asian), life threatening infection, kidney failure which can lead to dialysis, or allergic reactions such as rash, facial swelling or difficulty breathing including rapid breathing, feeling like you can't breathe in enough air, wheezing, or cough, which can be signs of lung problems.

Less common side effects that have been reported and may be related to carfilzomib therapy are decreased or worsening heart function including abnormal heart rhythm, reduced blood flow to the heart, inflammation of the heart or lining of the heart which may lead to heart failure, an accumulation of fluid around the heart, bleeding (including bleeding from the stomach, brain and lungs), inflammation of the pancreas, the development of holes through the wall of the gastro-intestinal tract and in rare cases intestinal obstruction. In addition, a condition known as hypertensive crisis has been reported uncommonly which can cause very high blood pressure, severe chest pain, severe headache, confusion, nausea and vomiting, stroke, multi-organ failure and severe anxiety.

Tumour lysis syndrome, myelodysplastic syndrome and posterior reversible encephalopathy syndrome, thrombotic microangiopathy, hepatitis B virus reactivation, and progressive multifocal leukoencephalopathy have also been reported as rare/uncommon conditions seen in patients taking carfilzomib. These are described below.

*Tumour lysis syndrome* is caused by rapid killing of tumour cells, and can lead to alteration in blood chemistries, and possibly, reduced kidney function. As a preventative measure against tumour lysis syndrome, you will be required to keep well hydrated and your blood chemistries will be regularly checked.

*Myelodysplastic syndrome* refers to a disorder that develops when the cells in the bone marrow do not work properly and have problems making new blood cells. A person with MDS may experience no symptoms or may experience fatigue, infection, easy bruising or bleeding. MDS can turn into a cancer of bone marrow cells called acute myeloid leukemia (AML).

*Posterior reversible encephalopathy syndrome (PRES)* is an uncommon condition that causes swelling of the brain and affects how it functions. A person with PRES may experience headaches, confusion, loss or decreased level of consciousness, blurred vision or blindness, seizures, and possibly death. If caught early and treated, PRES may be reversible.

*Thrombotic microangiopathy (TMA)* is an uncommon condition where thromboses (blood clots) form in small blood vessels. Symptoms include:

* Feeling sick (nausea) and/or vomiting
* Passing smaller amounts of urine or urine that is unusually dark in colour
* Anaemia (low red blood cell counts, which may make you feel tired or breathless)
* Low platelet counts, which may make you more likely to bleed or bruise
* Poor kidney function, this may be severe and sometime results in the need for dialysis until the kidneys recover
* Diarrhoea
* Fever

*Hepatitis B Virus (HBV) Reactivation* can occur in patients who have been exposed to hepatitis B in the past. If tests suggest that this is the case with you, then we will monitor your blood tests for evidence of hepatitis during treatment and may suggest that you take antiviral tablets. It is rare for this to cause jaundice or liver problems.

*Progressive Multifocal Leukoencephalopathy (PML)* is a rare and fatal brain infection that causes progressive damage to the brain. It has been reported rarely in patients taking carfilzomib, who have had or are having immunosuppressive therapy. Symptoms of PML may include general weakness, clumsiness and balance issues, and language problems. If you experience any of these symptoms, please contact your doctor immediately.

With treatment, most patients recover quickly, although some patients take longer to get better. You will be given steroid tablets with your carfilzomib treatment to help prevent TMA. TMA is related to other disorders such as Haemolytic Uraemic Syndrome (HUS) and Thrombotic Thrombocytopenic Purpura (TTP) which have also been reported in relation to cyclophosphamide.

Many of the side effects listed above are common to most chemotherapy drugs that are used to treat myeloma. Your clinical team will monitor you closely for these side effects and are experienced in dealing with them. If any of the side effects suddenly start or become worse than usual, then the trial doctor may need to review you and take extra blood tests. It is particularly important to let your trial doctor know if you experience severe nausea in the first 1-2 days after having Carfilzomib.

**Cyclophosphamide** – The most common side effects experienced with cyclophosphamide include a temporary drop in the number of blood cells made by the bone marrow (which may be severe), which can lead to an increased risk of infection (which may be severe), tiredness and breathlessness, bruising, nosebleeds, sore mouth and bleeding gums.

Other common side effects include nausea and vomiting, loss of appetite, hair loss, loss of fertility, irritation of the bladder and possibly a small amount of blood in your urine.

A less common side effect is abnormal heart rhythm and function (which may be serious or life threatening). Inflammation of the pancreas has also been uncommonly observed. There may be a small risk of development of other secondary cancers as a result of taking cyclophosphamide.

**Dexamethasone** - Each patient’s reaction to dexamethasone, a steroid, may be different, but it can occasionally cause problems:

*Irritation of the stomach lining*: Dexamethasone may irritate the lining of your stomach. Tell your trial doctor if you have indigestion or any other stomach problems. Your trial doctor can prescribe medicine to relieve these symptoms. Always take dexamethasone tablets with meals or a glass of milk.

*Increased appetite*: You may notice that you have an increased appetite while taking dexamethasone. This will stop when you are no longer taking the drug.

*Changes in blood sugar levels*: Occasionally dexamethasone may cause your blood sugar level to rise. During treatment you will have regular blood and urine tests to check this. Tell your trial doctor if you get very thirsty or if you are passing more urine than usual. You may need treatment if your blood sugar remains high. This treatment can usually be stopped once you have completed all your dexamethasone treatment.

*Fluid retention*: Dexamethasone may affect the salt and water balance in the body. You may notice that your ankles and/or fingers swell. Let your trial doctor know if this happens. This is usually only a problem with long-term treatment.

*Insomnia and mood disturbances:* Dexamethasone may cause difficulty sleeping, and mild mood disturbances such as irritability. You should let your trial doctor know if this happens, as these symptoms usually improve once the dose is adjusted. A small amount of patients will experience severe psychiatric or psychotic reactions such as depression and suicidal thoughts. Your mood and wellbeing will be closely monitored throughout the trial.

Abnormalities relating to the function of your glands may also occur, but are more likely related to myeloma or previous steroid therapy. Reduced vision due to glaucoma or increased pressure in the eyes may also occur but is not commonly reported. There is a chance that a virus or bacteria which you have been infected with in the past may reactivate when taking dexamethasone.

Once again, the side effects of cyclophosphamide and dexamethasone are familiar to the clinical team looking after you, who have experience in managing them.

If you become suddenly unwell between hospital visits and especially if you develop fevers, breathing difficulties, chest pain, bleeding (e.g. nosebleeds), leg swelling, please telephone immediately for advice from your hospital team, as you may need to be admitted to hospital.

When you join the trial your trial doctor or nurse will give you a contact card to let you know the correct number to call, you should carry this with you at all times. If you are admitted to a hospital or have to see your GP in between hospital visits, please remember to show them the contact card in case they need to speak to your trial doctor.

You may experience some, or none, of the symptoms listed above. It is important to understand that the side effects list is not exhaustive as we cannot predict every side effect or the severity of side effects. Further information can be obtained from your trial doctor regarding the full list of possible side effects which might be experienced when taking the trial drugs.

## **Exposure to radiation**

As part of your routine tests for your myeloma, you will have imaging (X-ray/MRI/CT scan or PET-CT scan) taken of your arms, legs, skull, chest, spine and pelvis. These are routine for all patients with myeloma, so that we can assess whether your bones have been affected by myeloma. You may need more than one type of scan. Your trial doctors will be able to explain when and why you need these. You will not have any additional X-rays or scans above and beyond what would be part of your routine clinical care and the risks from the radiation exposure are considered to be very small indeed.

You may also have a MUGA scan if an echocardiogram cannot be performed. MUGA scans require injection of a radioactive material called a ‘tracer’ into your blood to capture a moving image of your heart. You may need to have up to two of these scans if part of the routine clinical care at your hospital and the risks from this increased radiation exposure are slightly higher.

## **Harm to the unborn child**

The chemotherapy drugs used in this trial are possibly harmful to unborn babies and it is also possible that these drugs may be present in breast milk. During and after chemotherapy if sperm or eggs are produced they may be abnormal.

If you are pregnant or breastfeeding you will not be able to take part in the trial.

Women of childbearing age will be asked to have a pregnancy test before taking part in the trial and before the start of each cycle of chemotherapy to exclude the possibility of pregnancy.

Due to the possible effects of the trial treatment during pregnancy and lactation, women who could become pregnant must use one highly effective contraception method (which includes progestogen-only hormonal contraception, intrauterine device (IUD), intrauterine hormone-releasing system (IUS), bilateral tubal occlusion, vasectomized partner or sexual abstinence) from full trial registration until 12 months after your last dose of trial treatment.

It is possible that the trial treatment will affect sperm or semen and therefore you should not father a child during this trial, or for a safety period of 12 months after treatment. If your partner might become pregnant you must use condoms, and if they are of child bearing potential, advise them of the contraceptive requirements listed above for women who may become pregnant, from full trial registration until 12 months after your last dose of trial treatment.

If you, or your partner, become unexpectedly pregnant during the trial, or within 12 months of stopping treatment, you must inform your trial doctor immediately. We would discuss referral for specialist counselling on the possible risks to yourself, or your partner, and your unborn baby.

Due to these risks, if you or your partner become pregnant during or following trial treatment, we would like to monitor and follow up the pregnancy; in order to do this a pregnancy monitoring information sheet and consent form will be provided. In addition, if you were to breastfeed within a year of taking carfilzomib you should inform your trial doctor. We may ask you to consent to additional information being collected.

## **What are the possible benefits of taking part?**

The goal of this trial is to gain a greater understanding of the new treatment options available for myeloma patients and which is the best strategy for patients who are young enough for a stem cell transplant. By taking part you will be helping to answer important questions and it is hoped this will improve treatment for future patients. All patients in the trial will be treated with the best available treatment. We cannot promise the trial will help you but we hope the information we get from this trial will improve the treatment of people with multiple myeloma.

## **What happens when the trial stops?**

At the end of the trial, any further treatment that you may need will be decided by your own trial doctor. Whether further treatment is required or not, you will continue to be reviewed on a regular basis as do all patients with Multiple Myeloma.

Results from studies like this one are often presented at large medical meetings and published in medical journals to ensure that as many trial doctors as possible get to know about the results. This is how studies can improve the treatment and care for patients. Individual patients will not be identified in any report or publication. If you wish to see the published results from this trial, you should ask your hospital trial doctor.

## **Expenses and Payments**

You will not be paid for your participation in this clinical trial. Whenever you visit the hospital for a visit that would not be part of your normal routine care (this will happen during your maintenance treatment), you will be able to claim £5 towards your travel expenses. Your nurse can advise you on how to can claim back travel expenses from the NHS Trust/Health Board.

## **What if there is a problem?**

Any complaint about the way you have been dealt with during the clinical trial or any possible harm you might suffer will be addressed. Detailed information concerning this is given in Part 2 of this information sheet.

## **Will my participation in the trial be kept confidential?**

Yes. We will follow ethical and legal practice and all information about you will be handled in confidence. Detailed information concerning this is given in Part 2 of this information sheet.

**This completes PART 1.**

**If you think you might be interested in taking part in the trial, please read the additional information in PART 2 before making your decision.**

# PART 2

## **What if relevant new information becomes available?**

Sometimes we get new information about treatments being studied in trials. If this happens, your trial doctor will tell you and discuss with you whether you would like to continue in the trial. If you decide not to carry on, your trial doctortrial doctor will make arrangements for your care to continue outside the trial. If you decide to continue in the trial, you may be asked to sign an updated consent form.

In some circumstances your trial doctor might consider it best for you to withdraw from the trial. They will explain the reasons and arrange for your care to continue outside the trial.

If the trial is stopped for any other reason, your trial doctor will tell you and arrange your continuing care.

## **What will happen if I don’t want to carry on with the trial?**

You can withdraw from trial treatment at any time but we would like to continue to collect information about you through your trial doctor so that we know about your progress following trial treatment. We will also need to use the information collected up to your withdrawal. Any stored blood or tissue samples that can be identified as yours will be destroyed if you wish.

## **What if there is a problem?**

Every care will be taken in the course of this clinical trial. However in the unlikely event that you are injured by taking part, compensation may be available.

If you suspect that the injury is the result of the Sponsor’s (University College London) or the hospital's negligence then you may be able to claim compensation. After discussing with your trial doctor, please make the claim in writing to Dr Kwee Yong who is the Chief Investigator for the clinical trialand is based at UCL Cancer Institute, Department of Haematology, 72 Huntley Street, London, WC1E 4DD. The Chief Investigator will then pass the claim to the Sponsor’s Insurers, via the Sponsor’s office. You may have to bear the costs of the legal action initially, and you should consult a lawyer about this.

Participants may also be able to claim compensation for injury caused by participation in this clinical trial without the need to prove negligence on the part of University College London or another party. You should discuss this possibility with your trial doctor in the same way as above.

Regardless of this, if you wish to complain, or have any concerns about any aspect of the way you have been approached or treated by members of staff or about any side effects (adverse events) you may have experienced due to your participation in the clinical trial, the normal National Health Service complaints mechanisms are available to you. Please ask your trial doctor if you would like more information on this. Details can also be obtained from the Department of Health website: <http://www.dh.gov.uk>.

## **Will my taking part in this trial be kept confidential?**

Yes, all information collected during the trial will be kept strictly confidential. Details about you, your treatment, any side-effects you have, how the disease responds and how you are during and following trial treatment will be recorded in your medical notes at your hospital.

The trial staff at your hospital will then pass information relevant to your safety and participation in the trial to the Cancer Research UK & University College London Cancer Trials Centre (UCL CTC). This information will include your initials,date of birth, ethnicity and NHS number.

In order to make sure your bone marrow and blood samples cannot be mixed up with other patients’ when they are sent to the laboratories used by the trial, your initials, date of birth, NHS number and trial number will be marked on the sample and used by the laboratories. The laboratories will not share this information with anyone else. The central laboratory in Leeds (HMDS) will use the NHS number to log your samples so that they do not get mixed up with other patients’ samples.  When logging on their computers they will become aware of your full name but will not share this information with anyone else.

UCL CTC is registered under the UK Data Protection Act 1998 and all information held at UCL CTC will be stored securely and handled according to these data protection guidelines. When you join the trial you will be assigned a trial number by UCL CTC. All your trial data at UCL CTC will be linked by this number. This number will also be used to link your trial data to any tissue or blood samples you agree to being collected and sent to relevant laboratories.

Your ethnicity will be recorded for safety monitoring purposes for example to monitor side-effects which are more common in a particular ethnic group. This information will be held by the UCL CTC and only ever shared in a pseudo-anonymised format linked by your trial number only.

The information collected about you as part of the trial might be looked at by staff from UCL CTC, the company providing the trial medication, the sponsor (or representatives of the sponsor), regulatory authorities and your NHS Trust/Health Board. This is to ensure that the trial is being carried out properly and that the information collected is correct. These organisations will always keep information about you confidential. Your medical records may be viewed at the hospital where the trial is being conducted or at a secure location that is remote from the hospital. If your medical records are viewed remotely, one of the following options will be used:

1. The medical records will be viewed on a computer with a secure connection where it is not possible to save or download the records.
2. A small section of your medical records, with your name and contact details removed and identified by a code number only, will be sent to appropriate individuals.

The individuals looking at your medical records will ensure that they are not viewed by anyone else and will keep the information about you secure. No records containing your name will be stored outside of the hospital.

Your name will never be used in any reports about the trial. Where there is a possibility that your data may be sent outside the UK for regulatory or research purposes, UCL CTC will take reasonable steps to ensure the principles of the Data Protection Act are maintained.

Your trial doctor will tell your GP about your participation in the trial and UCL CTC may also use information from the NHS Information Centre to follow your progress once your trial treatment and trial visits have come to an end.

## **What will happen to any samples I give?**

These will be used for the tests and investigations into your disease described earlier in the **What tests will be done?** section.

Your blood, urine and bone marrow samples that are taken as part of your diagnosis and treatment will be analysed at your hospital in the same way as they would if you were being treated outside the trial. These samples will be stored at your local hospital laboratories and will be destroyed after analysis in line with hospital procedure.

We will also send samples to central laboratories (two laboratories at University College London, and another one called the HMDS, Haematological Malignancy Diagnostic Service, part of the Leeds Teaching Hospitals NHS Trust). These samples will be analysed to provide research results as part of the trial (see the **What do these tests involve?** section). The laboratories will handle your samples with the same duty of confidentiality as they would for any clinical sample.

With your permission, your data collected as part of the trial and samples taken during the trial will be stored for future studies in relation to multiple myeloma. All information about you and your tissue samples used for such research would be treated with the strictest confidence, and the details would be coded with your trial number so that only the authorised researcher would have access to your details. You will not be identified in the results of any future studies. Ethical approval will be obtained for any future studies. These samples will be stored at central laboratories in the UK (these may be laboratories in addition to the three laboratories listed above; samples will be stored indefinitely but all research done on these samples will be approved by an ethics committee.

Allowing your samples to be used for future research after the trial is optional, and does not affect your participations in the trial. If you do not give your permission for future research use of your samples, they will be destroyed by the 3 central laboratories at the end of the trial.

## **Will any genetic tests be done?**

### Yes, these are explained below:

#### Cytogenetics

This genetic test will be done on the bone marrow sample taken when you first join the trial. These tests are routinely carried out in many centres treating multiple myeloma patients and are used to see what genetic sub-type of multiple myeloma you have. **If your local hospital is not able to do this test, it will be done at a central laboratory at UCL. The central laboratory will handle your samples with the same duty of confidentiality as they would for any clinical sample.**

#### Genetic mutations affecting pathways in cancer cells

### Some of the material taken during your diagnosis and treatment will be sent to central laboratories at UCL to analyse the genetic features of your disease. This will help us to understand if such genetic features influence how you respond to the different treatments. You will not be identified in the results of these studies and you will not be informed of your individual results, so there should not be any implications for you or your family members.

If you give us permission to store surplus material from the samples collected during the trial, the samples may be used for future genetic tests. Ethical approval will be obtained for any future tests on your samples.

Some of the genetic tests we do as part of this trial, and in future research, will look at inherited (‘germline’) variations in your genes which you inherited from your parents and which you may have passed to your children. These tests are not ones which are done routinely in genetic clinics, and you will not be informed of your individual results, so there will not be any implications for you or your family members. These tests are done in order to understand whether any genetic changes found in your myeloma cells are specific to your myeloma.

## **What will happen to the results of the trial?**

When all patients taking part have completed the trial and it is complete the results will be published in a medical journal and presented at national and international meetings. It will not be possible to identify you in any publication or presentation of the research findings. If you would like to obtain a copy of the published results, please ask your trial doctor.

## **Who is organising and funding the research?**

The trial is being sponsored by University College London and run by the ‘Cancer Research UK & UCL Cancer Trials Centre’ (UCL CTC) who are part of University College London. Amgen Ltd (formerly Onyx Pharmaceuticals Inc.) are providing funding as well as supplying Carfilzomib free of charge for the trial. Your trial doctor will not be paid for including you in the trial.

## **Who has reviewed the trial?**

All research in the NHS is looked at by an independent group of people, called a Research Ethics Committee, to protect the interests of any patients that may take part. This trial has been reviewed and granted a favourable opinion by the City and East London Research Ethics Committee and has also been approved by the Research and Development department at your hospital and the Cancer Research UK Clinical Trials Advisory and Awards Committee (CTAAC).

## **Thank You**

Thank you for considering taking part in this trial and for taking the time to read this patient information sheet, which is yours to keep. If you decide to take part in the trial, you will also be given a copy of your signed consent form.

## **Sources of Further Information and contact details**

Please discuss any questions you may have with your trial doctor or members of the research team:

Your trial doctor is:

Name: Contact phone number:

Your research/specialist nurse is:

Name: Contact phone number:

Alternatively if you or your relatives have any questions about this trial you may wish to contact one of the following organisations that are independent of the hospital at which you are being treated:

* **Macmillan Cancer Support** provides practical, medical and financial support and work towards the improving cancer care. They can be contacted at:

Tel: 0808 808 00 00 (freephone)

Or visit their website at:

<http://www.macmillan.org.uk/HowWeCanHelp/HowWeCanHelp.aspx>

* **Cancerhelp (Cancer Research UK)** who provide all aspects of information for people with cancer. Their contact details are:

Tel: 0808 800 4040 (freephone)

Or visit their website at: http://cancerhelp.cancerresearchuk.org/

* **Myeloma UK,** Lower Ground Floor, 37 York Place, Edinburgh, EH1 3HP

Freephone: 0800 980 3332; [www.myeloma.org.uk](http://www.myeloma.org.uk)

## **Glossary**

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| --- | --- | --- |
| **Abbreviation** | **Full Name** | **What it means** |
| CT scan | Computer Tomography | Using X-Rays to create a 2D picture of inside the body. The image produced is very detailed. |
| ECG | Electrocardiogram | A test that measures the electrical impulses that make your heart beat. |
| I.V. | Intravenous | Drugs administered into a vein are administered intravenously. Many chemotherapy drugs are given this way. |
| MRI scan | Magnetic Resonance Imaging scan | Using a magnetic field to create a picture of inside the body. This is very useful for telling the difference between muscle, soft tissue and bone. |
| MUGA scan | Multiple-gated acquisition scan | A scan which uses a radioactive tracer put into the blood and a gamma camera to capture a moving image of your heartbeat. |
| PET-CT scan | Positron Emission Tomography– Computer Tomography | A PET-CT combines a CT scan with a small amount of a radioactive drug injected. This allows active cells to show up on the scan, some of which will be cancer cells. |
| PICC line | Peripherally inserted central catheter | A tube placed into a vein and kept in place for several days. This allows drugs to be given repeatedly or continuously without patients having to stay in hospital, and avoids repeated needle sticks. |
| UCL | University College London | This is the organisation that takes responsibility for the running of the trial, known as the Sponsor. |
| UCL CTC | Cancer Research UK & UCL Cancer Trials Centre | The organisation carrying out the day to day work on the trial. |