The UNIVERSITY OF CHICAGO

The Division of the Biological Sciences • The University of Chicago Medical Center

CONSENT/AUTHORIZATION BY SUBJECT FOR PARTICIPATION IN A RESEARCH PROTOCOL

NCT number: NCT01816971

Protocol Number: **12-1725** Name of Subject: _____

Medical History Number: _____

STUDY TITLE: Open-label, Single-arm, Phase 2 Study of the Initial and Post-Transplant Treatment with Carfilzomib, Lenalidomide and Low Dose Dexamethasone (CRd) in Transplant Candidates with Newly Diagnosed, Multiple Myeloma Requiring Systemic Chemotherapy

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You are being asked to participate in a research study. A member of the research team will explain what is involved in this study and how it will affect you. This consent form describes the study procedures, the risks and benefits of participation, as well as how your confidentiality will be maintained. Please take your time to ask questions and feel comfortable making a decision whether to participate or not. This process is called informed consent. If you decide to participate in this study, you will be asked to sign this form.

You are being asked to take part in this study because you have been recently diagnosed with multiple myeloma and you are a candidate for autologous stem cell transplantation.

The lead site for this study is the University of Chicago. Amgen Inc. is providing funding for this study

WHY IS THIS STUDY BEING DONE?

This study is being done to learn more about a combination of 3 drugs called Revlimid® (lenalidomide), carfilzomib and dexamethasone given to persons with newly diagnosed multiple myeloma.

Carfilzomib (Kyprolis®) is approved by the U.S. Food and Drug Administration (FDA) forfor use in certain U.S. patients with relapsed and refractory multiple myeloma that have tried and failed other therapies. It has not been approved to be used for any other disease or condition. In this study, carfilzomib is an experimental study drug because it is not approved for use in all patients in the United States, and it is not approved by some regulatory authorities (the agencies that are responsible for approving the use of a medicine in a country, such as the European Medicines Agency and Health Canada).

Lenalidomide (Revlimid®) has been approved in the United States by the FDA for the treatment of specific types of myelodysplastic syndrome and in combination with dexamethasone for patients with multiple myeloma who have received at least 1 prior therapy.

Dexamethasone, an FDA approved drug, is commonly used either alone or in combination with other drugs to treat multiple myeloma.

The combination of lenalidomide and dexamethasone is approved by the FDA to treat multiple myeloma. However, the combination of carfilzomib, lenalidomide and dexamethasone, in this study, is considered experimental.

This study is being done to find if the combination of carfilzomib and lenalidomide with dexamethasone followed by transplant will improve your multiple myeloma more than the combination without transplant.

During the study, all subjects will receive the same dose of carfilzomib, lenalidomide and dexamethasone. You will receive 4 cycles of this combination and then proceed to transplant. After transplant, you will have four more cycles of the study drug combination. Some subjects may experience important or serious side effects, and these are more likely to occur at higher doses.

HOW MANY PEOPLE WILL TAKE PART IN THE STUDY?

About 40 people at the University of Chicago and about 70 people at sites throughout the United States and Canada will participate in the study.

WHAT IS INVOLVED IN THE STUDY?

If you decide to take part in this study you must agree to come for all scheduled study visits.

You will need to come in for a screening visit and a baseline visit before starting the study. These visits may take several hours. You will also need to come in on Days 1, 2, 8, 9, 15, and 16 of each cycle for Cycles 1-8. For Cycles 9-18 you will need to come in on Days 1, 2, 15, and 16. You might also be required to come in on Day 22 of each cycle. The Day 1, 8 and 15 visits will take about 4-6 hours. The Day 2, 9 and 16 visits will take about 4 hours. If you are required to come in for Day 22 visits, it will take about an hour.

Before the research starts (screening)

After signing this consent form, you will be asked to undergo some screening tests or procedures to find out if you can be in the study. These tests and procedures are likely to be part of standard cancer care and may be done even if it turns out that you do not take part in the research study. If you have had some of these tests or procedures recently, they may or may not have to be repeated.

- Medical history review – questions about your health, your current and recent medications and any tests you have had during the last four weeks, prior treatments, and any allergies.
- Physical examination – including vital signs (blood pressure, pulse, breathing rate and temperature), height, weight, and level of activity (how easily you perform daily activities and what might be giving you difficulty)
- Electrocardiogram (ECG) – a measurement of your heart's electrical activity
- Neurological examination will be performed and you will be asked if you have any neurologic symptoms. This will check your motor and sensory skills, balance and coordination, mental status reflexes, and nerve function. The exam will include a light touch and pinprick of your hands and feet to test for numbness.
- You will be asked to complete a neurological symptoms questionnaire
- Blood samples (approximately 5 tablespoons) will be collected for tests to check your general health and the degree of your multiple myeloma.
- You will need to collect urine samples for routine tests to check your health. You will need to collect your urine over a 24-hour period and provide a fresh sample for these tests.
    - You will be given a container to collect your urine samples. When you wake up in the morning, do not collect the first urine of the day but note that time on the container as the start time. You will collect all other urine that day and the first morning urine of the next day. This should be marked on the bottle as the end time. You should refrigerate the urine as it is collected.
- Pregnancy test will be done if you are a woman of child-bearing potential. This will be done using the blood or urine samples you provide. You will need to have

a negative pregnancy test within 10–14 days of starting lenalidomide and 24 hours before lenalidomide is prescribed.

- Bone marrow aspiration and/or biopsy – removal of a small amount of fluid and cells through a needle inserted into the hip or chest bone.
    - Two samples of bone marrow aspirate (the liquid portion of the bone marrow) will be collected to measure your disease. Part of this sample may be used for research purposes if you give consent (see "Additional Optional Research Studies" section)
- A skeletal survey – x-rays of your bones
- CT-PET scan – a detailed computer image of the area of your disease
- Optional research bone marrow, blood samples, and cheek swabs will be collected at the same time as the other screening samples so there should only be one needle stick, but extra tubes will be collected. Please see "Additional Optional Research Studies."

If these tests show that you are eligible to participate in the study, you will be able to begin taking the study drugs. If you do not meet the eligibility criteria, you will not be able to participate in this study.

Registration into Revlimid REMS® Program

Before you can take part in this study, you must register into and follow the requirements of the Revlimid REMS® program of Celgene Corporation (the maker of lenalidomide). This program provides education and counseling on the risks of harm to unborn children, blood clots and reduced blood counts related to lenalidomide. More information will be provided later in this consent form.

Study Drug and Administration

During this study, you will take all 3 study drugs (lenalidomide, dexamethasone, and carfilzomib) as described below. The study drugs will be given in 28-day cycles. You may also be given medications to help treat or prevent side effects of the study drugs.

Everyone in the study will receive standard doses of carfilzomib, lenalidomide and dexamethasone. **You will be given a diary to help you keep track of the study drugs you will take at home.**

As long as you do not have a side effect that makes it unsafe to continue, you will receive 4 cycles of the study drugs. The first 4 cycles are called 'induction'. After 4 cycles are completed, you will continue to stem-cell collection and transplant. If you have a response

sooner than 4 cycles, your study doctor may decide to have stem-cell collection earlier but then continue the administration of carfilzomib, lenalidomide and dexamethasone for a total of 4 'induction' cycles. Once the transplant's side-effects have resolved, (no more than 3 months after the completion of transplant), you will continue receiving carfilzomib, lenalidomide and dexamethasone for up to 4 cycles. This is called 'consolidation.'

After Cycle 8, you may be able to continue taking the study drugs as long as your cancer is not worsening and you do not experience any unsafe side effects. This continued study drug administration can be up to 10 cycles and is called 'maintenance'.

If, after the first 4 cycles of 'induction', you become ineligible for transplant, you may be considered for continued administration of carfilzomib, lenalidomide and dexamethasone for a total of 18 cycles.

Cycles 1-4 (Induction)

You can take the study drugs any time during the day but you should take them at the same time every day.

Lenalidomide

You will take lenalidomide on Days 1-21 of each cycle. Lenalidomide is a capsule (pill) that you will take by mouth once a day. You must take lenalidomide at the same time every day with water and swallow the capsules whole. **Do not break, chew or open the capsules.**

If you miss a dose, take it as soon as you remember on the same day.

If you miss taking your dose for the entire day, take your regular dose the next scheduled day **(do NOT take double your regular dose to make up for the missed dose).**
If you throw-up (vomit) after taking your lenalidomide dose you should NOT take another dose that day.

If you take more than your prescribed dose of lenalidomide, you should seek emergency medical care, if needed, and contact the study staff immediately.

Women who are pregnant or able to get pregnant should not touch lenalidomide capsules or bottles unless they are wearing gloves. This is because lenalidomide can cause serious harm to an unborn baby as described later in this consent.

Any unused lenalidomide should be returned as instructed through the Revlimid REMS® program.

Dexamethasone

You will take dexamethasone once a day on Days 1, 8, 15, and 22 of each cycle. Dexamethasone may be taken by mouth or as an IV infusion (through a needle in a vein). The IV infusion may take several minutes. Dexamethasone should be taken with food.

Carfilzomib

Carfilzomib will be given by IV infusion on Days 1, 2, 8, 9, 15, and 16 of each cycle. Each infusion will take between 10 and 30 minutes.

Before each infusion you will need to drink approximately 6 to 8 cups of water to get extra fluids during the first 2 cycles. IV hydration may also be given prior to and during the study drug administration.

You will have a rest period during the last week of each cycle (Days 23-28). This means that you will not be taking any study drugs on these days.

The following table will help you understand when you take each of the study drugs during the Induction cycles.

	Days										
	1	**2**	**3-7**	**8**	**9**	**10-14**	**15**	**16**	**17-21**	**22**	**23-28**
Lenalidomide (by mouth)	X	X	X	X	X	X	X	X	X		
Dexamethasone (by mouth or IV)	X			X			X			X	
Carfilzomib (IV infusion)	X	X		X	X		X	X			

On the days that you are scheduled to take both carfilzomib and dexamethasone, please take your dexamethasone 30 minutes to 4 hours **before** your carfilzomib dose.

On the days that you are scheduled to take both carfilzomib and lenalidomide, please take your lenalidomide at least 4 hours **after** you finish your carfilzomib infusion.

This means that on days when you are scheduled to take all 3 study drugs, first take your dexamethasone at least 30 minutes before you take carfilzomib, and then take your lenalidomide dose 4 hours after you take carfilzomib.

Support medications

While taking the study drugs, you will be given medications to help treat and prevent side effects. Your study doctor or nurse will explain in detail how and when to take these medications.

This will include antibiotics and antivirals (to reduce the risk of certain infections) and anti-heart burn drugs. You will also be required to take daily aspirin or another anti blood clotting medication to lower the risk of clots forming in your blood vessels, and valacyclovir to prevent herpes zoster virus (chicken pox virus), which causes shingles.

You may also be given allopurinol to treat gout, excess uric acid in your blood, which may be caused by your cancer drugs. You may also be taking allopurinol two days before Cycle 1 day 1 to prevent tumor lysis syndrome. Tumor lysis syndrome involves side effects that can happen after receiving cancer medications, and may include fevers, chills/rigors, difficulty breathing, nausea, vomiting, involuntary muscle convulsions, weakness, cramping, seizures, and decreased urine output (less than 500 milliliters of urine in 24 hours).

Collection of stem cells for transplant

Your study doctor believes you are a candidate for transplant which is considered routine care for myeloma. If you experience a response to the study drugs (your cancer gets better or at least does not get worse), you may have stem cells collected for a stem cell transplant at any time after at least 4 cycles of the study drugs. If you show a response sooner than 4 cycles, you may have stem cells collected at this time but must still complete 4 cycles before transplant.

After completion of the induction cycles, you will proceed to stem cell transplantation. If you are not eligible for stem cell transplantation, you may continue on 'Maintenance' for a total of 18 cycles, if the study doctor thinks this is best for you.

Consolidation (Cycles 5-8)

3 months after stem cell transplantation (70-90 days, but no more than 120 days), you will start the Consolidation portion of the study.

During consolidation, you will receive carfilzomib on Days 1, 2, 8, 9, 15, and 16 of each cycle. You will continue to take lenalidomide on Days 1-21 and dexamethasone on Days 1, 8, 15 and 22. Cycles will remain 28 days long.

The following table will help you understand when you take each of the study drugs during the Consolidation cycles.

	Days										
	1	**2**	**3-7**	**8**	**9**	**10-14**	**15**	**16**	**17-21**	**22**	**23-28**
Lenalidomide (by mouth)	X	X	X	X	X	X	X	X	X		
Dexamethasone (by mouth or IV)	X			X			X			X	
Carfilzomib (IV infusion)	X	X		X	X		X	X			

Maintenance (Cycles 9-18)

After 8 cycles of study drugs, you can continue to receive the combination, now called 'Maintenance', as long as your cancer does not worsen, your side effects are not too severe, and you want to continue.

During maintenance, you will receive carfilzomib on Days 1, 2, 15, and 16 of each cycle. You will continue to take lenalidomide on Days 1-22 and dexamethasone on Days 1, 8, 15 and 22. Cycles will remain 28 days long.

If you have negative side effects to either lenalidomide or carfilzomib you can continue to take either drug with or without dexamethasone at the discretion of your study doctor.

The following table will help you understand when you take each of the study drugs during the Maintenance cycles.

	Days										
	1	**2**	**3-7**	**8**	**9**	**10-14**	**15**	**16**	**17-21**	**22**	**23-28**
Lenalidomide (by mouth)	X	X	X	X	X	X	X	X	X		
Dexamethasone (by mouth or IV)	X			X			X			X	
Carfilzomib (IV infusion)	X	X					X	X			

Study Visits and Procedures

While taking lenalidomide, you will need to have regular pregnancy tests (blood or urine) if you are a woman who is able to get to get pregnant and who have regular or no menstrual cycles (periods). These will be done weekly during Cycle 1, once every 28 days afterwards (Day 1 of Cycles 2+), if you have to hold or miss a dose due to side effects, if you miss a period or have unusual menstrual bleeding at the time you stop taking the study drugs, and 14 and 28 days after stopping the study drugs.

A bone marrow aspiration and/or biopsy will be performed at least 2-3 times throughout the study, but will not be performed at each cycle. It may be performed at any time to see if you have experienced a response to the study drugs or to check for new symptoms. It will also be done at the end of Cycle 4, the end of Cycle 8 and at the end of the study. An extra sample will be collected at each of these times, if you agree to the optional research samples explained later in this consent.

A CT/PET scan will be done when clinically indicated, at the end of Cycle 4, on Day 1 of Cycles 5-18, the end of treatment, and during long-term follow up.

Cycles 1 – 4

Day 1

- Medical history update – questions about your health, medications/tests you have had and any symptoms or side effects you have experienced since your last visit
- Physical examination, including checking your vital signs, height, weight, and level of activity
- Neurological examination will be performed and you will be asked if you have any neurologic symptoms
- You will be asked to complete a neurological symptoms questionnaire

- Blood samples (approximately 5 tablespoons) will be collected for tests to check general health and the status of your myeloma. You will need to collect a urine sample over a 24-hour period (as described under 'screening') for routine tests to check your health.
- Pregnancy test will be done if you are a woman that is able to get pregnant and have regular or no menstrual cycles (periods). This will be done using the blood or urine samples you provide for the tests described above.
- Study Drug – You will be given enough lenalidomide and dexamethasone (if you will be taking it by mouth) for 1 Cycle. You will also receive your infusion of carfilzomib.
- Review study diary with a member of the research team
- **Return study diary to a member of the research team (starting after Cycle 1)**

Day 2

- Vital signs
- Blood samples (about 1 tablespoon) for tests to check your health will be collected during Cycles 1 and 2 only or if requested by your study doctor
- Study drugs administered – carfilzomib and lenalidomide

Days 3-7

- Study Drug – lenalidomide at home

Day 8

- Medical history update – questions about your health, medications/tests you have had and any symptoms or side effects you have experienced since your last visit
- Vital signs
- Blood samples (approximately 1 tablespoon) will be collected for tests to check your health
- Pregnancy test will be done if you are a woman that is able to get pregnant and have regular or no menstrual cycles during Cycle 1 only. This will be done using the blood or urine samples you provide for the tests described above.
- Study drugs administered - dexamethasone, carfilzomib, and lenalidomide

Day 9

- Medical history update – questions about your health, medications/tests you have had and any symptoms or side effects you have experienced since your last visit
- Vital signs
- Blood samples (approximately 1 tablespoon) will be collected for tests to check

your health or if requested by your study doctor

- Study drugs administered - carfilzomib and lenalidomide

Days 10-14

- You will take lenalidomide at home

Day 15

- Medical history update – questions about your health, medications/tests you have had and any symptoms or side effects you have experienced since your last visit
- Vital signs
- Blood samples (approximately 5 tablespoons) will be collected for tests to check your health and the status of your multiple myeloma. This will also include optional research tests if you agree to have them done.
- You will need to collect a urine sample over a 24-hour period (as described under 'screening') for routine tests to check your health.
- Pregnancy test will be done if you are a woman that is able to get pregnant and have regular or no menstrual cycles during Cycle 1 only. This will be done using the blood or urine samples you provide for the tests described above.
- Study drugs administered - dexamethasone, carfilzomib, and lenalidomide

Day 16

- Vital signs
- Blood samples (about 1 tablespoon) for tests to check your health will be collected during Cycles 1 and 2 only or if requested by your study doctor
- Study drugs administered - carfilzomib and lenalidomide

Days 17-21

- You will take lenalidomide at home

Day 22

- Pregnancy test will be done if you are a woman that is able to get pregnant and have regular or no menstrual cycles during Cycle 1 only. You will need to provide a urine or blood sample (1 teaspoon) for this test.
- Study drug administered – dexamethasone alone

End of Cycle 4 (or later) for Subjects Getting a Stem Cell Transplant

- Vital signs
- You will need to collect urine samples over a 24-hour period (as described under 'screening') for routine tests to check your health.
- Bone marrow aspiration and/or biopsy
    - Two samples of bone marrow aspirate (the liquid portion of the bone marrow) will be collected to measure your disease. Part of the sample may also be used for other research purposes if you give consent (see "Additional Optional Research Studies")
- **Return and Review Study Drug Diary with a member of the research team**
- Blood samples (approximately 5 tablespoons) will be collected for tests to check your health and multiple myeloma. This will also include optional research tests if you agree to have them done.
- CT-PET scan – a detailed computer image of the area of your disease (at the end of cycle 4)

Cycles 5 – 8

Day 1

- Medical history update – questions about your health, medications/tests you have had and any symptoms or side effects you have experienced since your last visit
- Physical examination, including checking your vital signs, height, weight, and level of activity
- Neurological examination will be performed and you will be asked if you have any neurologic symptoms
- You will be asked to complete a neurological symptoms questionnaire
- Blood samples (approximately 5 tablespoons) will be collected for tests to check your general health and tests to check the status of your multiple myeloma. You will need to collect a urine sample over a 24-hour period (as described under 'screening') for routine tests to check your health.
- Pregnancy test will be done if you are a woman that is able to get pregnant and have regular or no menstrual cycles (periods). This will be done using the blood or urine samples you provide for the tests described above.
- Study drugs administered - dexamethasone, carfilzomib, and lenalidomide
- Review study diary with a member of the research team
- Return study diary to a member of the research team (starting after Cycle 1)
- CT-PET scan – a detailed computer image of the area of your disease

Day 2

- Vitals signs
- Study drugs administered - carfilzomib and lenalidomide

Days 3-7

- Study Drug –lenalidomide at home

Day 8

- Medical history update – questions about your health, medications/tests you have had and any symptoms or side effects you have experienced since your last visit
- Vital signs
- Study drugs administered - dexamethasone, carfilzomib, and lenalidomide

Day 9

- Medical history update – questions about your health, medications/tests you have had and any symptoms or side effects you have experienced since your last visit
- Vital signs
- Study drugs administered - carfilzomib and lenalidomide

Days 10-14

- You will take lenalidomide at home

Day 15

- Medical history update – questions about your health, medications/tests you have had and any symptoms or side effects you have experienced since your last visit
- Vital signs
- Blood samples (approximately 5 tablespoons) will be collected for tests to check your health and the status of your multiple myeloma.
- Pregnancy test will be done if you are a woman that is able to get pregnant and have regular or no menstrual cycles during Cycle 1 only. This will be done using the blood or urine samples you provide for the tests described above.
- Study drugs administered - dexamethasone, carfilzomib, and lenalidomide

Day 16

- Vital signs
- Study drugs administered - carfilzomib and lenalidomide

Days 17-21

- You will take lenalidomide at home

Day 22

- Study drug administered – dexamethasone alone

End of Cycle 8

- Blood samples (approximately 5 tablespoons) will be collected for tests to check your general health and to check your multiple myeloma.
- Bone marrow aspiration and/or biopsy
  - Two samples of bone marrow aspirate (the liquid portion of the bone marrow) will be collected to measure your disease. Part of the sample may also be used for other research purposes if you give consent (see "Additional Optional Research Studies")
- Return and review study diary with a member of the research team

Maintenance (Cycles 9-18)

Day 1

- Medical history update – questions about your health, medications/tests you have had and any symptoms or side effects you have experienced since your last visit
- Physical examination, including checking your height, vital signs, weight, and level of activity
- Neurological examination will be performed and you will be asked if you have any neurologic symptoms.
- Questionnaire about any neurological side effects
- Blood samples (approximately 5 tablespoons) will be collected for tests to check your general health and to check your multiple myeloma.
- You will need to collect urine samples over a 24-hour period (as described under 'screening') for routine tests to check your health.
- Pregnancy test will be done if you are a woman that is able to get pregnant and have regular or no menstrual cycles (periods). This will be done using the blood or urine samples you provide for the tests described above.
- Study drugs administered – dexamethasone, carfilzomib, and lenalidomide
- CT-PET scan – a detailed computer image of the area of your disease

Day 2

- Vital signs
- Study drugs administered - carfilzomib and lenalidomide

Days 3-7

- You will take lenalidomide at home

Day 8

- Study drugs administered - dexamethasone and lenalidomide

Days 9-14

- You will take lenalidomide at home

Day 15

- Vital signs
- Study drugs administered - dexamethasone, carfilzomib, and lenalidomide

Day 16

- Vital signs
- Pregnancy test will be done if you are a woman that is able to get pregnant and have regular or no menstrual cycles (periods). This will be done using the blood or urine samples you provide for the tests described above.
- Study drugs administered - carfilzomib and lenalidomide

Days 17-21

- You will take lenalidomide at home

Day 22

- Blood samples (approximately 5 tablespoons) will be collected for tests to check your general health and to check your multiple myeloma.
- Study drugs administered – dexamethasone and lenalidomide

End of Study Visit

- Medical history update – questions about your health, medications/tests you have had and any symptoms or side effects you have experienced since your last visit
- Physical examination, including checking your weight, height, vital signs and level of activity
- Neurological examination will be performed and you will be asked if you have any neurologic symptoms.

- Questionnaire about any neurological side effects
- Skeletal survey (x-rays of your bones)
- ECG
- Blood samples (approximately 5 tablespoons) will be collected for tests to check your general health and to check your multiple myeloma. This will also include optional research tests if you agree to have them done.
- Bone marrow aspiration and/or biopsy.
    - Two samples of bone marrow aspirate (the liquid portion of the bone marrow) will be collected to measure your disease. Part of the sample may also be used for other research purposes if you give consent (see "Additional Optional Research Studies" section)
- You will need to collect a urine sample over a 24-hour period (as described under 'screening') and provide a fresh sample for routine tests to check your health.
- Pregnancy test will be done if you are a woman that is able to get pregnant and have regular or no menstrual cycles (periods). This will be done using the blood or urine samples you provide for the tests described above.
- Return and review study diary with a member of the research team
- Return all unused lenalidomide as instructed through the Revlimid REMS® program. All unused study drug capsule, all study drug bottles, and drug diary must be returned to a member of the research team.
- CT-PET scan – a detailed computer image of the area of your disease

Long Term Follow-up

If your myeloma did not worsen while on this study, you will be contacted every 3 months for 5 years from the end-of-treatment visit to check how you are doing and the status of your myeloma. It is recommended that after you have completed participation in this study, you receive lenalidomide alone at the last highest dose you received and which did not cause unacceptable side effects (last tolerated dose). This will be discussed with you and your doctor. A CT/PET scan will be performed one year after your end of treatment bone marrow biopsy. You will need to have two bone marrow biopsy samples done 1, 2, 3, and 5 years after your end of study visit to check the status of your disease (plus or minus 30 days).

During this study, Dr. Jakubowiak and his research team will collect information about you for research purposes. This will include your name, contact information (address, telephone numbers, and/or email), social security number (for overall-survival follow-up), medical record number, insurance information, demographic information (gender,

birth date, race/ethnicity), medical history (including current medications), cancer history (including diagnosis and treatment history), dates (of consent, drug administration, side effects and any medical procedures and/or tests), results of physical and neurological exams, weight, height, vital signs, performance status, side effects, results of blood and urine tests, pregnancy test results (if applicable), blood, urine, and tissue samples and reports, diaries and questionnaires, bone marrow aspirate/biopsy samples and results, ECG and results, x-rays and reports including tumor measurements, and the results of any other tests to check your health or disease status.

HOW LONG WILL I BE IN THE STUDY?

We think you will be on study treatment for at least 4 cycles and up to 18 cycles (about 4 to 18 months).

After 4 cycles, if you are still a transplant candidate, and your myeloma gets better from the study drugs, you may have stem cells collected for a stem cell transplant. During transplant, you will be considered "off study" and will be re-screened after transplant to make sure you can continue on the study drugs, carfilzomib, lenalidomide and dexamethasone.

If you are no longer a transplant candidate after 4 cycles, you may be considered to continue receiving carfilzomib, lenalidomide and dexamethasone as discussed with your study doctor.

After 8 cycles of carfilzomib, lenalidomide and dexamethasone, and if your disease is stable or if you have responded and your side effects are not too severe, you may continue on maintenance for as long as you are benefitting and want to continue. You or your insurance company will be responsible for all costs (except for carfilzomib, which will be provided by Amgen) if you choose to continue on maintenance.

If your myeloma did not worsen while on study, you will be contacted every 3 months for 5 years from the end-of-study visit to check how you are doing and the status of your myeloma.

You can stop taking part in this study at any time. It is important to tell the study doctor if you are thinking about stopping, so your study doctor can look at risks of stopping the lenalidomide, carfilzomib and dexamethasone combination drug administration.

In some cases, abrupt stopping of a drug can have risks. You may be asked to have additional laboratory tests and physical examinations if your study doctor feels it is

necessary. Another reason to tell your study physician that you are thinking about stopping is to discuss what follow-up care and testing could be most helpful for you.

Dr. Jakubowiak may decide to take you off of the study without your consent if:

- You are unable to meet the requirements of the study,
- Your medical condition changes,
- The study drug is no longer available,
- New information becomes available that indicates that participation in this study is not in your best interest, or
- If the study is stopped.

WHAT ARE THE RISKS OF THE STUDY?

There are risks to taking part in any research study. One risk is that you may get a drug or dose of a drug that does not help treat your disease or that makes your condition or disease worse. Another risk is that there may be side effects associated with the study drugs.

All chemotherapy drugs have side effects, which can range from mild and reversible to severe, long lasting and possibly **life-threatening**. There is a great deal of unpredictability among side effects of different drugs and between individuals. For experimental drugs, not all of the risks are known. **You need to tell the research doctor or a member of the study team immediately if you experience any side effects.** Also notify your regular doctor as soon as possible.

Since many drugs used to treat cancer are designed to cause the rapidly dividing cancer cells in your body to slow down or die, these drugs can also cause other rapidly dividing normal cells in your body to slow down or die. These include the blood cells that help to fight infection (white blood cells), the blood cells that help the blood clot (platelets), and the blood cells that carry oxygen in your body (red blood cells). When anticancer drugs cause a decrease in these blood cells, it is called bone marrow suppression. While you are participating in this research study, your blood cell levels will be monitored closely.

Please notify your study doctor and your regular doctor if possible, if any of the following happens:

A fever of 100.5 or above: This could be a sign of an infection. If you have a low white blood cell count, this can be serious, **life-threatening or fatal**. You may have to take antibiotics or be admitted to the hospital.

- **<u>Low energy or shortness of breath</u>:** This could be a sign of anemia (not enough red blood cells). If this becomes severe, you may need to come into the clinic or hospital to have a transfusion of red blood cells.
- **<u>You bruise easily, or, when injured, you do not stop bleeding</u>:** This could be a sign that your platelets (blood cells that help with clotting) are low. **This can be serious or life-threatening.** You may need to come into the clinic or hospital for a transfusion of platelets.

Many cancers, including myeloma, are linked with an increased risk of blood clots forming that could lead to swelling in the legs and arms. These clots may travel to the lungs causing shortness of breath or to the brain causing a stroke. **This may become serious and life threatening.** Lenalidomide, one of the study drugs, can increase this risk.

Other common side effects include nausea, vomiting, and loss of appetite. You may also experience constipation, loose stools or diarrhea. It is important to drink more water and/or other fluids if you have diarrhea. If the diarrhea becomes severe, you may have to be hospitalized and receive intravenous fluids.

Everyone in the study will be watched carefully for side effects. You will be monitored to keep track of your blood counts and organ function, particularly your kidney and liver function. If you experience side effects, they may go away after you stop taking the study drug. Some side effects can be mild; but others can be long lasting and may never go away. Some may be **life-threatening or fatal.**

Since the effect of the study drug(s) taken with other medications may not be known, it is important that you tell the research doctor about all drugs, prescription and non-prescription drugs, herbal preparations and nutritional supplements that you are taking or planning to take.

<u>Risks Associated with Carfilzomib</u>

Carfilzomib (Kyprolis) is approved to be used only in certain patients with multiple myeloma that have tried and failed other therapies. It has not been approved to be used for any other disease or condition. In this study, carfilzomib is an investigational study drug because it is not approved for use in all patients, and it is not approved by some regulatory authorities (the agencies that are responsible for approving the use of a medicine in a country). You will be told about the known risks, which are the side effects reported previously by others who took carfilzomib. However, your doctors do not know all the side effects that you may experience. As with all investigational drugs, all risks may not have been identified at this time. **There may be serious unexpected or unforeseen risks while**

taking carfilzomib, including death. It is known that nearly everyone who takes carfilzomib will have some side effects while on the drug. Many of these side effects may be mild but some side effects **can be serious and even fatal.**

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

As of 19 January 2018, approximately 4,172 subjects have received carfilzomib in Amgen-sponsored clinical trials and business-partner-sponsored clinical trials.

As of 15 March 2018, approximately 5,283 subjects have received carfilzomib in investigator- sponsored trials (ISTs).

Since it was first approved for sale, approximately 78,647 patients have been prescribed carfilzomib (Kyprolis®) for treatment.

Before you take carfilzomib, your doctor needs to know if you have any:

- Heart problems, including a history of chest pain (angina), heart attack, heart failure, irregular heartbeat, or if you have ever taken a medicine for your heart
- Lung problems, including a history of shortness of breath (dyspnea) at rest or with activity
- Kidney problems, including kidney failure or if you have ever received dialysis
- Liver problems, including a history of hepatitis, fatty liver, or if you have ever been told your liver is not working properly
- Unusual bleeding, including easy bruising, bleeding from an injury, such as a cut that does not stop bleeding in a normal amount of time, or internal bleeding, which can indicate you have low platelets
- Blood clots in your veins
- Any other major disease for which you were hospitalized or received medication

Talk to your doctor or nurse if any of these apply to you before using carfilzomib. You may need extra tests to check that your heart, kidneys and liver are working properly.

Conditions You Need To Look Out For

You must look out for certain symptoms while you are taking carfilzomib to reduce the risk of problems. Carfilzomib can make some conditions worse or cause serious side effects. Carfilzomib may cause all, some, or none of the side effects listed below. There may also be unknown side effects from taking carfilzomib alone or with other drugs you may be taking. Tell your doctor or nurse as soon as possible if you get any of these:

- Chest pains, shortness of breath, or if there is swelling of your ankles and feet, which may be symptoms of heart problems.

- Difficulty breathing, including shortness of breath (dyspnea) at rest or with activity or a cough, rapid breathing, feeling like you can't breathe in enough air, wheezing, or cough, which can be signs of lung problems.
- Extremely high blood pressure, severe chest pain, severe headache, confusion, blurred vision, nausea and vomiting, or severe anxiety, which may be signs of a condition known as hypertensive crisis.
- Shortness of breath with everyday activities or at rest, irregular heartbeat, racing pulse, tiredness, dizziness, and fainting spells, which can be signs of a condition known as pulmonary hypertension.
- Swollen ankles, feet or hands, loss of appetite, passing less urine, or abnormal blood test results, which may be symptoms of kidney problems or kidney failure.
- Irregular heartbeat, kidney failure or abnormal blood test results which may be associated with Tumor Lysis Syndrome, which can be caused by the rapid breakdown of tumor cells.
- A reaction to carfilzomib infusion, which can include the following symptoms: fever, chills or shaking, joint pain, muscle pain, facial flushing or swelling, weakness, shortness of breath, low blood pressure, fainting, chest tightness, or chest pain.
- Unusual bruising or bleeding, such as a cut that does not stop bleeding in a normal amount of time or internal bleeding such as coughing up blood, vomiting up blood, dark tarry stools, or bright red blood in your stools.
- Leg pain (which could be a symptom of blood clots in the deep veins of the leg), chest pain or shortness of breath (which may be a symptom of blood clots in the lungs).
- Yellowing of your skin and eyes (jaundice), abdominal pain or swelling, nausea or vomiting, which could be signs of liver problems, including liver failure.
- Bleeding, bruising, weakness, confusion, fever, nausea, vomiting and diarrhea, and acute kidney failure, which may be signs of a blood conditions known as Thrombotic Microangiopathy (including Thrombotic Thrombocytopenic Purpura/Hemolytic uremic syndrome (TTP/HUS).
- Headaches, confusion, seizures, blindness, and high blood pressure (hypertension), which may be symptoms of a neurologic condition known as Posterior Reversible Encephalopathy Syndrome (PRES).

The chance of these and other side effects happening to you is shown in the table below;

Body System	Very Common (may affect more than 1 in 10 people)	Common (may affect up to 1 in 10 people)	Uncommon (may affect up to 1 in 100 people)	Rare (may affect up to 1 in 1000 people)
Blood	Low red blood cell count, which may cause tiredness and fatigue; Low platelets, which may cause easy bruising or bleeding; Low white blood cell count, which may decrease your ability to fight infection	Low white blood cell count associated with fever	Hemolytic uremic syndrome (HUS) (see 'Conditions you need to look out for')	Thrombotic thrombocytopenic purpura (TTP) (see 'Conditions you need to look out for'); Thrombotic microangiopathy (see 'Conditions you need to look out for')
Heart		Heart failure*, and heart problems including rapid, strong or irregular heartbeat	Heart attack; Reduced blood flow to the heart; Abnormal amount of fluid between the heart and the lining around the heart; Swelling and irritation of the lining around the heart	
Lung	Shortness of breath; Cough, cough with phlegm	Blood clot in the lungs; Fluid in the lungs; Nose bleed; Change in voice or hoarseness; Pain in throat; Wheezing; Pulmonary hypertension (see 'Conditions you need to look out for')	Lung problems (see 'Conditions you need to look out for'); Bleeding in the lungs	
Eye		Blurred vision; Cataract		

Body System	Very Common (may affect more than 1 in 10 people)	Common (may affect up to 1 in 10 people)	Uncommon (may affect up to 1 in 100 people)	Rare (may affect up to 1 in 1000 people)
Intestine	Diarrhea; Nausea; Constipation; Vomiting; Stomach Pain	Indigestion; Toothache	Perforation in stomach, small intestine, or large bowel; Bleeding in the stomach and bowels	
General	Tiredness (fatigue); Fever; Swelling of the hands, feet or ankles; Chills; General weakness	Pain; Feeling too hot; Pain, swelling, irritation or discomfort where you received the injection into your vein; Infusion reactions (see 'Conditions you need to look out for')	Multi-organ failure	
Liver		Liver problems including an increase in your liver enzyme in the blood	Liver failure; Itchy skin, yellow skin, very dark urine and very pale stools which may be caused by a blockage in the flow of bile from the liver (cholestasis)	
Infections	Respiratory tract infection; Pneumonia	Sore throat; Bronchitis; Runny nose or nasal congestion; Urinary tract infection; Inflammation of the nose and throat; Flu-like symptoms (influenza); Serious infection in the blood (sepsis); Viral infection;		

Body System	Very Common (may affect more than 1 in 10 people)	Common (may affect up to 1 in 10 people)	Uncommon (may affect up to 1 in 100 people)	Rare (may affect up to 1 in 1000 people)
		Infection and/or irritation of your stomach and bowels; Lung infection		
Metabolism	Decreased appetite	Dehydration	Tumor lysis syndrome (TLS) (see "Conditions you need to look out for')	
Bone and Muscle	Back pain; Joint pain; Pain in limbs, hands or feet; Muscle spasms	Bone and muscle pain; Chest pain; Muscle weakness; Aching muscles		
Nervous System	Headache; Dizziness; Numbness.	Abnormal sensation such as tingling or decreased sensation in arms and/or legs	Bleeding in the brain	Posterior reversible encephalopathy syndrome (PRES) (see 'Conditions you need to look out for')
Psychiatric	Insomnia (difficulty sleeping)	Anxiety		
Kidney		Kidney problems, including decreased ability to make urine, increased creatinine in the blood, and kidney failure needing dialysis		
Skin		Rash; Itchy skin; Redness of the skin; Increased sweating		
Tests	Changes to blood tests (decreased blood levels of potassium, increased	Changes to blood tests (decreased blood levels of sodium, magnesium, protein, calcium or		

Body System	Very Common (may affect more than 1 in 10 people)	Common (may affect up to 1 in 10 people)	Uncommon (may affect up to 1 in 100 people)	Rare (may affect up to 1 in 1000 people)
	blood levels of sugar and/or creatinine)	phosphate, increased blood levels of calcium, uric acid, potassium, bilirubin, or c-reactive protein)		
Immune System			Allergy to carfilzomib	
Blood vessels	High blood pressure (hypertension)	Low blood pressure (hypotension); Blood clots in the veins; Flushing	Stroke; Bleeding; Extremely high blood pressure (see 'Conditions you need to look out for')	
Ear and labyrinth		Ringing in the ears		

*The risk of developing heart failure when receiving carfilzomib is higher if you are 75 years of age or older. This risk is also higher if you are Asian.

The following side effects have been seen in people who received carfilzomib. It is unknown if they were caused by carfilzomib, you may or may not experience these side effects:

- Tiredness
- Infection
- easy bruising or bleeding, which may be symptoms of a blood condition known as Myelodysplastic syndrome/Acute Myeloid Leukemia (MDS/AML)
- Tenderness of pain in the abdomen that gets more intense with motion or touch
- abdominal bloating or distention
- nausea and vomiting
- diarrhea
- constipation or the inability to pass gas which may be symptoms of swelling of the thin tissue that lines the inner wall of the abdomen and covers most of the abdominal organs.

Driving and Using Machines

You may experience fatigue, dizziness, fainting, and/or a drop in blood pressure after treatment with carfilzomib. This may impair your ability to drive or operate machinery. If you have these symptoms, you should not drive a car or operate machinery.

Hydration Risks

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

Risks Associated with Dexamethasone

The most common side effects of dexamethasone that have been seen in humans with multiple myeloma are listed below:

- Central nervous effects (such as agitation, nervousness, mood swings, personality changes)
- Bleeding of the gut or peptic ulcer
- Blood clots in the lung
- Serious infections
- Acne
- Increased hair growth
- Cataracts (clouding of the lens of the eye)
- Glaucoma (high fluid pressure within the eye which can lead to damage of the optic nerve)
- Osteoporosis (loss of bone density or softening of the bones)
- Swelling of the face
- Hypertension (high blood pressure), including hypertension in the veins/arteries of the lungs
- Diabetes
- Fungus growth in mouth and/or esophagus
- Muscle weakness affecting mostly the muscles of the thighs and arms
- Nausea, vomiting
- Formation of a hole in the small or large bowel particularly in people with pre-existing bowel problems
- Irritation and bleeding of the esophagus
- Insomnia
- Increased appetite
- Weight gain
- Weight loss due to the body not being able to break down and use protein
- Decreased tolerance for starchy foods

- Heart failure in people who have previous heart conditions
- Allergic reaction (this may include redness of the face, shortness of breath, perspiration, abdominal cramps, fast heart beat and low blood pressure)
- Convulsions
- Brain swelling
- Dizziness
- Headache
- Inflammation of the pancreas
- Abdominal swelling
- Fluid retention (swelling)
- Loss of potassium
- Tired feeling
- Skin bruising
- Swelling / redness of the skin
- Increased sweating
- Itching
- Low hormone levels which can cause you to feel unusually tired, weak, and to lose your appetite
- Hiccups
- Feeling achy
- Black, tarry stools

Risks Associated with Revlimid (Lenalidomide)

Lenalidomide has been studied in healthy volunteers and in persons with cancer of the blood and in patients with other diseases. As with any other drug, there may be side effects or risks associated with lenalidomide, some of which are not yet known.

Listed below are the side effects experienced by 6,600 subjects who have participated in previous and ongoing studies involving lenalidomide. Side effects may be mild to very severe.

Common Side Effects (10% or more of persons)

Side effects considered serious are bolded.

- **Neutropenia** or a decrease in white blood cells that can make you more prone to infections, fatigue or feeling tired. You may need to have blood transfusions or certain medicines if your blood counts go too low.

- Fatigue or feeling tired
- **Anemia** or a decrease in red blood cells that can cause tiredness
- **Thrombocytopenia** or a decrease in platelets which can cause you to bruise or bleed easily
- Constipation or difficulty moving your bowels
- Diarrhea or loose/frequent bowel movements
- Nausea
- Loss of appetite
- **Back pain**
- Joint pain
- Muscle cramps
- Swelling of the arms and legs
- Problems falling asleep or staying asleep
- **Fever**
- Cough
- **Shortness of breath** or difficulty catching your breath
- Upper respiratory infection
- Rash
- Itching and dry skin
- Lack or loss of strength
- Dizziness
- Headache

Less Common Serious side effects (1% or more of persons and not listed in bold above)

- Fever with neutropenia which is a decrease in white blood cells that help fight infections
- Irregular heartbeat
- Deep vein thrombosis or blood clots in larger blood vessels
- Pneumonia or an infection of the lungs
- Progression of the disease
- Sepsis or an infection of the blood
- Dehydration or loss of water from the body, organ or body part, as from illness or lack of fluid
- Kidney failure or inability of the kidneys to remove waste from the body
- Growth of abnormal tissue under the skin
- Formation of a hole in the small or large bowel
- Not enough blood flow to the bowel
- Multi organ failure
- Swelling of the tissue that lines the eyelids and surface of the eye

- Bleeding in the eye
- Swelling of the pancreas, stomach, intestines or prostate (which may cause nausea, vomiting, abdominal cramps, fullness of abdomen, tenderness when touched, pain in the upper stomach, low blood pressure, severe sweating, cold and clammy body, slight jaundice, weight loss, white or pale colored stool, chronic diarrhea, urinary tract infections, inability to urinate, leaking of urine, and blood in urine)
- Abnormal liver function (which may cause the yellowing of the skin and whites of the eyes; tenderness or swelling of the upper right quadrant in the abdomen and fever; dark urine, light-colored, bloody or black bowel movements; vomiting, diarrhea; loss of appetite; unexplained weight differences; or fatigue and weakness)
- Increase in white blood cells (which may cause fever, sweating and headache)
- Infection of digestive system (which may cause vomiting, diarrhea, nausea, abdominal cramps, abdominal pain, increased heart rate, and lethargy
- Scars in the lungs, which may cause chest pain, cough, shortness of breath, wheezing, weight loss, exhaustion, night sweats, chills and clubbing a build-up of tissue in the fingers, causing the end of the fingers to become enlarged and the nails to curve downward)
- Damaged airways in the lungs, which may cause restricted amount of air getting into the lungs
- Bleeding in the air spaces of the lungs
- Pulmonary embolism or blood clot in or around the lungs

The following events have been reported from clinical studies and in studies after the drug was approved:

- Rare angioedema (an allergic skin disease which includes small areas of swelling involving the skin and/or the lining of your nose, mouth, stomach and intestines)
- Serious skin reactions including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). SJS and TEN are serious allergic skin reactions that begin as a rash in one area and later cover more of the body leading to separation of the top layer of skin (could be body-wide) which have been reported with lenalidomide. These side effects have the potential to result in **death.**
- Occasional irregular heartbeat, heart attack, and congestive heart failure (condition where the heart becomes weak and cannot pump enough blood to the rest of the body) have been reported with the use of lenalidomide.
- Tumor lysis syndrome (TLS) and tumor flare reaction (TFR) have commonly been observed in persons with a type of blood cancer called Chronic

Lymphocytic Leukemia (CLL), and uncommonly in persons with other lymphomas (immune system cancer), who received lenalidomide. There have been rare reports of TLS in persons with Multiple Myeloma (MM) that received lenalidomide, and no reports in persons with Myelodysplastic Syndrome (MDS) that received lenalidomide. Tumor lysis syndrome can happen with or without treatment of cancer. Tumor flare reaction is a condition that involves any of the following: increase in size of the cancerous lymph nodes, rash and slight fever.

- The rare side effect of rhabdomyolysis has been seen with lenalidomide. This is a serious condition involving destruction of skeletal muscle that can lead to kidney damage. Signs and symptoms include dark, red or cola colored urine, muscle tenderness and stiffness, aching (myalgia) or weakness.

Hematological Toxicity

Lenalidomide is associated with significant neutropenia (decrease in white blood cells that help fight infection) and thrombocytopenia (decrease in platelets that help with blood clotting). You will have your blood counts checked frequently when starting lenalidomide.

Deep Vein Thrombosis (DVT) and Pulmonary Embolism (PE)

Lenalidomide has shown an increased risk of deep vein thrombosis (blood clot in a larger blood vessel) and pulmonary embolism (a blood clot in or around the lungs) in some people with certain medical conditions. The study staff will ask you about any health conditions you may have that may increase your chance of developing blood clots. The risk of blood clots may also be increased when lenalidomide is combined with other drugs known to cause blood clots such as steroids, other forms of cancer drugs, hormone replacement therapy, birth control pills, and erythropoietin (a drug given to help increase the red cell count). You should let your doctor know if you take birth control pills or hormone replacement therapy.

You may be asked to take a blood thinner such as aspirin if your doctor feels that you are at increased risk for blood clots. If your platelet count becomes low, the blood thinners may need to be stopped temporarily.

You will be instructed on the signs and symptoms of DVT and PE, including shortness of breath, chest pain or swelling of the arm and or leg. If symptoms of DVT or PE occur you should contact your study doctor, healthcare provider or get emergency medical care right away.

Reports of disease progression into a type of blood cancer called acute myeloid leukemia (AML) have been reported from Myelodysplastic Syndrome (MDS) studies. It is unclear whether

lenalidomide increases the risk of AML or if progression into a blood cancer is caused by the natural course of the disease. AML is the rapid multiplication of abnormal cells which accumulate in the bone marrow and interfere with the production of normal blood cells. AML is a very serious condition which may result in **death.**

Second new cancers

According to researchers, people with cancer have a higher risk of developing a second new cancer when compared to people without cancer. You should make your study doctor aware of your medical history and any concerns you may have regarding the increased risk of other cancers.

Other Risks associated with Lenalidomide

Lenalidomide has been shown to increase the level of digoxin in the blood in some people. Tell your doctor if you are taking digoxin.

Often, the side effects improve when the drug is stopped or delayed between research study cycles, but sometimes a new treatment is needed to manage the side effects. Your health care team may give you medicines to help lessen or treat side effects. Many side effects go away soon after you stop taking study drug. In some cases, side effects can be serious, long lasting, or may never go away.

Very rarely, subjects have had serious side effects after taking the study drugs which sometimes required hospital care, transfusions, intravenous therapies, or even led to **death**. Your study doctor will monitor you carefully for any side effects; however, if you experience any side effects please tell your study doctor or nurse.

If any doctor, other than the study physician, prescribes medication for you, even if it is for another condition, or you are taking any over-the-counter medications or vitamins, it is very important that you inform the study staff. This is important because the interaction of some medications and supplements may cause serious side effects.

Risks Associated with Allopurinol

Allopurinol is a medication used to decrease the level of uric acid in your blood. Some side effects of allopurinol are:

- Upset stomach
- Diarrhea
- Sleepiness
- Eye irritation

- Skin rash – in rare cases, the skin rash may be severe. The chance of getting a skin rash is increased if you are also taking amoxicillin or ampicillin, two antibiotics related to penicillin. If you develop a skin rash at any time while taking allopurinol, notify your doctor immediately.
- Since allopurinol can cause drowsiness, please be careful with activities that require alertness, such as driving or operating heavy machinery.

You may wish to take allopurinol with food or after meals in order to cut down on stomach upset.

Risks Associated with Valacyclovir

- Headache
- Nausea
- Vomiting
- Diarrhea
- Abdominal pain
- Dizziness
- Agitation
- Confusion
- Delirium
- Psychosis (abnormal condition of the mind)
- Encephalopathy (disorder of the brain), which may cause loss of cognitive function, subtle personality changes, inability to concentrate, lethargy, and depressed consciousness
- Hallucinations
- Seizure
- Rash
- Fatigue
- Decreased white blood cell count, which may decrease your ability to fight infection
- Thrombotic thrombocytopenic purpura/Hemolytic uremic syndrome, which may cause very low red blood cell and platelet count. You may experience unusual bruising and bleeding or unexplained fever.
- Aseptic meningitis, which may cause disorientation, incontinence, headache, resistance to flexion of the neck, drowsiness, difficulty walking, or seizure
- Kidney failure, which may cause little or no urine when you urinate, swelling, especially in legs and feet, not feeling like eating, feeling confused, anxious and restless, or sleepy, pain in the back just below the rib cage (flank pain).

- The full risks of using valacyclovir when pregnant are not known. Therefore, females must not be pregnant or breastfeeding (valacyclovir is passed through breast milk) in order to participate in this study.
- If you have a poor kidney function, the dose of valacyclovir must be reduced. Please talk to your study doctor about the correct dose of valacyclovir.

Risks Associated with Study Procedures

Risks of Having Blood Drawn

Routine needle sticks for blood samples may cause pain, bruising and rarely, fainting or infection at the site where blood is drawn. Care will be taken to avoid these complications.

Risks Bone Marrow Biopsy/Aspiration

Having bone marrow collected may cause pain, bruising, bleeding, redness, swelling, and/or infection at the site of needle entry. An allergic reaction (mild, such as wheezing, rash, hives, low blood pressure or severe **life-threatening** anaphylactic reaction) to the anesthetic may occur. A scar may form at the site of needle entry. Care will be taken to avoid these complications.

Risks of Optional Research Testing on Blood and Bone Marrow Tissue Samples

There are very few risks to you from research blood and bone marrow testing. The samples will be taken at the same time as your routine blood and bone marrow samples, so no additional procedures are required. Risks of blood draws and bone marrow are described above. The research samples will only be taken after the routine tests are drawn. The same needle stick can be used with additional tubes for the blood and bone marrow.

The greatest risk for the optional research studies is the release of information from the research records on your blood, bone marrow and cheek swab samples. You may be concerned that if your genetic information becomes available outside of the research purposes it may raise concerns with employment or insurance coverage for you or your family. This research is not aimed, however, at studying inherited genetic characteristics (traits passed through families).

The University of Chicago will make every effort to ensure that your samples and results of research testing are kept private. Your identity will be maintained as confidential as possible within the limits of the law. Results of research testing on your blood, bone marrow and cheek swab samples will not be put in your health record. Also, people outside the research process will not have access to results about any one person which will help to protect your privacy. The chance that this information will be given to someone else is very small.

Radiation Risks Associated with Scans and X-Rays

While you are in this research study, x-rays, CT, PET, and Bone Scans, and/or other radioactive agents may be used to evaluate your disease. The total amount of radiation that you will get from these tests is relatively small and is not likely to be harmful to you or affect your disease.

Bone survey (also called a skeletal survey)

This is a series of X-rays of all the bones in the body. You must not have a bone survey if you think you could be pregnant.

Reproductive Risks:

Pregnancy Risk:

Lenalidomide is related to thalidomide. Thalidomide is known to cause **severe life-threatening** human birth defects**.** If lenalidomide is taken during pregnancy, it may cause birth defects or **death** to an unborn baby. Females must not become pregnant while taking lenalidomide. You have been informed of the risk of birth defects. If you are female, you agree not to become pregnant while taking lenalidomide. For this reason, lenalidomide is provided to subjects under a special distribution program called **Revlimid REMS®.**

In order to participate in this study you must register into and follow the requirements of the Revlimid REMS® program of Celgene Corporation. This program provides education and counseling on the risks of fetal exposure, blood clots and reduced blood counts. You will be required to receive counseling every 28 days while taking lenalidomide, follow the pregnancy testing and birth control requirements of the program that are appropriate for you and take telephone surveys regarding your compliance with the program. Both men and women enrolled in this study are required to register for the Revlimid REMS® program.

Pregnancy Risk – Females:

If you are a female who can get pregnant, you will be required to have two negative pregnancy tests: the first test within 10-14 days before lenalidomide is prescribed and the second test within 24 hours before lenalidomide is prescribed.

For this study a woman who can get pregnant is a sexually mature female who: 1) has not undergone a hysterectomy (the surgical removal of the uterus) or bilateral oophorectomy (the surgical removal of both ovaries) or 2) has not been naturally postmenopausal for at least 24 consecutive months.

You will be required to use **TWO** reliable forms of birth control, one highly effective method and one additional effective method at the same time or practice complete abstinence from heterosexual intercourse (not having heterosexual sex) during the following time periods related

to this study: 1) for at least 28 days before starting lenalidomide; 2) throughout lenalidomide administration, including interruptions in administration; and 3) for at least 28 days after stopping lenalidomide. The following are the acceptable birth control methods:

Highly Effective Methods	Additional Effective Methods
Intrauterine device (IUD)	Latex condom
Hormonal (birth control pills, injections, implants)	Diaphragm
Tubal ligation	Cervical Cap
Partner's vasectomy	

You must not breastfeed a baby while you are participating in this study and for at least 28 days after you have stopped lenalidomide.

Females who can get pregnant with regular or no menstrual cycles must agree to have pregnancy tests weekly for the first 28 days and then every 28 days while taking lenalidomide, at the time lenalidomide is stopped, and 28 days following stopping lenalidomide. If menstrual cycles are irregular, the pregnancy testing must occur weekly for the first 28 days and then every 14 days while taking lenalidomide, at stopping of lenalidomide, and at days 14 and 28 following stopping of lenalidomide.

If you have any reason to suspect you are pregnant, you must IMMEDIATELY stop taking lenalidomide and tell your doctor.

Males:
Lenalidomide is present at very low levels in human semen of healthy men for three days after stopping the drug, according to a study. For some men, such as men with kidney problems, lenalidomide may be present in semen for more than three days. For these reasons, to be safe, all male subjects receiving lenalidomide must use a latex condom during any sexual contact with a pregnant female or with a female who can get pregnant (as defined above) while you are participating in this study, including times when lenalidomide is temporarily stopped, and for at least 28 days after permanently stopping the drug, even if you have had a successful vasectomy.

You must **NEVER** donate blood, sperm, or semen while you are participating in this study and for at least 28 days after you have stopped taking the drug.

ALL SUBJECTS:
You will be counseled at least every 28 days while taking lenalidomide and again one last time when you stop taking lenalidomide about not sharing lenalidomide (and other study drugs), the potential risks of fetal (unborn baby) exposure, refraining from blood and other donations, the risk of changes in blood counts and blood clots, and you will be reminded not to break, chew or open lenalidomide capsules. You will be provided with the "Lenalidomide Information Sheet for Persons Enrolled in Clinical Research Studies" with each new supply of lenalidomide as a reminder of these safety issues.

You must **NEVER** share lenalidomide (or other study drugs) with someone else. You must **NEVER** donate blood while you are participating in this study and for at least 28 days after you have been discontinued from the study. You must receive counseling and complete phone surveys as required by the **Revlimid REMS®** program.

In the case of suspected pregnancy:
If a female subject or the partner of a male subject suspects pregnancy this should immediately be reported to the study doctor. The doctor will advise you of the possible risks to your unborn baby and discuss options for managing the pregnancy with you. Because of possible risks to your unborn baby, the study drugs will be stopped permanently. Male subjects who fail to follow birth control requirements will also have their drugs stopped.

There may be other risks that could arise which are not reasonably foreseeable. If new information becomes available which could influence your willingness to continue, this new information will be discussed with you in a timely manner.

ARE THERE ANY BENEFITS TO TAKING PART IN THE STUDY?
If you agree to take part in this study, there may or may not be direct medical benefit to you. We hope the information learned from this study will benefit other individuals with multiple myeloma in the future.

WHAT OTHER OPTIONS ARE THERE?
Instead of being in this study, you have these options:

- Standard treatments with FDA approved drugs including:
  - Melphalan and prednisone
  - Dexamethasone alone or in combination with other drugs (including lenalidomide outside of this study)
  - Bortezomib alone or in combination with other drugs
  - Cytoxan alone or in combination with other drugs

    - Thalidomide alone or in combination with other drugs
- Taking part in another research study
- Not getting treatment for your cancer
- Getting comfort care (also called palliative care). This type of care may help to reduce pain, tiredness, appetite problems and other problems caused by the cancer. It does not treat the cancer directly, but instead tries to improve how you feel.

The decision whether or not you wish to participate in this study will not affect your care at the University of Chicago Medical Center.

WHAT ARE THE COSTS?

Clinical services provided during a clinical trial are either research-related or related to usual medical care. Research-related services are done to complete the research and the costs are not the responsibility of you or your insurance.

The costs that are considered research-related for this study include the following: carfilzomib as long as you receive it on this study, and study samples which include bone marrow aspirate (collected during routine procedures) and blood at screening, time of response (to confirm complete response), and/or end-of-treatment visit, buccal mucosa swab will be collected at screening only.

Usual medical care costs include any and all services that are considered medically necessary for your disease. This will include the costs of dexamethasone, lenalidomide and any other medications you are given, administration of all drugs, all costs of a stem cell transplant including hospital stays, certain blood work, urinalysis, pregnancy tests, 24-hour urine tests, bone marrow biopsies, physical exams, vital signs, height, weight, performance status, urine tests, ECG's, neurological assessment and skeletal surveys. The cost of this usual, ongoing medical care will be the responsibility of you or your insurance, and may include deductibles and co-payments. Similarly, this care will be subject to all the same requirements and restrictions of your insurance.

If you suffer an unanticipated injury as a direct result of this research and require emergency medical treatment, the University of Chicago Medical Center will provide such treatment at the University of Chicago Medical Center at no cost to you. You must notify Dr. Jakubowiak as promptly as possible after your injury in order to receive this care. An injury is "unanticipated" if it is not one of the known effects of a study drug, medical device or procedure, and is not the result of your disease or condition. The costs of any non-emergency care for such an injury will be billed to you or your insurance or the study as appropriate. If you think that you have

suffered a research related injury, you must let Dr. Jakubowiak know right away.

WILL I BE PAID FOR MY PARTICIPATION?
You will not be paid to participate.

Your participation in this research study may help in the development of drugs and/or therapies from which Amgen Inc (the maker of carfilzomib) or others may get a financial benefit. There are no plans to pay you for any patents or discoveries that come from this research.

WHAT ABOUT CONFIDENTIALITY?
Study records that identify you will be kept confidential. The University of Chicago will take steps to protect your personal data. Your study records will be available to the study doctor, research nurse, data coordinator, and other research staff. Upon enrolling in this study, you will be assigned an identification number. All records related to the study will use this identification number. This information will be kept indefinitely. Your study records will be stored in secured databases and locked offices.

The data collected in this study will be used for the purpose described in the form. By signing this form, you are allowing the research team access to your medical records, which include Protected Health Information. Protected Health Information (PHI) consists of any health information that is collected about you, which could include your medical history and new information collected as a result of this study. The research team includes the individuals listed on this consent form and other personnel involved in this study at the University of Chicago.

As part of the study, Dr. Jakubowiak and his research team will report the results of your study-related procedures and tests explained above to:

- The Multiple Myeloma Research Consortium, Inc. (an organization consortium that provides financial and administrative support for the conduct of clinical trials to member institutions) and its contractors or designees,
- Amgen (provider of carfilzomib), and/or its representatives and collaborators,
- Researchers at other institutions, which are participating in this study.
- Adaptive Biotechnologies (the lab responsible for testing one of your bone marrow samples)

These would include your demographic information (initials, medical record, subject ID number, race/ethnicity, background, gender, date of birth) medical history (including current medications), cancer history (including diagnosis and treatment history), dates (of consent, drug

administration, side effects and any medical procedures and/or tests), results of physical and neurological exams, weight, height, vital signs, performance status, side effects, results of blood and urine tests, pregnancy test results (if applicable), blood, urine, and tissue samples and reports, diaries and questionnaires, bone marrow aspirate/biopsy samples and results, ECG and results, x-rays and reports including tumor measurements, and the results of any other tests to check your health or disease status. This information is being sent to assure the quality of how the study is run, and to allow for the following activities: gathering and analyzing study data, confirming study results, publishing study results, reporting on side effects, and for research directly related to the study drug in disease therapy and diagnosis.

The study sponsor or their representatives, including monitoring agencies, may also review your medical record. Please note that these individuals may share your health information with someone else.

Your PHI may be shared with governmental agencies, including the National Cancer Institute for federally mandated reporting purposes. Your records may be reviewed by federal agencies whose responsibility is to protect human subjects in research including the Food and Drug Administration (FDA) and Office of Human Research Protections (OHRP). In addition, representatives of the University of Chicago, including the Institutional Review Board, a committee that oversees the research at the University of Chicago, may also view the records of the research. If your research record is reviewed by any of these groups, they may also need to review your entire medical record.

If health information is shared outside the University of Chicago, the same laws that the University of Chicago must obey may not protect your health information.

The results from tests and/or procedures performed as part of this study may become part of your medical record. During your participation in this study, you will have access to your medical record. Dr. Jakubowiak is not required to release to you research information that is not part of your medical record.

This consent form will be kept by the research team for at least six years. The study results will be kept in your research record and be used by the research team indefinitely. At the time of study completion, either the research information not already in your medical record will be destroyed or information identifying you will be removed from study results. Any research information in your medical record will be kept indefinitely.

Data from this study may be used in medical publications or presentations. Your name and other identifying information will be removed before this data is used. If we wish to use identifying information in publications, we will ask for your approval at that time.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

WHAT ARE MY RIGHTS AS A PARTICIPANT?

Taking part in this study is voluntary. If you choose not to participate in this study, your care at the University of Chicago/University of Chicago Medical Center will not be affected. You may choose not to participate at any time during the study. Leaving the study will not affect your care at the University of Chicago/University of Chicago Medical Center.

If you choose to no longer be in the study and you do not want any of your future health information to be used, you must inform Dr. Jakubowiak in writing at the address on the first page. Dr. Jakubowiak may still use your information that was collected prior to your written notice.

We will tell you about significant new information that may affect your willingness to stay in this study.

You will be given a signed copy of this document. This consent/authorization form document does not have an expiration date.

WHOM DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?

You have talked to _____ about this study and you had the opportunity to ask questions concerning any and all aspects of the research. If you have further questions about the study, you may call Dr. Jakubowiak at (773) 834-1592.

If you have a research related injury, you should immediately contact Dr. Jakubowiak at (773) 834-1592 or the Hematology/Oncology answering service at (773) 702-4400 and they will page your doctor or covering physician.

If you have any questions concerning your rights in this research study you may contact the Institutional Review Board, which is concerned with the protection of subjects in research projects.

You may reach the Committee office between 8:30 am and 5:00 pm, Monday through Friday, by calling (773) 702-6505 or by writing: Institutional Review Board, University of Chicago, 5841 S. Maryland Ave., MC7132, I-625, Chicago, Illinois 60637.

ADDITIONAL OPTIONAL SAMPLES FOR RESEARCH STUDIES

In order to better understand and develop treatments for cancer, you are being asked to donate additional bone marrow cells, blood samples and cells from the inside of your mouth (collected using buccal mucosa swabs) for research purposes. These cells may be used for many different purposes, including markers of response and markers for individualized therapy. Researchers will look for a comparison between certain biological measures (called biomarkers) in your bone marrow samples and compare it with other individuals to see if a pattern of those biological measures can possibly predict the response to the combination of the study drugs. These cells will not be used for any clinical purposes. In addition, a small part of the cells may be frozen and stored away, making them available for additional testing in the future. Cells that are stored in the frozen state may someday be used to create cell lines (a group of cells that are kept growing in the laboratory for research purposes). If additional testing is done on these samples, you will not be contacted for permission to use your sample for this additional research.

This sub-study includes the discovery of genes and/or the analysis genes to identify possible drug response markers. Genes are the parts of our cells that control the characteristics we inherit from our parents, the color of our eyes and hair, and may also show trends toward certain diseases or medical conditions. This sub-study is not aimed at studying inherited genetic characteristics (traits passed through families). The goal of this research study is to determine if these genes help to predict which people will or will not respond to the study drug combination.

Genetic research can be done by testing individual genes, or groups of genes, or all of the body's genes. In this consent form, when genetic research is described, it includes the possibility that any of these methods might be used. During this research, it is possible that all of your genetic material will be determined, including those genes that may cause other diseases. This information will not be shared with you.

What is involved?

If you partake in this optional research study, extra bone marrow samples will be collected. This will be done at the same time at your regularly scheduled sampling in the main part of the research at your Screening visit, after Cycle 4, after Cycle 8, at the time of complete response (to confirm your response) and/or at your End of Study visit. While you are undergoing the "aspiration" (withdrawal) part of the bone marrow biopsy an additional 2-3 tablespoons of bone

marrow will be removed. This will not involve an additional stick with the needle but may result in increased discomfort.

Additional peripheral blood samples (approximately 2-4 tablespoons) will be collected at the time you are scheduled for other blood tests necessary for your disease treatment during your screening visit, after Cycle 4, after Cycle 8, at time of complete response (to confirm your response), and/or at your End of Study visit.

If you partake in this optional research study we will collect a cheek swab from each cheek by wiping the inside of your cheek with a cotton swab. This will be done at the time your other screening samples are collected.

Research Use

Genetic Research

Many types of research use normal or diseased (cancerous) samples. Researchers can study proteins, RNA and DNA (genes). The study of genes (DNA) is often called genetic research. Your samples may be looked at:

- To see if a trait is passed down in families from one generation to the next (inherited). This type of research may help to explain why some cancers run in families or why some people have side effects of treatment while others do not. This is often studied through blood cells and DNA (genes).
- To learn about changes in the body that happen after you were born (non-inherited). For example, being in the sun too much can cause changes in cells that lead to skin cancer.

This research is attempting to better understand the genetic causes of multiple myeloma and to develop improved methods for the diagnosis and treatment. The samples collected, as part of this study will be used as researchers are interested in studying particular genes in cells collected from your blood, bone marrow, and from inside your mouth (buccal cell sample).

All blood, bone marrow and buccal cell samples will be sent for special freezing and storage. These samples will be labeled with a unique code and be stored at the University of Chicago. In addition, the samples may be sent out to an outside lab for further research as described above. We will take measures to protect the privacy and security of all your personal information including your social security number, but we cannot guarantee complete confidentiality of study data. This information may be kept indefinitely. The samples will be labeled with your initials and your assigned study number.

Stopping Participation in this Optional Blood Collection Sub-Study
You may withdraw your consent at any time. You may remain in the main study and not have any additional samples taken. You can also request previously collected samples to be removed. In such case, you should notify Dr. Jakubowiak at the address on the first page of this consent form.

Please mark your choice regarding participation in **optional research blood** studies below**.**
Please mark **only one** box below.

I will participate. [_]

Initial: _____ Date: _____

I will not participate. [_]

Initial: _____ Date: _____

Please mark your choice regarding participation in **optional research bone marrow** studies below.
Please mark **only one** box below.

I will participate. [_]

Initial: _____ Date: _____

I will not participate. [_]

Initial: _____ Date: _____

I will not participate in donating *extra* samples but my response research sample may be used by the University of Chicago for research described above. [_]

Initial: _____ Date: _____

Please mark your choice regarding participation in **optional research cheek swab** studies below.

Please mark **only one** box below.

I will participate. [_]

Initial: _____ Date: _____

I will not participate. [_]

Initial: _____ Date: _____

IS THERE ANYTHING ELSE I SHOULD KNOW?

You should know that Dr. Andrzej Jakubowiak is paid as a consultant by Amgen Inc. the makers of the study drug. The University of Chicago believes you should be aware of this information because you are thinking about being in this study.

CONSENT

SUBJECT

The research project and the procedures associated with it have been explained to me. The experimental procedures have been identified and no guarantee has been given about the possible results. I will receive a signed copy of this consent form for my records.

I agree to participate in this study. My participation is voluntary and I do not have to sign this form if I do not want to be part of this research study.

Signature of Subject: _____

Date: _____ Time: _____ AM/PM (Circle)

PERSON OBTAINING CONSENT

I have explained to _____ the nature and purpose of the study and the risks involved. I have answered and will answer all questions to the best of my ability. I will give a signed copy of the consent form to the subject.

Signature of Person Obtaining Consent: _____

Date: _____ Time: _____ AM/PM (Circle)

INVESTIGATOR/PHYSICIAN

Signature of Investigator/Physician: _____

Date: _____ Time: _____ AM/PM (Circle)