PATIENT INFORMATION SHEET AND INFORMED CONSENT

Randomized, national, open-label, multicenter, phase III trial studying induction therapy with bortezomib/lenalidomide/dexamethasone (VRD-GEM), followed by high-dose chemotherapy with melphalan-200 versus busulfan-melphalan (BUMEL), and consolidation with VRD in patients under 65 years old with newly-diagnosed, multiple myeloma.

Protocol code: GEM2012MENOS65

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Introduction

We invite you to participate in this clinical trial. Before you decide whether or not you wish to participate, it is important that you understand the potential risks and benefits, as well as possible alternatives. Therefore, we are providing this sheet with the intention that it, along with the explanations given by your doctor, will provide you with the essential information about the study. The law requires that you are given all necessary information so that you can make a free and informed decision to participate in the trial, and that you understand that all of the medical information obtained as a result of your participation will be used to benefit current and future patients. Thanks to this study, it will be possible to obtain scientific evidence that will help to increase and improve medical knowledge about your disease and the type of treatment used.

Above all, you should know that your participation is voluntary. If you decide to participate in this study you will need to give your express consent by signing this document. You will be given a copy, and you will be able to ask the physicians in charge of the study any questions you may have about it, at any time.

If you choose to participate in the study, you will be required to visit the trial site on the dates set by your study physician. If you are unable to attend any of the visits, you should contact your study doctor and s/he will arrange a new date for the visit.

You should also be aware that you can withdraw from the study at any time without giving an explanation, and without this affecting the medical care you receive; as well, throughout the trial you will be promptly informed of any relevant information that may affect your decision to participate. You should also know that you will not be reimbursed for any expenses incurred from your visits to the site.

This trial will be carried out at different public sites. If you would like to know which sites these are, you can ask your physician (the study investigator).

DETAILED INFORMATION ABOUT THIS STUDY

In this trial, your doctor will use a treatment regimen that includes six cycles of induction treatment with bortezomib (Velcade®), lenalidomide (Revlimid®) and dexamethasone (VRD). The combination of these three drugs may be the most effective means of disease reduction before autologous stem cell transplantation (ASCT). A good response to induction treatment is very important in predicting the beneficial effect of autologous transplantation. After the third treatment cycle with VRD, stem cells will be collected from your own blood (self-donation) and then frozen in order to be re-infused intravenously later.

When you have finished the six treatment cycles with VRD, you will proceed to autologous transplant as long as you are responding to treatment. Autologous transplant consists of administering high-dose chemotherapy to eliminate myeloma cells, followed by infusion of your previously frozen stem cells. The high-dose chemotherapy will consist of one of the following two options:

1. Group A: high-dose intravenous melphalan-200 (considered the standard treatment).
2. Group B: intravenous melphalan at 140 mg/m2 together with busulfan (Busilvex®). In a non-randomized study conducted by the *Grupo Español de Mieloma* (Spanish Myeloma Group) the combination was shown to be superior to melphalan at a dose of 200 mg/m2 in terms of disease-free survival. However, a comparison is needed of the type proposed in this study, to determine whether or not melphalán-140 plus busulfan (Busilvex®) combination therapy is superior to treatment with melphalan-200.

Finally, at three months after autologous transplant, two cycles of VRD will be administered with the aim of further reducing the disease.

Later in this document we will explain in more detail what these treatments consist of. The drugs in these therapies have already been used, and their safety and efficacy assessed, in a considerable number of multiple myeloma patients. The core mechanism of action consists of interfering with one or more essential biological processes of the disease cells, which prevents the cells from multiplying and promotes their elimination from the body.

1. OBJECTIVE OF THE STUDY

The overall objective is the maximum reduction and elimination, if possible, of the amount of myeloma cells present in your body by way of comprehensive treatment which includes: VRD induction therapy, autologous transplant and consolidation with VRD.

The specific primary objective is to study whether autologous transplant combined with melphalan-140 plus intravenous busulfan (Busilvex®) is superior to the established or standard treatment with melfalán-200 in terms of disease-free survival. The specific secondary objectives are: to achieve the greatest number of best responses (the study of which is known as minimal residual disease) after each treatment phase; prolonged overall survival, as well as possible toxicities of the drugs administered.

2. DESCRIPTION OF THE STUDY

Only patients under 65 years old with previously untreated multiple myeloma, and for whom possible autologous transplant is not contraindicated will be allowed to participate this study. A total of 460 patients will be included.

Both bortezomib (Velcade®) and lenalidomide (Revlimid®), the experimental drugs in this study, used in combination with dexamethasone have been shown to be effective in patients with newly-diagnosed myeloma in studies in which both regimens have been used separately. Our

objective is to achieve noticeable efficacy by administering them in combination without an increase in toxicity. As detailed below, after induction treatment with six cycles of VRD, the patient will proceed to autologous transplant followed by two consolidation cycles with VRD. The conditioning regimens for autologous transplant will either be melphalan-200 or melphalan140/ busulfan (Busilvex®); the treatment regimen will be chosen at random. Comparing the efficacy of these treatments is one of the most important objectives of this clinical trial, and random allocation is a basic methodological requirement within the framework of scientific research.

Laboratory analyses and disease assessments will be performed throughout the study, to verify how you are tolerating the drugs and evaluate how the drugs are acting. In addition, part of the samples will be sent to centralized laboratories (samples will be analyzed centrally at one of the following four hospitals: *Hospital Clínico Universitario de Salamanca*, *Hospital Doce de Octubre* and *Hospital la Fe de Valencia*), *Centro de Investigaciones Médicas Aplicadas (CIMA)* in Pamplona where more complex tests will be carried out, which are important for prognosis and adequate control of the disease. Each patient should expect to participate in the study for approximately 12 months. Neither you nor your doctor will decide whether you will be allocated to autologous transplant with melphalan-200 or with melphalan-140/busulfan (Busilvex®). Allocation will be decided at random by a computer-telephone system, which in clinical research is known as randomization.

Your doctor will also be able to administer treatment with granulocyte colony-stimulating factors (G-CSF) at any time during the study.

Screening phase

During the three weeks before treatment begins, you will undergo tests and procedures to determine whether you are eligible to participate in the study. These tests are the same as those needed to diagnose your disease and determine its progression. These tests and procedures are: a complete physical exam, weight, size, vital signs, ECOG performance status, x-rays, electrocardiogram, blood tests [including serology for hepatitis B, hepatitis C and human immunodeficiency virus (HIV)], urine test, evaluation of the stage of bone disease and bone marrow aspiration. In special cases, other radiological tests may be carried out (CT scan, MRI or PET/CT). Your doctor can explain how these tests will be done and what the specific purpose will be in terms of managing the status of your health.

Treatment phases

As soon as you have completed the screening phase of the study, you will receive treatment in hospital in accordance with the following phases:

Phase I (Induction treatment): Will consist of six cycles of VRD administered in intervals of four weeks. The dose and form of administration are detailed below:

- Bortezomib (Velcade®) 1.3 mg/m^2 administered subcutaneously on days 1, 4, 8 and 11 of the cycle.
- Lenalidomide (Revlimid®) 25 mg/day taken orally, on days 1 to 21 of the cycle.
- Dexamethasone 40 mg/day taken orally, days 1 to 4 and 9 to 12 of the cycle.

When the third induction cycle is complete, your doctor will administer treatment with granulocyte colony-stimulating factors (G-CSF), for the purpose of stem cell collection and subsequent autologous transplantation.

You will receive heparin prophylaxis in this phase of treatment in order to avoid possible complications with blood coagulation.

Phase II (autologous transplant): Autologous transplant with high-dose chemotherapy followed by salvage therapy with stem cells obtained from the patient's own blood are part of the established treatment for patients with myeloma under 65 years old. To date, the best treatment has been melphalan-200. This study is looking at whether or not melphalan-140 combined with

busulfan (Busilvex®) is more effective; therefore, at the beginning of the study, each patient will be randomly allocated to one of the two treatment options:

- Group A: intravenous melphalan 100 mg/m^2, days -3 and -2.
- Group B: intravenous busulfan (Busilvex®) 3.2 mg/Kg, days -5, -4 and -3 and melphalan 140 mg/m2 day -2.

Phase III (Consolidation): Two cycles of VRD administered at the same dose as during the induction treatment, to be initiated three months after autologous transplant.

During this treatment phase you will receive antithrombotic prophylaxis with acetylsalicylic acid (ASA) as long as you are not allergic to this medication.

In the induction and consolidation phases, you will also receive monthly treatments with bisphosphonates, for up to a maximum of two years.

Treatment Interruption

None of the treatments can be interrupted unless one of the following circumstances occurs:

- You decide to interrupt treatment.
- The treatment is clearly ineffective and your disease is worsening.
- The appearance of intolerable side effects or another disease, which makes it medically advisable to leave the study.
- On the advice of your attending physician
- Serious non-compliance with protocol guidelines
- Due to administrative problems beyond the control of the sponsor which cannot be resolved with the authorities involved.

Should you decide to leave the study, it is recommended that before you do you attend an end-of-treatment visit for your own safety. During your participation in the study your will not be able to receive treatment with investigational immunologic or chemotherapy drugs, other than bortezomib (Velcade®) or lenalidomide (Revlimid®).

End-of-Treatment Visit

This visit will take place within the 30 days after the last dose of study medication is administered. At this visit, it will be necessary for you to go to the hospital so your doctor can examine you and perform blood and urine tests.

Contraception

The majority of medications used to treat malignant blood diseases affect sperm and eggs. For this reason, both women and men should be well aware that they must use two effective methods of birth control during their participation in this study if they engage in sexual activity. If you or your partner becomes pregnant during the study you should inform your study physician immediately. He or she will explain the potential risks to the fetus and the different options available to treat the pregnancy. The study physician will ask permission from you or your partner to obtain information about your pregnancy and the health of your newborn.

Laboratory tests show that bortezomib (Velcade®) may be harmful to DNA. Based on this information, it's possible that bortezomib (Velcade®) causes infertility in men as well as women (i.e., they will not be able to get pregnant or have children).

3. SIDE EFFECTS AND RISKS

While participating in the study, the risk that you may experience side effects from any of the study drugs cannot be ruled out. If they do occur, they may be mild or severe. In addition, in this study different adverse effects may occur as a result of the treatment arm you are assigned to,

due to continuous exposure to the different drugs or not.

Chemotherapy [melphalan and busulfan (Busilvex®)], not only attacks disease cells, it also harms some of the body's normal cells, especially those which multiply rapidly. These are mainly the cells of the digestive system, hair cells, and normal blood cells. For this reason nausea, vomiting, bladder inflammation and worsening hemogram results (a test that measures the amount of blood cells in the body), which may have already deteriorated due to the disease itself.

A decrease in the number of red blood cells (anemia) can cause fatigue, decreased stress tolerance and shortness of breath. This can be adequately controlled by a transfusion of concentrated red blood cells. The number of platelets in the blood can also decrease (called thrombocytopenia). This is associated with a risk of bleeding that can be life-threatening, because platelets are essential for the repair of broken blood vessels. If the number of platelets drops, transfusions can be given to replenish these cells and thus lower the risk of bleeding. A decrease in the white blood cell count (called leukopenia) is clearly associated with an increased risk of infections, which may be serious. These infections may cause a number of complications. Your doctor has a wide array of powerful antibiotics available to treat this problem, which will be used to try to protect you against the action of any infectious agents while the neutropenia lasts. As well, it may be necessary to administer medicine to prevent anemia and neutropenia (a decrease in a certain type of white blood cells) that results from the treatment.

If you suffer any side effect that your medical team did not advise you of, you will need to report this as soon as possible so that you can be examined and given the appropriate treatment. If a serious or life-threatening reaction were to occur, your physician will be able to discontinue the study treatment immediately.

Other drugs and supplements can affect the action of the study drugs [bortezomib (Velcade®) and lenalidomide (Revlimid®)]. Tell your study physician of any medication and supplements you are taking during the course of the trial.

As a result of the procedures carried out during your participation in the trial, such as taking samples for analysis or the subcutaneous administration of bortezomib (Velcade®), you may experience pain, burning and, rarely, infection at the puncture site. As well, during bone marrow aspiration you may suffer an allergic reaction due to the local anesthetic.

With respect to the principle experimental study drugs [bortezomib (Velcade®) and lenalidomide (Revlimid®)], very rare or unknown side effects cannot be ruled out and you should be aware of this, however it is unlikely that you will experience these. The most notable side effects that have been observed in human subjects, related to the use of both drugs, are described below.

ADVERSE EFFECTS OF BORTEZOMIB (VELCADE®)

The following adverse reactions were considered by the investigators to be at least probably or possibly related to bortezomib, during five phase II non-comparative clinical trials and 1 phase III comparative clinical trial with bortezomib versus dexamethasone in 663 patients with refractory or relapsed multiple myeloma, of which 331 received bortezomib as monotherapy. The safety database contains data for patients with multiple myeloma or B-cell lymphocitic leukemia (B-LLC). Patients were treated with bortezomib as monotherapy, or in combination with dexamethasone.

Adverse effects are listed below classified by organs and systems and by frequency groups. Frequency is defined as: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥

1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000), unknown frequency (cannot be determined from available data).

Adverse reactions are listed in order of decreasing severity within each frequency interval.

Infections and infestations

Very common:	herpes zoster (including disseminated), pneumonia, nasopharyngitis, upper respiratory tract infection.
Common:	bronchitis, sinusitis, herpes simplex virus, bacteremic sepsis, lower respiratory tract infection, pleural effusion, urinary tract infection, gastroenteritis, oral thrush, postherpetic neuralgia.
Uncommon:	pneumococcal pneumonia, bronchopneumonia, catheter-related complication, infusion-site infection, pleural infection, empyema, hemophilus infection, cytomegalovirus infections, flu, mononucleosis infecciosa, varicella, yeast infection, fungal infection, blepharitis, disseminated Herpes zoster, skin infections, herpetic meningoencephalitis*, septic shock*.

Benign and malignant neoplasms (including cysts and polyps)

Uncommon:	Tumor lysis syndrome

Blood and lymphatic system disorders

Very common:	thrombocytopenia, neutropenia, anemia.
Common:	leucopenia, lymphopenia, pancytopenia, febrile neutropenia.
Uncommon:	hemolytic anemia, thrombocytopenia purpura, lymphadenopathy.

Immune system disorders

Uncommon:	immune complex mediated hypersensitivity or other types of hypersensitivities, immune complex mediated potential reactions such as serum sickness, arthritis with rash and proliferative glomerulonephritis, angioedema*.

Endocrine disorders

Uncommon:	inadequate secretion of antidiuretic hormone (ADH).

Metabolic and nutritional disorders

Very common:	loss of appetite, dehydration.

Common:	hypokalemia, hyperglycemia, hypoglycemia, hyponatremia, hypercalcemia.
Uncommon:	hyperkalemia, cachexia, hypercalcemia, hypocalcemia, hypernatremia, hyperuricemia, vitamin B12 deficiency, increased appetite, hypomagnesemia, hypophosphatemia.

Psychiatric disorders

Very common:	insomnia, anxiety.
Common:	confusion, depression.
Uncommon:	agitation, delirium, hallucinations, restlessness, mood fluctuations, changes in mental status, sleep disturbances, irritability.

Nervous system disorders

Very common:	sensorimotor peripheral neuropathy, sensory peripheral neuropathy, paresthesia, headaches, dizziness (excluding vertigo).
Common:	polyneuropathy, worsening of peripheral neuropathy, dysguesia, dysesthesia, hypoesthesia, trembling, fainting, postural dizziness.
Uncommon:	paraplegia, intracranial hemorrhage, subarachnoid hemorrhage, convulsions, motor peripheral neuropathy, paresthesia, attention deficit hyperactivity disorder, ageusia, drowsiness, migraine, cognitive disorders, neuromotor disorders, sciatica, mononeuropathy, speech disorders, restless leg syndrome, change in consciousness, encephalopathy*, posterior reversible encephalopathy syndrome * , progressive multifocal leukoencephalopathy (PML).
Rare:	Autonomic neuropathy*.

Eye disorders

Common:	blurred vision, conjunctival bleeding, conjunctivitis.
Uncommon:	ocular bleeding, vision disorders, dry eyes, conjunctivitis, ocular secretions, photophobia, irritation, increased tearing, conjunctival hyperemia, swelling.

Rare:	Herpes zoster opthalmicus*. Partial or total loss of vision in one or both eyes, which may be caused by optic nerve damage. Vision loss may or may not be reversible.

Inner ear and labyrinth disorders

Common:	Vertigo.
Uncommon:	deafness, tinnitus, hypoacousis or other types of hearing loss.

Cardiac disorders

Common:	congestive heart failure, tachycardia, atrial fibrillation, palpitations, pulmonary edema and acute pulmonary edema.
Uncommon:	heart failure, cardiogenic shock, myocardial infarction, angina pectoris, breast disease, complete atrioventricular block, tachycardia, sinus tachycardia, supraventricular tachycardia, arrhythmia, atrial flutter, cardiac tamponade*, cardiorespiratory arrest*.
Rare:	newly decreased left-ventricle ejection fraction, pericarditis*, pericardial effusion, pericardial disease.

Vascular disorders

Common:	hypotension, orthostatic (postural) hypotension, phlebitis, hematoma, hypertension, petechiae.
Uncommon:	cerebral hemorrhage, subdural hematoma, vasculitis, cerebrovascular accident, pulmonary hypertension, bruising, purpura, venous insufficiency, vasodilation, hemorrhaging, flushing, hot flashes.

Respiratory, thoracic and mediastinal disorders

Very common:	dyspnea, cough.
Common:	dyspnea exertional, epistaxis, runny nose. Hypoxia, pleural effusion, chest pain.
Uncommon:	respiratory distress, pulmonary congestion, asthma, respiratory alkalosis, tachypnea, wheezing, nasal congestion, snoring, rhinitis, hyperventilation, orthopnea, breast pain, throat discomfort or pain, productive cough, decreased oxygen saturation, hemoptysis, pleural pain,

	pneumonitis*, interstitial lung disease*, respiratory failure*, alveolar hemorrhage*
Rare:	acute respiratory distress syndrome*.

Gastrointestinal disorders

Very common:	vomiting, diarrhea, nausea, constipation, abdominal pain.
Common:	stomatitis, dyspepsia, loose stools, abdominal pain, flatulence, distension, hiccups, mouth ulcers, pharyngolaryngeal pain, pharyngitis, dry mouth, dysphagia, gastrointestinal bleeding, rectal bleeding, gastro-esophageal reflux disease, gastritis.
Uncommon:	acute pancreatitis, ileus paralytic, antibiotic-associated colitis, colitis, hematemesis, bloody diarrhea, enteritis, enterocolitis, abdominal discomfort, belching, gastrointestinal motility disorder, intestinal obstruction, mouth pain, gagging, changes in bowel habits, spleen pain, esophagitis, gastritis, gastrointestinal pain, bleeding gums, painful gums, hiatal hernia, irritable bowel syndrome, oral mucosal petechiae, hypersalivation, dirty tongue, tongue discoloration, fecal impaction.

Hepatobiliary disorders

Uncommon:	hepatitis, hepatic hemorrhage, hypoproteinemia, hyperbilirubinemia.

Skin and subcutaneous tissue disorders

Very common:	rash.
Common:	periorbital edema, urticaria, itchy rash, pruritus, erythema, increased sweating, dry skin, eczema, cellulitis.
Uncommon:	erythematous rash, photosensitivity reaction, contusion, generalized pruritus, macular rash, papular rash, psoriasis, generalized rash, eyelid edema, facial edema, dermatitis, alopecia, nail disorders, skin discoloration, atopic dermatitis, change in hair texture, rash that feels hot, night sweats, pain with pressure, ichtyosis, cutaneous nodule.
Rare:	vasculitic rash*, leukocytoclastic vasculitis *.

Musculoskeletal, conjunctive tissue and bone disorders

Very common:	myalgia, arthralgia, bone pain.
Common:	muscle weakness, musculoskeletal pain, muscle cramps, back pain, peripheral swelling.
Uncommon:	muscle spasm, muscle contractions or muscle heaviness, muscle stiffness, swollen joints, joint stiffness, pain in the buttocks, puffiness, jaw pain, pain in the extremities.

Renal and urinary disorders

Common:	renal failure, dysuria, hematuria.
Uncommon:	acute renal failure, oliguria, renal colic, proteinuria, urinary retention, frequent urination, difficult urination, abdominal pain, urinary incontinence, urgency of urination.

Disorders of the reproductive organs and breast

Uncommon:	testicular pain, erectile dysfunction.

General disorders and administration site conditions

Very common:	fatigue, pyrexia, asthenia, peripheral edema.
Common:	weakness, lethargy, stiffness, discomfort, flu-like illness, chest pain, localized pain, edema, neuralgia.
Uncommon:	falls, mucosal bleeding, inflammation of mucous membranes, phlebitis at injection site, inflammation due to extravasation, hypersensitivity to touch, erythema and/or pain at the injection site, feeling cold, sensation of pressure on the chest, groin pain with chest discomfort, tightness of the chest, general physical deterioration.

Additional investigations

Common:	weight-loss, increased serum lactate dehydrogenase, elevated alanine aminotransferase, elevated aspartate aminotransferase, increased serum creatinine, increased serum alkaline phosphatase, unspecific change in liver function tests.

Uncommon:	elevated bilirubin, increased serum urea, increased gamma-glutamyltransferase, elevated serum amylase, decreased red blood cell count, decreased white blood cell count, decreased serum bicarbonate, heart arrhythmia, elevated C-reactive protein, decreased serum phosphate, weight-gain, decreased serum albumin.

Traumatic injury and poisoning

Uncommon:	catheter-related complication, post-procedural pain, post-procedural bleeding, burns.

*From post-marketing sources.

RISKS ASSOCIATED WITH LENALIDOMIDE (REVLIMID®)

Taking a medication always involves risk. Although it is possible that the study drugs are associated with unforeseen or unknown risks, you will be monitored closely for any problems. Do not hesitate to contact your study physician or tell him or her of any discomfort or concern you may have, even if you believe these are not related to the study drugs.

Risks of lenalidomide

Lenalidomide has been studied in healthy volunteers as well as patients with cancers of the blood and other organs, or other diseases. As with any experimental treatment, lenalidomide may carry risks or produce side effects, some of them as yet unknown.

Following is a list of the most common or clinically significant side effects that have occurred in already completed studies or those still in progress, where there is a reasonable possibility that the reaction is related to lenalidomide. In some cases, the side effects are serious or long-lasting; it is also possible that they will never disappear, or cause death. This list is not exhaustive, however your study physician will address any doubts you may have and provide you with further information if you wish.

Very common side effects (probability of occurring greater than 10%):

Decreased number of white blood cells (with or without fever) [leukopenia, neutropenia, febrile neutropenia, granulocytopenia, lymphopenia]. Anemia. Decrease in the number of cells that help blood to coagulate [thrombocytopenia]. Blurred vision. Diarrhea. Pain [upper abdominal pain, abdominal pain, dental pain]. Constipation. Nausea. Vomiting. Feelings of weakness and discomfort [asthenia]. Tiredness [fatigue]. Swelling [edema, peripheral edema]. Fever [pyrexia]. Chills. Pneumonia or other infections [pneumonia, bronchitis, upper respiratory tract infection, urinary tract infection, erysipelas, gastroenteritis, herpes simplex, herpes zoster, flu, lower respiratory tract infection, sinusitis, sepsis, bacteremia]. Irritation of the nose and//or throat [rhinopharynringitis, pharyngitis]. Nasal congestion [rhinitis]. Weight loss. Loss of appetite. Blood chemistry imbalance [hypokalemia, hypocalcemia, hypophosphatemia, hypomagnesemia, hyponatremia]. Muscle, joint and non-cardiac chest pain [pain in one limb, arthralgia, back pain, bone pain, muscle spasms, osteomuscular pain, muscle cramps, chest pain and myalgia]. Dizziness. Change in sense of taste [dysgeusia]. Headaches. Change in

sense of touch [hypoesthesia]. Pain and reduced nerve sensitivity [neuropathy, peripheral neuropathy, sensitive peripheral neuropathy]. Tremor. Cough. Difficulty breathing [dyspnea]. Nosebleeds [epistaxis]. Blood clots in the lower extremities, lungs, heart, brain and other organs [pulmonary embolism, deep vein thrombosis]. Dry skin. Itching [pruritus]. Allergic reaction [rash, hypersensitivity (in the 'uncommon side effects' category)].

Common side effects (probability of occurring between 1% and 10%):

Abnormally low level of all blood cells [pancytopenia]. Heart attack [acute myocardial infarction]. Alteration in heart rate [Auricular fibrillation, palpitations, tachycardia]. Heart failure [cardiac insufficiency, congestive heart failure]. Decrease in supply of oxygen to the heart tissue [myocardial ischemia]. Clouding of the eye lens [cataract]. Dry mouth. Indigestion [dyspepsia]. Reduced intestinal activity [gastrointestinal motility disorder]. Falls. Depressed level of consciousness with drowsiness, listlessness and apathy [lethargy]. Changes in liver function [changes in liver function tests, increased alanine-aminotransferase, increased gamma-glutamyl transferase]. Fluid loss [dehydration]. Diabetes [diabetes mellitus]. Increased blood sugar [hyperglycemia]. Increased uric acid in the blood [hyperuricemia]. Accumulation of iron in the body [iron overload]. Muscle weakness. Cancer [acute myeloid leukemia, B lymphocyte lymphoma, basal cell carcinoma, squamous cell carcinoma]. Ictus [cerebrovascular accident]. Tingling [paresthesia]. Fainting [syncope]. Depression, changes in mood. Kidney failure [renal failure]. Respiratory disorders [respiratory distress]. Excessive sweating [hyperhidrosis]. Night sweats. Accumulation of blood under the skin [hematoma]. High or low blood pressure [hypertension, hypotension]. Lack of blood flow to the limbs [peripheral ischemia]. Vein clots [thrombosis]. Rapid increase in tumor growth [tumor flare].

The following risks were also reported after marketing of lenalidomide, and Celgene considers them to be related to the drug:

- Inflammation of the lungs [pneumonitis]
- Excessive or insufficient thyroid activity [hyperthyroidism and hypothyroidism]
- Serious allergic reactions, such as:
    - Swelling beneath the skin (angioedema).
    - Serious allergic reactions that can affect the mucous membranes surrounding the nose, mouth, stomach and intestines, or rash with peeling away of the outer layer of the skin [Stevens-Johnson syndrome and toxic epidermal necrolysis].
- Rapid death of cancer cells and the accumulation of their byproducts, which produces an imbalance in body chemistry that can cause kidney damage (tumor lysis syndrome).

New cancers

In clinical trials studying newly-diagnosed multiple myeloma, a greater number of new cancers have occurred such as acute leukemia (blood cancers) and lymphatic cancers, in patients who received treatment with melphalan and lenalidomide, or first with melphalan and hematopoietic stem cell transplantation followed by lenalidomide, than in patients treated with melphalan and/or hematopoietic stem cell transplantation followed by placebo (capsules without active medication). A greater number of skin cancers and solid tumors have been reported when lenalidomide is administered together with dexamethasone. Patients should inform their doctors of their medical history and possible concerns with respect to this increased risk of developing other cancers. You doctor will monitor you closely during treatment for the appearance of any new cancers.

Other risks

If a doctor other than your study physician prescribes medication for another illness, or if you are taking any other over the counter medication or vitamin supplements, you should inform a member of the clinical study staff. It is important that you do so, as interactions with certain medications can cause serious side effects.

Also inform your study doctor of any illnesses or allergies you currently have or have had in the past, and all of the medication you are taking, including over the counter, vitamins, herbal supplements and any homeopathic therapies or alternative medicines. It is important that you do this because a potential interaction with certain medicines, vitamins or other products may cause serious or possibly unknown side effects.

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

Your disease may not improve, or may become worse during the study. If you would like more information on the risks and side effects, ask your study physician.

Risks associated with pregnancy

Lenalidomide is structurally related to thalidomide, a drug which produces severe and life-threatening birth defects. If lenalidomide is taken during pregnancy it can produce congenital birth defects or death of the fetus. Women should not become pregnant during treatment with lenalidomide because, as has already been explained, the risk of congenital birth defects in humans is unknown. If you are a woman, you must commit to not becoming pregnant while receiving treatment with lenalidomide.

There is a greater probability of blood clots forming in patients treated with lenalidomide and dexamethasone. Therefore, it is not advisable to take hormone replacement therapy or birth control pills without first telling your doctor, so that she or he can weigh the risks and benefits of doing so.

Lenalidomide remains present in the semen of healthy men, in very small concentrations, for up to three days after treatment interruption. In patients who cannot eliminate lenalidomide from their system, such as those with kidney problems, the drug may be present for more than three days. As a precaution, all male patients whose partner is pregnant or able to have children should use condoms when engaging in sexual activity during treatment with lenalidomide, during temporary treatment interruptions and for 28 days after treatment has stopped,.

RISKS ASSOCIATED WITH BUSULFAN (Busilvex®)

Like melphalan, busulfan (Busilvex®) is an agent that can harm your cells' DNA. It attacks myeloma cells as well as normal bone marrow cells, causing the number of white blood cells, platelets and red blood cells to drop. This in turn can lead to an increased risk of infection, bleeding and anemia. For this reason, the patient's own stem cells are administered as "salvage therapy" (autologous transplant). Other side effects of busulfan (Busilvex®) include epilepsy(for which preventive treatment is given) or changes in liver function (known as hepatic veno-occlusive disease), which is an uncommon side effect when busulfan (Busilvex®) is administered intravenously, as is the case in this study. To avoid neurological toxicities, during treatment with busulfan (Busilvex®) you will receive prophylactic treatment with diphenylhydantoin and/or clonazepam/lorazepam as specified by your doctor.

4. EXPECTED BENEFITS AND ALTERNATIVE TREATMENTS

Currently, only conventional chemotherapy is approved as induction treatment. Conventional chemotherapy is the combined drug regimen considered by the international medical community to be the classic or standard treatment. More specifically, in the case of induction of remission in multiple myeloma, this conventional chemotherapy would include the following

treatment cycle options: VAD (regimen comprising vincristine, Adriamycin and dexamethasone), cyclophosphamide and dexamethasone, or VBMCP (regimen comprising vincristine, BCNU, melphalan, cyclophosphamide and prednisone) alternated with VBAD (regimen comprising vincristine, BCNU, Adriamycin and dexamethasone). The Spanish Myeloma Group and others have demonstrated that the results of chemotherapy are inferior to those obtained with combination therapy using bortezomib, thalidomide and dexamethasone (VTD). However, the latter combination is not yet approved by health authorities; and yet, the use of lenalidomide (Revlimid®) in place of thalidomide, in combination with bortezomib/dexamethasone may be less toxic and more effective.

Further, autologous transplant together with standard melphalan-200 treatment would, in the best of circumstances, have an efficacy similar to combination melphalan-140 and busulfan (Busilvex®). Consolidation treatment with VRD is not yet approved and therefore cannot be administered outside the context of clinical trials.

In addition, whether or not you as an individual benefit from the treatment of your disease, the results of the study, even if they are negative, will help investigators to understand more about the disease and these novel therapies, which will undoubtedly help future patients. In any event, your doctor will advise you of any investigational drugs available for the treatment of your disease. We would also like to remind you that it is your fundamental right to withdraw from the study at any time, without having to give an explanation and without this affecting the medical care you continue to receive.

5. LIABILITY AND INSURANCE

PETHEMA Foundation, as the sponsor of this study, has signed an insurance policy with HDI Hanover International, policy no. 130/001/008644. The terms and provisions of the coverage include liability for hypothetical injuries derived from participation in the study, and which are in strict compliance with legal requirements established in Royal Decree 223/2004 on clinical trials.

We also advise you that it is possible that your participation in a clinical trial may change material aspects of your private life and your legal situation, which may cause the conditions stated in certain types insurance or other contracts to vary (life insurance, for example).

6. CONFIDENTIALITY AND AUTHORIZATION TO ACCESS AND USE MEDICAL INFORMATION

All of the information in this clinical trial is considered confidential, respecting anonymity at all times, as outlined in current legislation (the Spanish constitution, Act 29/2006, of 26 July, on Guarantees and Rational Use of Medicines and Medical Devices, Organic Law on the Protection of Personal Data (LOPD 15/1999), Royal Decree 223/2004 on clinical trials, etc.)

By signing this document, you authorize direct access to your medical records by persons who have legitimate reasons to consult them for the purpose of supervising, monitoring and/or inspecting the quality of the trial as required by Good Clinical Practice regulations. Such access will be in compliance with applicable legislation on data protection, protecting your identity, and under an obligation of confidentiality.

Data collected over the course of the study will be included in a file belonging to the trial site. You will be able to exercise your ARCO rights (Access, Rectification, Cancellation and Opposition) on these data with the attending study physician.

In the case of transfer of clinical data to third countries, the sponsor will guarantee the same level of confidentiality and identity protection as in Spain.

The clinical study staff, the Clinical Research Ethics Committee, regulatory bodies, the auditor, trial coordinator, the sponsor and its representatives will need to review your medical

information for use in this study for the purpose of accurately record all of the necessary information. Health authorities and regulatory bodies may also have access to your medical records for the purpose of reviewing the findings of the study.

You will also be able to access your information once the study is completed. If you feel it's appropriate, you also have the right to receive a copy of the medical information collected from you throughout the study. You can also ask to be informed of the results of the study.

Only data from your clinical records that are related to the study will be subject to verification by third parties. Whenever possible, this verification will be done in the presence of the Principle Investigators or Co-investigators, who are responsible for guaranteeing the confidentiality of medical records belonging to trial participants. Data collected for the study will be identified by a code and only the principal investigator/collaborators will be able to link these data to you and your medical history.

The sponsor will be in control of all data obtained in the study, and comply with all applicable legislation in force where the data is collected.

7. PUBILCATION OF DATA

All data collected in the trial will be published in its concluded form, in one or more scientific articles. In compliance with the appropriate duty of confidentiality, no personally identifiable information related to participants will be included in the study.

8. ADDITIONAL INFORMATION

During your participation in the study, you will be informed by your doctor as soon as possible of any new information related to the drugs used in this study that may also affect your ability or willingness to participate.

Please be advised that conducting this study requires a specific amount of research and time. Therefore, the hospital as well as the professionals who participate in it, including the investigator, will receive monetary compensation from the sponsor.

This research study has been reviewed and approved by the Ethics Committee of your hospital. Any questions or concerns you may have should be addressed with your attending study physician, Dr. _____ as soon as possible. You can also call the following number _____.

WRITTEN INFORMED CONSENT OF THE PATIENT

Randomized, national, open-label, multicenter, phase III trial studying induction therapy with bortezomib/lenalidomide/dexamethasone (VRD-GEM), followed by high-dose chemotherapy with melphalan-200 versus busulfan-melphalan (BUMEL), and consolidation with VRD in patients under 65 years old with newly-diagnosed, multiple myeloma.

Protocol code: *GEM2012MENOS65*

I, (full name), _____

I have had the opportunity to ask questions about the study.

I have received adequate information about the study.

I have read the information sheet that was given to me.

I have spoken to Dr. _____

I understand that my participation in this study is voluntary.

I understand that I may with withdraw from the study:

1. At any time;
2. Without having to give an explanation
3. Without this affecting my medical care

By signing this consent form, I voluntarily agree to participate in this clinic trail and I authorize the use of all information obtained from it. I understand that I will receive a signed copy of this written informed consent form.

_____ _____

Signature of the Patient Date

_____ _____

Name and signature of the Investigator Date

VERBAL INFORMED CONSENT IN THE PRESENCE OF WITNESSES

Randomized, national, open-label, multicenter, phase III trial studying induction therapy with bortezomib/lenalidomide/dexamethasone (VRD-GEM), followed by high-dose chemotherapy with melphalan-200 vs. busulfan-melphalan (BUMEL), and consolidation with VRD in patients under 65 years old with newly-diagnosed, multiple myeloma.

Protocol code: *GEM2012MENOS65*

I, (full name), _____

state, under my sole responsibility, that (name of the patient participating in the trial): _____

Has had the opportunity to ask questions about the study.

Has received adequate information about the study.

Has read the information sheet provided to him/her.

Has spoken with Dr._____

Understands that his/her participation is voluntary.

Understands that s/he may withdraw from the study:

1. At any time
2. Without having to give an explanation
3. Without this affecting his/her medical care

_____ _____

Signature of the Witness Date

_____ _____

Name and signature of the Investigator Date

INFORMED CONSENT BY A LEGAL REPRESENTATIVE

Randomized, national, open-label, multicenter, phase III trial studying induction therapy with bortezomib/Lenalidomide/dexamethasone (VRD-GEM), followed by high-dose chemotherapy with melphalan-200 versus busulfan-melphalan (BUMEL), and consolidation with VRD in patients under 65 years old with newly-diagnosed multiple myeloma.

Protocol code: *GEM2012MENOS65*

I, (full name), _____

In my capacity as the: (relationship to the patient) _____ of (name of the participant) _____

I have read the information sheet that was given to me

I have had the opportunity to ask questions about the study.

I have received satisfactory answers

I have received adequate information about the study.

I have spoken with Dr. _____

I understand that his/her participation is voluntary.

I understand that s/he can withdraw from the study:

1. At any time
2. Without having to give an explanation
3. Without this affecting his/her medical care

(Name of the patient) _____ has received all relevant information about the study in my presence, adapted to his/her level of understanding. S/he has been informed that only data from his/her medical records that are related to the study will be verified by third parties, and agrees to participate in the study. By signing this form, I give my consent in order that said person may participate in this study.

_____ _____

Signature of the Representative Date

_____ _____

Signature of the Investigator Date