
CLINIC TRIAL PROTOCOL

Drugs: Bortezomib (Velcade®), Lenalidomide (Revlimid®) and IV Busulfan (Busilvex®).

Protocol Code: GEM2012MENOS65

Protocol Date: July 01, 2013

Study Title: A 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 (MEL-200) versus busulfan-melphalan (BUMEL), and consolidation with VRD-GEM in patients under 65 years old with newly-diagnosed, symptomatic multiple myeloma.

Development Phase: III

EudraCT number: 2012-005683-10

Sponsor: PETHEMA Foundation

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PROTOCOL SIGNATURE PAGE

Protocol code: GEM2012MENOS65

I have read this protocol and agree to oversee and lead the conduct of this clinical trial in accordance with the protocol stipulations, informed consent, Good Clinical Practice guidelines and ICH and the Declaration of Helsinki.

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Dr. Joaquín Díaz Mediavilla	-----	-----
(PETHEMA representative)	Signature	Date

Principal Investigator:

_____	_____	_____
Name	Signature	Date

LIST OF ABBREVIATIONS

AE	Adverse Event
ALT	Alanine Transaminase
AST	Aspartate Transaminase
CREC	Clinical Research Ethics Committee
MC	Monoclonal Component
CRF	Case Report Form
CTC	(NCI) Common Toxicity Criteria
ECOG	Eastern Cooperative Oncology Group
MRD	Minimal Residual Disease
HVOD	Hepatic Venous-occlusive Disease
G-CSF	Granulocyte-colony Stimulating Factor
GEM	Spanish Myeloma Group
ICH	International Conference on Harmonization
IF	Immunofixation
IMWG	International Myeloma Working Group
IV	Intravenous
ULN	Upper Limit of Normal
Mg	Milligram
ml	Milliliter
MM	Multiple Myeloma
mm ³	Cubic Milliliter
Mmol	Millimole
BM	Bone Marrow
NCI	National Cancer Institute
NYHA	New York Heart Association
HSC	Hematopoietic Stem Cells
CR	Complete Response
PR	Partial Response
SAE	Serious Adverse Event
SFLC	Serum Free Light Chain
OS	Overall Survival
PFS	Progression-Free Survival
SPM	Second Primary Malignancies
VGPR	Very Good Partial Response

1. Summary

1.1. Type of application

Clinical trial studying a drug in new conditions of use

1.2. Sponsor identification

PETHEMA Foundation

TIN: G-81245706

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1.3. Study title

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

1.4. Protocol code

GEM2012MENOS65

1.5. Trial Coordinators

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1.6. Anticipated trial sites

See Appendix 1

1.7. Clinical Research Ethics Committees

See Appendix 2

1.8. Name and qualification of persons responsible for monitoring:

Trial Form Support (TFS)

1.9. Experimental and control drugs: dosing, dosage form, route of administration and therapeutic group

- Experimental drug: bortezomib (Velcade ®)
Dosage form: Vials of sterile, lyophilized powder to be reconstituted
Route of administration: Subcutaneous
Therapeutic group: Proteasome inhibitors. Antineoplastics (L01XX32)
- Experimental drug: lenalidomide (Revlimid®)
Dosage Form: Capsules
Route of Administration: Oral
Therapeutic group: Immunomodulator (L04AX04)
- Experimental drug: busulfan (Busilvex ®)
Dosage Form: Vials of 6 mg/ml, 10 ml/vial
Route of Administration: Intravenous
Therapeutic group: Cytotoxic agents (alkylating agents) (L01AB01)
- Dexamethasone
Form: 20 mg, 10 mg, and 5 mg capsules.
Route of Administration: Oral
Therapeutic group: Corticosteroids
Comments: Dexamethasone will not be supplied by the sponsor since it is a drug routinely used to treat MM and is part of the standard therapy required to treat this MM patients. The commercial drug forms normally used at each trial site will be used.
- Melphalan
Form: Vials of sterile, lyophilized powder that contains 50 mg of melphalan, and 10 ml vials of solvent/diluent
Administration: Intravenous
Therapeutic group: Cytotoxic agents (alkylating agents)
Comments: Melphalan will not be supplied by the sponsor as it is a drug routinely used to treat MM and is part of the standard therapy required to treat MM patients. The commercial drug forms normally used at each trial site will be used.

1.10. Clinical Trial Phase

Phase III

1.11. Study objectives

The primary objectives are:

- Progression-free survival (PFS) after autologous stem cell transplantation with BUMEL versus MEL-200 in patients who have received prior VRD-GEM induction treatment.

The secondary objectives are:

- Complete response (CR) rates with negative immunofixation after each phase of treatment (induction, autologous stem cell transplant and consolidation).
- Evaluation of minimal residual disease (MRD) in patients with immunofixation negative-CR after each phase of treatment (induction, autologous stem cell transplant and consolidation).
- Overall survival (OS) after ASCT with BUMEL versus MEL-200.
- To evaluate the safety and tolerability of induction and consolidation treatments.

1.12. Study design

This protocol is a national, multicenter, comparative, open-label, randomized trial comparing the PFS of two pre-transplant conditioning regimens (BUMEL versus MEL-200).

A total of 460 patients will be enrolled in the study. Scheduled evaluations and study visits will take place during the **pre-treatment, treatment and follow-up periods**.

The **pre-treatment period** includes the screening visit in which participants provide informed consent in writing in order to take part in the study. The patient is then assessed to determine his/her eligibility. The selection process will begin 21 days before the first dose of medication is administered (days -21 to 0). During the **treatment period**, eligible patients will be included in the study and given six cycles of induction treatment with bortezomib/ lenalidomide / dexamethasone (VRD-GEM). Each cycle will last 28 days, during which SC bortezomib will be administered on days 1, 4, 8 and 11, oral lenalidomide on days 1-21 of each cycle, and oral dexamethasone on days 1-4 and 9-12 of the cycle.

After the first three induction cycles, and in the absence of progression or unacceptable toxicity, peripheral blood hematopoietic stem cells will be mobilized and collected using G-CSF for later autologous transplantation. Patients will be randomized in a 1:1 allocation ratio to receive conditioning treatment with MEL-200 versus BUMEL.

Randomization will take place at the beginning of the study, once the screening is complete and the patient's eligibility verified. Three months after transplantation, patients will receive two cycles of consolidation treatment with VRD-GEM at the same doses administered during induction treatment.

Once the treatment phase is complete, patients will begin the **follow-up** phase in which they will be visited every three months to evaluate disease progression and survival.

1.13. Disease under study

Multiple Myeloma (MM).

1.14. Primary endpoints

Primary efficacy endpoint:

- Progression-free survival (PFS) after both conditioning regimens

Secondary efficacy endpoints:

- Rates of complete response after each phase of treatment (induction, autologous transplant and consolidation).
- Sequential studies of negative minimal residual disease (MRD) in patients who have achieved complete response after each stage of treatment (induction, autologous transplant and consolidation).
- Overall survival.
- Safety of combined VRD-GEM therapy during induction and consolidation, and of both conditioning regimens.

1.15. Study population

Population under study

Patients \leq 65 with newly-diagnosed multiple myeloma who have not received prior treatment.

Number of patients

A total of 460 patients will be included in the study. Enrollment will be competitive, and therefore limited numbers of patients at participating sites are not anticipated.

1.16. Duration of treatment

Patients included in the trial will receive induction chemotherapy for 24 weeks. After the first three cycles, mobilization and harvesting of hematopoietic stem cells will begin, followed by autologous stem cell transplantation after the sixth cycle with a rest period

of 4 to 12 weeks between the last cycle and transplantation. Two cycles of consolidation will be given three months (10-14 weeks) after transplantation.

1.17. Schedule and estimated completion date

The planned approximate start date of the study is May 2013; it is estimated that recruitment will be finished by May 2017, so that the last patient recruited will finish consolidation treatment in May 2018. The clinical trial report should be completed in May 2019.

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3. GENERAL INFORMATION

3.1. Trial identification

3.1.1. Protocol code

GEM2012MENOS65

3.1.2. Study title

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

3.2. Type of clinical trial

Clinical trial with a drug in new conditions of use

3.3. Description of the study products

- Busulfan (Busilvex®)
60 mg vials of busulfan in 10 mL (6 mg/mL concentration)
Intravenous administration
Pierre Fabre Medicament

- Bortezomib (Velcade®)
Vials of lyophilized powder to be reconstituted (3.5 mg)
Subcutaneous administration
Johnson & Johnson Pharmaceutical Research & Development (J&J&D)

- Lenalidomide (Revlimid®)
25 mg, 15 mg, 10 mg and 5 mg hard capsules
Oral administration
Celgene

- Dexamethasone
20 mg, 10 mg, and 5 mg capsules
Oral administration

Dexamthesaone will not be supplied by the sponsor as it is routinely used to treat MM and is part of the standard therapy required to treat this type of patient. The commercial drug forms normally used at each trial site will be used.

- Melphalan

Vials of sterile, lyophilized powder that contains 50 mg of melphalan, and 10 ml vials of solvent/diluent

Intravenous administration

Melphalan will not be supplied by the sponsor as it is routinely used to treat MM and is part of the standard therapy required to treat this type of patient. The commercial drug forms normally used at each trial site will be used.

3.4. Sponsor information

PETHEMA Foundation

CIF (Tax ID Number): G-81245706

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3.5. Monitor identification

Trial Form Support (TFS)

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3.6. Information on sites and investigators participating in the trial:

See Appendix 1

3.7. Estimated trial duration

Recruitment: until May 2017

Follow-up period: May 2018

Clinical trial report: May 2019

3.8. Planned number of patients

460 patients

3.9. List of tables

Table 1: Dose adjustment levels

Table 2: Intracycle dose adjustment due to thrombocytopenia

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4. INTRODUCTION AND RATIONALE OF THE STUDY

4.1. Scientific background

4.1.1. Overview of multiple myeloma

Multiple Myeloma (MM) is a B-cell neoplasm in which B-cells are in their final stage of development (plasma cells). It is the second most common blood cancer, with an incidence of approximately 4 cases per 100,000 inhabitants annually. Multiple Myeloma continues to be an incurable disease. As the disease progresses, it weakens resistance to infections and causes significant skeletal destruction (including bone pain, pathological fractures and hypercalcemia), anemia, renal failure and, less frequently, neurological complications and hyperviscosity, all of which are responsible for morbidity and subsequent mortality in MM patients.¹ Survival in patients with MM has improved significantly in recent years, especially in those diagnosed after 2001². This improvement has been observed primarily in young patients, under 65 years old, who are also eligible for autologous stem cell transplantation thanks, in part, to the introduction of new drugs. However, even in patients who have received the new drugs during pre-transplant induction treatment, PFS remains at around 33 months³, a fact which justifies the search for new treatment options to improve prognosis for this disease.

4.1.2. Current multiple myeloma treatment

The treatment of choice for younger multiple myeloma (MM) patients consists of induction treatment followed by intensification with high-dose chemotherapy and hematopoietic stem cell transplant (ASCT). However, achieving complete response (CR) post-transplant is crucial to obtaining prolonged PFS and OS⁴. Thus, in the experience of the MD Anderson Cancer Center, the average survival of patients with CR post-transplant ranges from 8 to 14 years, compared with just 4 to 5 years for patients who have achieved partial response⁶. A study conducted by the Spanish Group demonstrates that achieving CR post-transplant is associated with prolonged OS and PFS⁷. Studies using more sensitive techniques such as flow cytometry enable greater depths of complete response to be identified, which have a higher impact on PFS and OS. As well, recent studies carried out by the Spanish Group^{8,9} demonstrate that achieving CR with negative minimal residual disease (MRD) using flow cytometry is associated with more prolonged rates of PFS and OS than it is for patients in CR with persistent residual disease.

Patients with an increased probability of achieving CR post-transplant show an increased sensitivity to induction treatment measured by the pre-transplant level of monoclonal component (M-protein). Thus, patients with <10 g/L of serum M-protein have a probability of achieving CR of between 50% and 70%, compared with only 15% for those with >10 g/L and less than 10% for those with >20 g/L.

The use of 'classic' treatments such as VAD (vincristine, Adriamycin and dexamethasone), cyclophosphamide and dexamethasone or combination chemotherapy (VBMCP/VBAD used widely in Spain), can achieve a pre-transplant CR of between 5% and 10% and a post-transplant CR of 35%-40%, with a median survival of approximately 6 years⁴. The number of patients that survive and remain in CR for more than 10 years is less than 10%.

The combination thalidomide/dexamethasone (TD) produces an overall response rate of between 58% and 76% when used as first-line induction treatment. However, the pre-transplant CR rate is low (5%-14% according to the series). On the other hand, TD is a suboptimal regimen for patients with extramedullary plasmacytomas or high-risk cytogenetics^{3,11}.

The combination bortezomib/dexamethasone (VD) produces results similar to those obtained with conventional chemotherapy, with an overall response rate of 65% and a pre-transplant CR of 12%, increasing to 88% and 35% post-transplant, respectively^{12,13}. In a large study carried out by the French Group IFM comparing VAD and VD

therapies, the CR, VGPR and PFS rates were higher with VD in both standard-risk patients as well as patients with poor-prognosis cytogenetics¹⁴.

Lenalidomide is the drug most recently approved for the treatment of MM. The combination of lenalidomide/dexamethasone produces a pre-transplant response rate of 91%, including 56% CR +VGPR¹⁵.

Use of double combination therapies has not improved response rates over conventional chemotherapy. However, triple combination therapies produce higher rates of pre- and post-transplant CR. The combination of PAD (bortezomib, Adriamycin, dexamethasone) produces a 95% overall response rate with a CR of 24% and 43% pre-transplant and post-transplant, respectively¹⁶. In this study, using the standard dose of bortezomib (1.3 mg/m²) nearly 50% of patients had neuropathy (mainly grade 1-2). When the dose of bortezomib was reduced to 1 mg/m², the incidence of neuropathy fell to 16% and the overall response rate was 89%. However, the rates of CR post-induction and post-transplant also fell to 11% and 37%, respectively¹⁷.

The combination VTD (bortezomib, thalidomide, dexamethasone) has been studied in two randomized, phase III trials. In a study conducted by the Italian Group, the combination VTD showed both higher pre-transplant (19% vs. 5%) and post-transplant (42% vs. 30%) CR rates compared to TD¹¹. The estimated PFS at three years was significantly better with the combination VTD compared to TD (68% vs. 56%, p=0.0057). In the Spanish Group study, the post-induction CR rate was higher with VTD (35%) compared with TD (14%) and VBMCP/VBAD/bortezomib (21%). The post-transplant CR rate is higher with VTD compared with TD and VBMCP/VBAD/bortezomib (46% vs. 24% vs. 38%)³. With an average follow-up of 27 months, the PFS rate was higher with VTD (median not reached) compared with TD (27 months) and VBMCP/VBAD/bortezomib (36 months), although there were no significant differences in OS. In patients with high-risk cytogenetics or extramedullary plasmacytomas, VTD also showed greater overall response and CR rates compared with the other two regimens³.

In a phase I/II trial studying patients with newly diagnosed myeloma, the combination VRD (bortezomib, lenalidomide, dexamethasone) produced a CR/nCR rate of 39%¹⁸. In a phase II study conducted by the French Group, treatment with three cycles of VRD induction treatment pre-transplant, achieved a CR rate of 28% which increased to 35% post-transplant¹⁹.

The most significant and limiting toxicity associated with the administration of bortezomib is peripheral neuropathy. The incidence of grades 1-4 peripheral neuropathy with different combinations of bortezomib varies between 30% and 76% according to the series, of which approximately 10% to 15% correspond to grade 3-4 peripheral neuropathy. In a recent phase III study, it was shown that subcutaneous administration of bortezomib significantly reduced the incidence of peripheral neuropathy while still maintaining efficacy. In this study, the incidence of peripheral neuropathy of any grade associated with subcutaneous bortezomib is 38%, compared to 53% ($p=0.044$) using intravenous bortezomib, and the incidence of grade 3-4 peripheral neuropathy is 6% vs. 16% ($p=0.012$)²⁰.

Standard conditioning treatment for ASCT is melphalan-200 (MEL200). With the aim of improving results, other combinations have been tried such as CVB (cyclophosphamide, etoposide, carmustine), increasing the dose of melphalan to 220 mg/m², or using melphalan together with total body irradiation, but without success⁴. In a study conducted by the Spanish Group, the combination busulfan/melphalan (BUMEL) was superior to MEL200 in terms of PFS; however, BUMEL was associated with a greater incidence of hepatic veno-occlusive disease (VOD), which is attributed to erratic absorption of oral busulfan. However, in an update of the series, conditioning with BUMEL was associated with a significantly prolonged PFS²¹. On the other hand, in a recent phase II study of 55 patients with relapsed or de novo myeloma with BUMEL using intravenous busulfan, the CR/nCR rate post-transplant was 49% with no cases of VOD observed²².

Post-transplant consolidation consists of administering full-dose treatment regimens over a short period, with the aim of improving depth of response. Bortezomib²³ as well as lenalidomide as monotherapy²⁴ has been used successfully, increasing the rate of CR/nCR and overall response rates in approximately 15% of patients. The combination VTD has also been used as consolidation therapy. In a study by the Italian Group in which patients received ASCT followed by four cycles of consolidation, molecular CR rates of 18% were achieved which is associated with maintained remission and low probability of relapse²⁵. In the French Group study, administration of two cycles of post-transplant consolidation therapy with VTD with low doses of bortezomib (1 mg/m²) plus thalidomide (100 mg) achieved an increase in the CR rate from 23% to 36%²⁶. In the phase III study by the Italian Group, consolidation with two cycles of VTD after induction with VTD and double autologous transplant increased the post-transplant CR rate from 42% to 49%²⁷. Molecular CR rates increased from 43% pre-consolidation to

67% post-consolidation. VRD has also been used as consolidation therapy. In a phase II trial, after induction with VRD and ASCT, consolidation with VRD increased the rate of CR from 35% to 52% post-transplant, half of which were stringent CR²⁸.

4.2. Rationale

Current MM treatment in younger patients includes induction followed by intensification with high-dose chemotherapy, followed by hematopoietic stem cell transplantation. Induction must be a highly effective anti-tumor treatment that allows for a high rate of post-transplant CR to be achieved, which corresponds to an increase in long-term survival²⁹. In this way, triple combinations with new drugs have been shown to be highly effective. The combination VRD has been shown to be highly effective as induction treatment in phase II trials,^{18,19} which is the basis for its use in this clinical trial.

With respect to pre-transplant conditioning, MEL200 is the standard treatment. That said, studies by the Spanish Group have shown a significantly greater prolonged PFS with BUMEL compared to MEL200, with no greater incidence of VOD observed when IV busulfan is administered. These data justify developing a phase III trial comparing BUMEL with IV busulfan versus MEL200 as the pre-transplant conditioning regimen.

Post-transplant consolidation, whether using drugs in monotherapy or in combination regimens, has proven highly effective in increasing overall response rates and CR^{25,27}. For this reason, the majority of studies now include several consolidation cycles in their design. In our study, we plan to administer two cycles of consolidation with VRD, a combination which has been used successfully as post-transplant consolidation and has been included in the design of a wide range of randomized clinical studies (EMN, BMT CTN 0702).

That said, peripheral neuropathy remains the principle limiting factor in the use of bortezomib. However, it has been shown in a phase III trial that subcutaneous administration of bortezomib in patients with relapsed myeloma substantially reduced the incidence of peripheral neuropathy, while still maintaining efficacy. These data support the use of subcutaneous bortezomib in our study.

As part of this study we plan to carry out an exhaustive patient follow-up with MRD studies after each stage of treatment, in order to demonstrate the eventual increased response in each phase.

4.3. Objectives

4.3.1. Primary objectives

- Progression-free survival after autologous transplant with BUMEL versus MEL-200 in patients who have previously received VRD-GEM as induction regimen.

4.3.2. Secondary objectives

- Complete response rates (CR) with negative immunofixation after each stage of treatment (induction, autologous transplant and consolidation).
- Evaluation of minimal residual disease (MRD) in patients with negative immunofixation (CR) after each stage of treatment (induction, autologous transplant and consolidation).
- Overall survival (OS) after ASCT with BUMEL versus MEL-200.
- Evaluate the safety and tolerability of induction and consolidation treatments

5. CLINICAL TRIAL TYPE AND DESIGN

5.1. Overall Design

This is an open-label, randomized, comparative, multicenter, national trial comparing the PFS of two pre-transplant conditioning regimens (BUMEL versus MEL-200), in patients who have previously received VRD-GEM as induction treatment.

5.2. Treatment Plan

Patients will be evaluated during visits that will take place over three periods: pre-treatment, treatment and follow-up.

The **pre-treatment period** includes the screening visit, in which an informed consent form is completed in order to participate in the study. The screening period takes place 21 days prior to the baseline visit.

Treatment period. Eligible patients will be included in the study and will receive six cycles of induction treatment with bortezomib, lenalidomide and dexamethasone (VRD-GEM). Each cycle will last four weeks. Bortezomib will always be administered subcutaneously, on days 1, 4, 8 and 11 of each cycle; lenalidomide will be administered on days 1-21 of the cycle, and dexamethasone on days 1-4 and 9-12 of the cycle.

Immediately after the third cycle, and in the absence of progression or unacceptable toxicity, mobilization of hematopoietic stem cells with G-CSF and subsequent

apheresis will take place. Patients who are screened and meet the inclusion criteria will then be randomized in a 1:1 allocation ratio to receive either autologous stem cell transplant using BUMEL as the conditioning regimen (arm A) or MEL200 (arm B).

Three months after transplantation, and as long as clinical and hematological conditions allow, all patients, independently of the conditioning regimen received, will receive two cycles of consolidation with VRD-GEM at the same doses as during induction.

After the treatment period is complete, an end-of-study visit will be conducted at least 30 days after receiving the last dose of the study drug.

Follow-up period. Once the end-of-study visit is completed after consolidation, the patient is no longer part of the study. After this time the standard follow-up visits will be made every three months to evaluate the patient's progression and survival (this is standard practice for patients with MM).

Appendix 3 details the schedule of visits.

5.3. Study procedures

Appendix 3 includes a diagram of the schedule of study procedures.

Before the first patient is included in the trial:

Before the first patient is included in the trial, hospitals which are unable to perform autologous stem cell transplantations onsite, must make an agreement with one of **the reference hospitals that will necessarily participate in the trial** that it will cover this procedure. The PI of the reference hospital must agree to commit to carry out the transplants in accordance with clinical trial regulations, and within the timeframe planned with respect to the date the induction period ends and application of the conditioning regimen assigned during randomization. As well, the reference hospital must provide the hospital that included the patient in the trial with a clinical report that details all of the criteria needed to record the data regarding the transplant in the clinical trial CRF.

Before initiating treatment with the study drug:

Warning about pregnancy

Lenalidomide causes deformities in primates similar to those described for thalidomide. For this reason, although as yet unknown, it is expected this drug will have teratogenic

effects in humans if taken during pregnancy. All women of reproductive potential or the partner of a woman of reproductive potential must use contraception during treatment with lenalidomide.

- A woman is considered to be of childbearing potential unless she meets one of the following criteria:
 - ✓ She is ≥ 50 years old and has had naturally-occurring amenorrhea for ≥ 1 year (amenorrhea associated with the use of chemotherapy does not rule out reproductive potential).
 - ✓ Premature ovarian failure confirmed by a gynecologist.
 - ✓ Bilateral salpingo-oophorectomy or hysterectomy.
 - ✓ XY genotype, Turner syndrome or uterine agenesis.

Second Primary Malignancies (SPM)

If hematological second primary malignancies (SPM) are detected during the trial, samples will be collected and sent to the reference centre of the Hospital de Salamanca for centralized analysis, and the results then sent to Celgene. In the case of non-hematological SPMs, stringent collection of any relevant patient data will be carried out for detailed analysis.

Screening procedures

Each patient must sign and date the informed consent form before any study procedures are carried out. However, all procedures that are part of the normal diagnostic routine for MM performed before informed consent is given are considered valid for screening, as long as they are performed in the 21 days prior to initiation of treatment. If there is a trial candidate awaiting diagnosis because they have not had a bone marrow aspiration, the sample will be sent to the reference laboratories as long as the informed consent form has been signed prior to this.

Procedures during the screening visit:

- Informed consent in writing is presented and explained
- Medical history is taken, including concomitant diseases. No concomitant medication should be recorded in the eCRF except those with possible anti-myeloma activity such as corticosteroids or clarithromycin.
- Complete physical exam, weight, height, vital signs and ECOG performance status.
- Electrocardiogram.
- Skeletal survey to detect bone lesions.

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- Any other radiological exam (magnetic resonance imaging or PET/CAT scans) in the event that extramedullary plasmacytomas are suspected.
 - Hemogram.
 - Biochemistry (including C-reactive protein, beta-2-microglobulin).
 - Complete serum and urine protein study: total protein, serum protein electrophoresis, 24-hour proteinuria and urine protein electrophoresis, immunoglobulin dosing and serum and urine immunofixation.
 - Serum free light chains (sFLC).
 - Bone marrow aspiration, including morphology, flow cytometry (with cell cycle analysis) cytogenetics and molecular biology. The latter tests will be performed centrally at the reference laboratories (see Appendix 8).
 - Pregnancy test (see Appendix 10).

General procedures during the induction period

On day 1 of each cycle (+/- 4 days), the following tests will be carried out:

- Physical exam
- ECOG performance status
- Hemogram
- General serum biochemistry
- Serum and urine protein electrophoresis for M-protein quantification. Immunofixation (IF) if the electrophoretic pattern is normal
- Administration of bisphosphonates
- Pregnancy test (see Appendix 10)
- Toxicity/adverse effects in accordance with NCI common toxicity criteria presented during the previous cycle.
- A hemogram test to coincide with administration of dose 4 of bortezomib (day 11 of the cycle).
- Response assessment

During the treatment period, for all patients for whom the goal is complete disappearance of the monoclonal component in both electrophoresis and immunofixation, the following procedures are required once this disappearance is confirmed (samples to be sent to reference laboratories):

- Serum free light chains (sFLC)
- Bone marrow analysis. Bone marrow studies will include: morphology, flow cytometry (to determine the level of minimal residual disease) and molecular biology.

Notes:

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- ❖ On day 1 of cycle 1, it will not be necessary to repeat collection of blood samples for biochemistry, quantification of immunoglobulins and monoclonal component, nor 24-hour urine collection for proteinuria, as long as these tests have been done for patient screening a maximum of two weeks before the start of treatment.
 - ❖ If one of the days of bortezomib administration falls on a holiday, administration can be brought forward or delayed, bearing in mind that at least 72 hours must elapse between consecutive doses.

Post-induction procedures

At least four weeks after the last cycle of induction is complete, the following tests will be carried out:

- Physical exam
- Hemogram
- General serum biochemistry, including creatinine, calcium, LDH, C-reactive protein and beta-2 microglobulin
- Serum and urine protein electrophoresis for M-protein quantification. Immunofixation (IF) if the electrophoretic pattern is normal.
- Detection of serum free light chains
- A skeletal survey will not be performed unless clinical data suggest an increase in or the appearance of new bone lesions.
- If extramedullary plasmacytomas are found, the same technique will be used to assess the response as that used at the time of diagnosis. The development of the plasmacytoma after the third treatment cycle should also be recorded using the same diagnostic test (CAT, MRI or PET/CAT). If the test is negative, it will not be necessary to repeat this when treatment has finished.
- Bone marrow aspiration, including morphology, flow cytometry and molecular biology (centralized at the reference laboratory).
- Toxicity/adverse effects in accordance with NCI common toxicity presented during the previous cycle.
- ECOG performance status.
- Response assessment.
- Pregnancy test (see Appendix 10).

General procedures during mobilization of stem cells

The relevant evaluations will be carried out in accordance with the practices of each site.

Randomization procedure for pre-transplant conditioning

At the time patients are registered in the electronic CRF, and once the inclusion/exclusion criteria are completed, all patients will be randomized and assigned in a 1:1 allocation ratio to receive one of the two conditioning regimens planned for the transplant phase (BUMEL or MEL200). Randomization will be carried out using the electronic CRF. This is an open-label study, meaning the investigator, the site staff, and the patient will know to which treatment arm the patient has been assigned. A number will be assigned to the patient and used to identify him/her on the CRF.

Procedures during autologous stem cell transplantation

- A complete evaluation of the disease will be completed before the transplant takes place (see section on post-induction procedures)
- The remaining pre-transplant tests will be the standard tests performed in accordance with the clinical practices of each site.
- During conditioning and transplantation:
 - Clinical and analytical monitoring will be carried out in accordance with the practices of each site.
 - Busulfan levels: in a sample of 30 patients selected from the first 60 cases randomized to the BUMEL treatment arm, blood samples will be collected at 2, 4 and 6 hours after each dose of busulfan. The plasma obtained after separation will be frozen at -20° C at the hospital where the sample collection takes place. The grouped samples will later be sent in the appropriate conditions for batch analysis at the 12 de Octubre Hospital in Madrid. Samples will be processed to determine busulfan plasma levels. The results of this analysis may lead to modifications aimed at improving the drug's bioavailability.
 - Relevant toxicity will be recorded during the procedure, in particular grade 3-4 mucositis, degree of gastrointestinal toxicity, bacteremia, pneumonias, fungal infections and hepatic veno-occlusive disease.

Procedures after autologous stem cell transplant

Three months after transplant the following tests will be carried out:

- Hemogram
- General serum biochemistry, including creatinine, calcium, LDH, C-reactive protein and beta-2-microglobulin.
- Serum and urine protein electrophoresis for M-protein quantification. Immunofixation (IF) if the electrophoretic pattern is normal
- Detection (centralized) of serum light chains

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- A skeletal survey will not be done unless there is clinical data to suggest an increase in or the appearance of new bone lesions.
 - If extramedullary plasmacytomas are found, the same technique will be used as that used at the time of diagnosis to assess the response (if in the assessment after the third cycle, or after induction, the plasmacytoma has disappeared, the imaging test will not be repeated).
 - Bone marrow aspiration including morphology, flow cytometry and molecular biology (centralized)
 - Toxicity/adverse effects in accordance with NCI common toxicity criteria presented during the previous cycle
 - ECOG performance status
 - Response assessment
 - Pregnancy test (see Appendix 10)

Procedures during consolidation cycles

After a post-transplant evaluation has been carried out, and the clinical and analytical conditions of the patient permitting, two cycles of consolidation will be administered. Ideally, consolidation will begin three months after autologous stem cell transplant. If the patient's overall health is affected or if secondary cytopenias occur as a result of the transplant procedure, consolidation may be delayed up to a maximum of six months post-transplantation.

On day 1 of cycle 2, and once cycle 2 is complete, the following should be carried out:

- Symptom-focused physical exam
- Hemogram.
- General serum biochemistry, including creatinine, calcium, LDH, C-reactive protein and beta-2-microglobulin.
- Serum and urine protein electrophoresis for M-protein quantification. Immunofixation (IF) if the electrophoretic pattern is normal
- During each cycle, a hemogram should be performed to coincide with the 4th administration of bortezomib [Velcade (day 11)].
- Toxicity/adverse effects in accordance with NCI common toxicity criteria presented during the previous cycle.
- ECOG performance status.
- Response assessment.
- Pregnancy test (see Appendix 10).

Notes:

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- ❖ It will not be necessary to repeat laboratory analyses on day 1 of consolidation cycle 1 as long as these tests have been carried out as part of the post-transplant evaluation a maximum of 15 days prior.
 - ❖ If one of the days on which bortezomib (Velcade®) is administered falls on a holiday, administration can be brought forward or delayed, bearing in mind at least 72 hours must elapse between consecutive doses.
 - ❖ If the platelet count is normal on day 1 of each cycle, it will not be necessary to carry out a control hemogram on each day of bortezomib (Velcade®) administration. This will only be carried out on day 11 of the cycle [before the 4th dose of bortezomib (Velcade®)].

Procedures during the end-of-study visit

The end-of-study visit will take place after the two consolidation cycles. The tests performed at this time may also serve as screening tests for any clinical trials studying maintenance treatment in this patient population.

Patients that discontinue the treatment protocol due to toxicity or progression should attend the end-of-study visit a minimum of four weeks after the last treatment cycle.

The tests to be carried out will include:

- Hemogram.
- General serum biochemistry, including creatinine, calcium, LDH, C-reactive protein and beta-2-microglobulin.
- Serum and urine protein electrophoresis for M-protein quantification. Immunofixation (IF) if the electrophoretic pattern is normal
- Re-evaluation of plasmacytomas that existed at the time the patient was included in the study, with the same imaging technique used at the beginning. This will be done only for patients in whom the plasmacytomas have not completely disappeared after transplant.
- Bone marrow aspiration including morphology, flow cytometry and molecular biology
- Toxicity/adverse effects in accordance with NCI common toxicity criteria presented during the previous cycle
- ECOG performance status
- Response assessment
- Pregnancy test (see Appendix 10)

Procedures during the follow-up phase

Once the end-of-study visit is complete, the patient is no longer a participant in the study. Following clinical care practice, a follow-up visit will be made every three months that will serve as long-term follow-up for the purpose of recording:

1. - Date of progression
2. - Date salvage therapy is initiated
3. - Survival

6. POPULATION UNDER STUDY

6.1. Inclusion criteria

All patients must meet the following inclusion criteria:

- The patient must, in the opinion of the investigator, be capable of complying with all requirements of the trial.
- Have signed the informed consent form
- Be between 18 and 65 years of age and a candidate for autologous stem cell transplant.
- Have an ECOG Performance Status ≤ 2 (or 3 if the ECOG is due to myeloma, e.g. pathological fracture)
- Newly diagnosed patient with symptomatic multiple myeloma based on standard criteria (Appendix 6), who has not received any prior chemotherapy treatment for MM.
- Patient must have measurable disease, defined by the following criteria:
 - For secretory MM, measurable disease is defined by any quantifiable value of serum M-protein (IgG ≥ 10 g/L or IgA ≥ 5 g/L) and/or, when applicable, an excretion of light chain in urine ≥ 200 mg/24 hours.
 - For oligo- or non-secretory multiple myeloma, measurable disease is defined by the presence of soft tissue (not bone) plasmacytomas, which is determined by clinical exam or radiographic techniques (e.g. MRI, CT scan).
- Life expectancy > 3 months.
- The patient must have the following laboratory values in the 21 days prior to initiation of treatment (day 1, cycle 1):
 - Platelet count $\geq 100 \times 10^9/L$ and absolute neutrophil count of $\geq 1.0 \times 10^9/L$
 - Corrected serum calcium < 14 mg/dL.
 - Aspartate transaminase (AST) and alanine transaminase (ALT) ≤ 2.5 x the upper limit of normal (ULN).
 - Total bilirubin within normal limits.
 - Serum creatinine ≤ 2 mg/dL

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- Women of childbearing potential and men (including vasectomized men whose partners are women of childbearing potential), must use two methods of contraception during the entire course of treatment, during dose interruptions and for up to three months after receiving the final dose, as well as meet all of the requirements set out in Appendix 10.

6.2. Exclusion criteria

Patients that present any of the following exclusion criteria cannot be included in the trial:

- Non-secretory myeloma without measurable plasmacytomas.
- Patients who have undergone prior treatment for multiple myeloma, with the exception of emergency treatment using steroid pulses, bisphosphonates, or radiotherapy received before beginning induction treatment.
- Peripheral neuropathy \geq grade 2 in the 21 days prior to inclusion.
- Known hypersensitivity to bortezomib, boric acid, mannitol or lenalidomide.
- Patients that have received any investigational agent in the 28 days prior to inclusion in the study.
- Patients who have had a myocardial infarction in the six months prior to inclusion in this study or who are a class III or IV according to the New York Heart Association (NYHA) functional classification system, heart failure, unstable angina, uncontrolled ventricular arrhythmias or acute ischemia detected by electrocardiogram, or nervous system disorders.
- Patients currently enrolled in another clinical trial or receiving any type of investigational agent.
- Patients who are seropositive for HBV, HCV or HIV.

6.3. Planned number of subjects

A total of 460 patients \leq 65 years old with symptomatic, newly-diagnosed multiple myeloma who have not received prior treatment for their condition will be enrolled in the study.

6.4. Withdrawal of patients from the trial

Patients will be withdrawn from the study when one of the following criteria is met:

- Confirmed disease progression.
- Unacceptable toxicity.

Patients will be informed that they may withdraw from the study whenever they wish, without this affecting their subsequent medical care in any way.

The investigator can, at his/her discretion, suspend treatment in patients under the following circumstances:

- Major protocol violations have occurred.
- At the request of the patient.
- Non-compliance with scheduled visits.
- Loss to follow-up
- Pregnancy or lack of contraceptive use
- Justified administrative reasons.
- General or specific changes in the patient that, in the opinion of the investigator, are reason to stop administering the medication of the scheduled study regimen.

Patients that withdraw from the study for any reason cannot be included again. When the patient withdraws, the main reason for his/her withdrawal should be documented and, if possible, the patient should be re-evaluated.

7. DESCRIPTON OF THE STUDY TREATMENT

7.1. Study materials

Bortezomib (Velcade®) for injection is a sterile lyophilized powder to be reconstituted, administered in vials that contain bortezomib (Velcade®) and mannitol in a 1:10 ratio. The drug will be supplied for the sponsor by Janssen, via B&C and later distributed by Farmavénix, S.A., free of charge for the purpose of conducting the trial.

Although bortezomib (Velcade®) can be administered both intravenously and subcutaneously, in this trial it will always be administered subcutaneously.

Lenalidomide (Revlimid®) for oral administration will come in the form of 25 mg, 15 mg, 10 mg and 5 mg capsules. It will be supplied for the sponsor by Celgene through Almac Clinical Service Limited and later distributed by Farmavénix, S.A. free of charge for the purpose of conducting the trial.

Dexamethasone for oral administration, will come in form of 20 mg, 10 mg and 5 mg capsules. Dexamethasone will not be supplied by the sponsor as it is routinely used to treat MM and is part of the standard therapy required to treat MM patients. The commercial drug forms normally used at each trial site will be used.

Busulfan (Busilvex®) for intravenous administration, contained in vials of 60 mg in 10 mL (in a 6 mg/mL concentration). It will be supplied for the sponsor by Pierre Fabre Ibérica S.A., through Pierre Fabre Ibérica S.A. and later distributed by Farmavénix, S.A. free of charge for the purpose of conducting the trial.

Melphalan for intravenous administration, will come in the form of vials of sterile, lyophilized powder containing 50 mg of melphalan and vials of 10 ml of solution/diluent. Each vial of melphalan will be reconstituted in 10 ml of diluent to a final concentration of 5 mg/ml. Melphalan will not be supplied by the sponsor as it is routinely used to treat MM and is part of the standard therapy required to treat MM patients. The commercial drug forms normally used at each trial site will be used. Traceability of the drug will be ensured although the drug may not be specifically labeled for the trial. The Pharmacy Service will be advised to record in their dispensing registers the trade name and batch number of the drug dispensed to each patient.

7.2. Preparation, care and storage of study drugs

Dexamethasone will be stored in accordance with routine storage and maintenance conditions at each hospital.

Bortezomib (Velcade®). Vials contain lyophilized bortezomib for injection and should be stored at room temperature. Stability data indicate that lyophilized products remain stable for at least 12 months if they are stored under the recommended conditions. Bortezomib is a cytotoxic antineoplastic and caution should be used when handling and preparing bortezomib solution. The pharmacist should prepare the drug using a vertical laminar flow biological safety cabinet and proper aseptic techniques. It is recommended that gloves and protective clothing are worn when preparing bortezomib.

Bortezomib should be administered in single-use vials containing 3.5 mg of bortezomib.

Each vial of bortezomib for injection should be reconstituted in a laminar flow hood, within eight hours prior to administration, with 1.4 ml of saline (0.9%) so that the reconstituted solution contains bortezomib at a concentration of 2.5 mg/ml. It is very important to bear in mind that the final concentration of the drug for subcutaneous administration is 2.5 times greater than that of the solution reconstituted for IV administration. The solution is completely dissolved in approximately 10 seconds. The reconstituted solution is clear, with a final pH of 4 to 7. Reconstituted bortezomib should be administered as soon as possible, and never more than 8 hours after reconstitution. If bortezomib solution comes into contact with skin, wash the skin immediately with soap, water and diluted hydrogen peroxide. If bortezomib solution comes into contact with mucous membranes, rinse thoroughly with water. Always contact a doctor if any part of the body comes into contact with the solution. All materials used during preparation of the drugs should be disposed of

according to established guidelines.

Although bortezomib can be administered both intravenously and subcutaneously, during this trial it will always be administered subcutaneously.

The initial dose of VELCADE® will be 1.3mg/m².

Calculation of volume of VELCADE (ml):

$$\frac{\text{Dose (mg/m}^2\text{)} \times \text{Patient BSA(m}^2\text{)}}{2.5 \text{ mg/mL}}$$

= Total volume of VELCADE to be administered

2.5 mg/mL= Reconstituted concentration for subcutaneous administration

Please bear in mind that the quantity of VELCADE contained in one vial (3.5 mg) may exceed the required dose.

The following table is shown for guidance purposes. However, calculations should be individualized for each patient.

Body Surface Area m ²	Total Required Dose (mg) with 1.3 mg/m ²	Volume for SC administration (ml)
1.5	1.95	0.78
1.6	2.08	0.83
1.7	2.21	0.88
1.8	2.34	0.94
1.9	2.47	0.99
2.0	2.60	1.04
2.1	2.73	1.09

Lenalidomide (Revlimid®): Lenalidomide capsules should be stored in tightly closed containers away from light, and according to the instructions on the label.

Busulfan (Busilvex®): Boxes and vials of Busilvex® should be stored at between 2°C and 8°C (in the freezer). The vials contain busulfan at a 6 mg/ml concentration in solution for infusion. One ml of concentrate contains 6 mg of busulfan (60 mg in 10 ml). After dilution, 1 ml of solution contains 0.5 mg of busulfan.

The vials have a shelf life of 2 years. Their chemical and physical stability during use after dilution has been confirmed for the following time periods:

- 8 hours (including infusion time) after dilution in injectable solution of 5% glucose or 9 mg/ml of sodium chloride (0.9%), at 20°C± 5° C;

- 12 hours after dilution in injectable solution of 5% glucose or 9 mg/ml of sodium chloride (0.9%), at 2°C-8°C, plus 4 hours storage at 20°C ± 5°C (including infusion time).

From a microbiological standpoint, the product should be used immediately after dilution. If it is not used immediately, storage times during use and its conditions prior to use of the drug are the responsibility of the user and will not, normally, exceed the previously stated time periods when the dilution takes place in controlled, aseptic conditions.

Busulfan is a cytotoxin and caution should be used when handling it; it is recommended that gloves and protective clothing are worn when doing so. If the product comes into contact with the skin or mucous membranes, the area should be washed immediately with copious amounts of water. The product should be prepared using a safety cabinet with vertical laminar flow.

Before using busulfan, it must be diluted with an injectable solution of sodium chloride (0.9%) or an injectable solution of glucose (5%). The amount of diluent should be equal to 10 times the volume of busulfan to obtain a final concentration of approximately 0.5 mg/ml.

Calculation applicable to the quantity of busulfan and diluent for one patient:

- Quantity of busulfan:
Ideal or adjusted weight (Kg) x busulfan dose (mg/Kg)
----- = A ml of busulfan to be diluted
6 (mg/ml)

- Amount of diluent:
(A ml of Busilvex®) x (10) = B ml of diluent

To prepare the final solution for infusion, the (A) ml of busulfan are added to the (B) ml of diluent (0.9% sodium chloride or 5% glucose). A non-polycarbonate syringe should be used. Busulfan should always be added to the diluent, never the other way around. The diluted solution should be mixed by carefully inverting and shaking. Only transparent, particulate-free solutions can be used.

The total prescribed dose should be administered within three hours.

Other intravenous solutions must not be administered concomitantly with this infusion.

Note: The dose of busulfan should be calculated as a function of the ideal (not actual) weight.

The ideal weight and adjusted ideal weight are calculated according to the formulas in Appendix 5.

7.3. Administration and treatment regimen

Induction treatment

All patients included in the study will receive 6 cycles of induction with VRD-GEM, to be administered every 4 weeks.

- Bortezomib (Velcade®) will be administered subcutaneously in one dose of 1.3 mg/m² on days 1, 4, 8 and 11, with a rest period from days 12 to 28.
- Lenalidomide (Revlimid®) will be administered orally in one dose 25 mg/d on days 1-21 of the cycle, with a rest period of 7 days (days 22-28).
- Dexamethasone will be administered orally in one dose of 40 mg/d on days 1-4 and 9-12 of the cycle.

VRD-GEM induction treatment regimen

	1	2	3	4	5	6	7	8	9	10	11	12	13-21	22-28
Velcade® 1.3 mg/m²	⇓			⇓				⇓			⇓			R e s t
Revlimid® 25 mg	⇓	⇓	⇓	⇓	⇓	⇓	⇓	⇓	⇓	⇓	⇓	⇓	⇓	
Dexamethasone 40 mg	⇓	⇓	⇓	⇓					⇓	⇓	⇓	⇓		

Mobilization and harvesting of hematopoietic stem cells

Mobilization of hematopoietic stem cells (HSCs) will be carried out using high-dose G-CSF after the third induction cycle. The dose of G-CSF used will be at the discretion of each transplant site. Apheresis will be initiated on day 4-5 of stimulation, once the number of CD34+ cells has been quantified. The minimum number of CD34+ cells needed to carry out the transplant will be determined at the discretion of each site, although a minimum of 2 x10⁶ CD34+/Kg is recommended, as well as cryopreservation, storage, defrosting and infusion of HSCs. If mobilization fails using the method indicated, the choice of a different mobilization method will be left up to

each site (preferably cyclophosphamide and G-CSF or G-CSF and plerixafor will be used).

Conditioning and autologous stem cell transplantation

The patient must not present any active infection which would contraindicate the transplant at the time conditioning is initiated.

The treatment groups will be:

➤ Group A - Melphalan 200 mg/m²

Patients will receive intravenous melphalan 100 mg/m² on days -3 and -2, as a slow bolus infusion. No more than 30 minutes should elapse between reconstitution of the drug and the end of the infusion. Infusion of melphalan at a dose of 200 mg/m² by IV on day -2 will also be permitted, according to each site's standard practice.

➤ Group B – Busulfan/Melphalan 200 mg/m²

Busulfan will be administered in a single dose of 3.2 mg/Kg daily via 3-hour infusion on days -5, -4 and -3 (total cumulative dose: 9.6 mg/Kg). If the patient's actual weight exceeds the ideal weight by more than 25%, calculate the dose adjusting for the patient's ideal weight or adjusted ideal weight (Appendix 5). Busulfan should always be administered through a central venous catheter. Melphalan will be administered in one dose of 140 mg/m² on day -2.

All patients should receive prophylaxis for neurological toxicity with diphenylhydantoin and/or clonazepam/lorazepam as per the existing protocol at each site, from 12 hours prior to 24 hours after administration of busulfan is finished.

Infusion of HSCs will begin on day 0.

Hydration, antiemetic treatment, prophylaxis for uric acid nephropathy and treatment of infections, as well as hemotherapy support and treatment with G-CSF post-transplant will be provided in line with each site's routine clinical practice.

Consolidation treatment

Three months after transplant, patients will be re-evaluated and if they have achieved a stable engraftment, defined by the presence of >1,500 granulocytes /mm³ and >100,000 platelets/mm³, they will receive two cycles of consolidation with VRD-GEM at the same doses and intervals as during induction. If hematological or extra-hematological toxicity occurs as a result of transplantation, consolidation can be delayed up to a maximum of 6 months post-transplant.

7.4. Dose adjustments and delays

All patients will be evaluated on day 1 of each new cycle (\pm 4 days), and attend an intermediate visit at which a hemogram will be carried out on day +11 to coincide with the 4th administration of bortezomib.

As a general rule, if recovery from hematological or non-hematological toxicity is not observed after a 4 week delay, the patient will be able to continue in the trial, the drug believed to be directly related to the toxicity will be withheld, and the patient will continue treatment with the remaining the drugs. Toxicities will be managed in accordance with NCI Common Toxicity Criteria (CTC), version 4.0 <http://ctep.cancer.gov/reporting/ctc.html>.

Table 1. Dose adjustment levels

Dose level	Lenalidomide	Bortezomib	Dexamethasone
Full dose	25 mg	1.3 mg/m ²	40 mg
Level -1 (Only applies to isolated neutropenia)	25 mg + G-CSF	1.0 mg/m ²	20 mg
Level -2	15 mg	0.7 mg/m ²	10 mg
Level -3	10 mg	-	-
Level -4	5 mg	-	-

7.4.1. VRD-GEM

ADJUSTMENTS FOR BORTEZOMIB-RELATED HEMATOLOGICAL TOXICITY

On day 1 of each cycle of VRD, the following values at least are required: neutrophils \geq 1000/mm³, and platelets \geq 50,000/mm³. If the patient does not show these values, a hemogram will be performed weekly until he or she recovers from the toxicity. The cycle can be delayed up to 4 weeks. If, after that time, the toxicity has not resolved, the cycle can be initiated and the drug suspected to be directly related to the toxicity withheld.

- On day 11, the minimum hematologic values required for the administration of bortezomib are: neutrophils \geq 500/mm³, and platelets \geq 30,000/mm³. When a dose of bortezomib is omitted due to hematological toxicity, that dose will not be replaced. Intracycle toxicities will be managed according to Tables 2 and 3.
- If, during a treatment cycle, two or more doses of bortezomib must be withheld due to hematological toxicity, the dose of bortezomib in the next cycle will be

reduced from 1.3 mg/m² to 1 mg/m² or from 1.0 mg/m² to 0.7 mg/m². The dose cannot be increased again later (Table 1).

ADJUSTMENTS FOR BORTEZOMIB-RELATED NON-HEMATOLOGICAL TOXICITY

- If the patient experiences any non-hematological toxicity grade ≥ 3 considered by the investigator to be associated with bortezomib, this should be discontinued until the toxicity returns to grade 1 or baseline. The dose will subsequently be reduced one level (Table 1).
- Patients who present neuropathic pain or peripheral neuropathy will be treated in accordance with Table 4.

ADJUSTMENTS FOR LENALIDOMIDE-RELATED HEMATOLOGICAL TOXICITY

On day 1 of each cycle of VRD, the patient must show at least the following values: neutrophils $\geq 1000/\text{mm}^3$, and platelets $\geq 50,000/\text{mm}^3$. If these values are not present, a hemogram will be performed each week until the patient has recovered from the toxicity. The cycle may be delayed up to a maximum of 4 weeks. If after that time the toxicity has not resolved, the cycle can be initiated and the drug suspected to be directly related to the toxicity withheld.

- On day 11 a control hemogram test will be carried out. Intracycle toxicity will be managed in accordance with Tables 2 and 3.
- G-CSF may be administered according to clinical judgment.
- Platelet transfusions are permitted.

ADJUSTMENTS FOR LENALIDOMIDE-RELATED NON-HEMATOLOGICAL TOXICITY

- If the patient experiences any non-hematological toxicity grade ≥ 3 , considered by the investigator to be related to lenalidomide, administration of the drug should be withheld until toxicity returns to grade 1 or baseline. The dose can subsequently be reduced by one level. (Table 1)
- In the case of renal failure, apply the adjustments in Table 5.

ADJUSTMENTS FOR DEXAMETHASONE-RELATED NON-HEMATOLOGICAL TOXICITY

- If the patient experiences any non-hematological toxicity grade ≥ 3 related to dexamethasone, the drug will be withheld until toxicity returns to grade ≤ 2 and reinitiated at a lower dose (Table 1).

-
- Hyperglycemia \geq grade 3 should be treated with insulin or other oral diabetes medication. The dose of dexamethasone will not be reduced except in cases where glucose levels cannot be controlled with appropriate diabetes medication.

RECORDING TOXICITY LEVELS DURING ASCT

- Mucositis grades III and IV, degree of gastrointestinal toxicity, bacteremias, pneumonias, and fungal infections will be recorded.
- All cases of VOD will be recorded. Baltimore Criteria will be used for this as long as these criteria are met within the first 60 days post-transplant.²⁹

Baltimore Criteria

Hiperbilirubinemia >2 mg/dl + 2 of the following:
<ul style="list-style-type: none">• Painful hepatomegaly
<ul style="list-style-type: none">• Ascites
<ul style="list-style-type: none">• Weight gain ($>5\%$ baseline weight)

Table 2: Dose adjustments due to intracycle thrombocytopenia.

Platelets	Lenalidomide	Platelets	Bortezomib
50,000-30,000	Continue dose unchanged. Platelet count every four days to see if dose needs to be adjusted. Resume in next cycle at one dose level lower.	50,000-30,000	Full dose
<30,000	Withhold dose. Weekly hemogram. Stop anticoagulation until platelet count is >30,000. Resume in next cycle at one dose level lower dose	10,000-30,000 with no evidence hemorrhage	Full dose Assess need for platelet transfusion based on clinical judgment
		<10,000 or evidence of hemorrhage	Withhold until platelet count is >10,000 and/or bleeding resolves. Platelet transfusion Resume in next cycle at one dose level lower
Repeatedly falls to <30,000	Withhold dose. Weekly hemogram. Stop anticoagulation until platelets	10,000-30,000 no evidence of bleeding	Full dose Assess need for platelet transfusion based on clinical judgment

	number >30,000. Resume at one dose level lower in next cycle	<10,000 or evidence of bleeding	Withhold therapy until platelets reach >10,000 and/or bleeding resolves. Platelet transfusion Resume at one dose level lower in next cycle
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Table 3. Dose adjustments due to intracycle neutropenia.

ANC	Lenalidomide	ANC	Bortezomib
<500	Withhold dose Administer G-CSF Weekly hemogram Resume dose one level lower when RAN>1,000	ANC 500-1000	Full dose
		ANC <500	Withhold dose Administer G-CSF Resume when ANC>500
Repeatedly falls to <500	Withhold dose Administer G-CSF Weekly hemogram Resume dose one level lower when RAN>1000	ANC 500-1000	Full dose
		ANC <500	Withhold dose Administer G-CSF Resume when ANC>500

Treatment of patients with sensitive neuropathy and/or neuropathic pain related to bortezomib (Velcade®):

		0	1	2	3	4
		Normal	Asymptomatic: loss of deep tendon reflexes or paresthesia with no loss of function	Altered sensitivity or paresthesia that limits function	Altered sensitivity or paresthesia that limits activities of daily living (ADL)	Disabled
0	Normal	✓	↓ 1	↓ 1	■ ↓ 2 ▲	X
1	Mild pain with no loss of function	↓ 1	↓ 1	↓ 1	■ ↓ 2 ▲	X
2	Moderate pain requiring analgesics that limits function, but does not limit activities of daily living	↓ 1	↓ 2	■ ↓ 2	■ ↓ 2 ▲	X
3	Severe pain that requires analgesics and limits activities of daily living	■ ↓ 2 ▲	■ ↓ 2 ▲	■ ↓ 2 ▲	X	X
4	Disabled	X	X	X	X	X

✓	No action
↓ 1	Reduce dose 1 level (from 1.3 to 1 mg/m ²)
↓ 2	Reduce dose 2 levels (from 1.3 to 0.7 mg/m ²)
X	Discontinue treatment with bortezomib (Velcade®)
■	Withhold bortezomib (Velcade®) treatment until toxicity has resolved to grade 1 or better
▲	Change of regimen: Administer bortezomib (Velcade®) once a week; if this change has already occurred, administer every 15 days

Table 5. Dose adjustments due to non-hematological toxicity.

Symptom	Lenalidomide	Bortezomib
Renal failure		
○ Cl creat >50 ml/min	Full dose	Full dose
○ Cl creat 30-50 ml/min	10 mg/d Can be increased to 15 mg/d if tolerated and there is no response after 2 cycles	Full dose
○ Cl creat <30 ml/min	15 mg/48h. Can be increased to 10 mg/d if tolerated	Full dose If dialysis needed, administer dose after dialysis
○ Dialysis	5 mg/d Administer dose after dialysis	Full dose Administer dose after dialysis
Neurologic		See posology table
Any non-hematological toxicity grade ≥ 3	Withhold dose. Resume at lower level once toxicity has resolved to grade 1 or baseline.	Withhold dose. Resume at lower level once toxicity has resolved to grade 1 or baseline.

7.5. Packaging and labeling

All study drugs will be administered as open-label. No blinding methods will be used in this trial.

Experimental drugs will be supplied to pharmacies packaged and labeled according to the standard requirements for clinical trials.

7.6. Supportive care

- All patients will receive bisphosphonates on a monthly basis during induction and consolidation treatments, for up to a maximum of two years.
- All patients will be given prophylaxis with low molecular weight heparin during induction treatment. During consolidation, patients will be given antithrombotic prophylaxis with ASA; patients who are allergic to ASA will continue prophylaxis with low molecular weight heparin.
- Prophylaxis against reactivation of infection by the varicella-zoster virus is required during treatment with bortezomib. Acyclovir will be administered for this purpose at a dose of 400 mg/12h while treatment lasts. Alternatively, acyclovir at 800 mg/24h, valacyclovir at 500 mg/8h or famciclovir at 500 mg/8h can be used. During treatment with IV busulfan, prophylaxis against neurological toxicity using diphenylhydantoin and/or clonazepam/lorazepam should be used, according to protocols in force at each site. The decision to administer antibiotic prophylaxis will be left up to each site.

7.7. Permitted medications

- Administration of G-CSF is permitted when considered necessary
- Transfusions of red blood cells and platelets are permitted at the investigator's judgment
- The following procedures are permitted during the trial: vertebroplasty, kyphoplasty, urgent orthopedic procedures, radiotherapy (when necessary for reasons other than disease progression).

7.8. Prohibited medications

- Any other investigational agent
- Any other antineoplastic treatment for MM different from that proposed in the study.

7.9. Compliance with treatment

All study drugs will be administered under prescription by the designated principal investigator or co-investigators. The pharmacist will keep the study drug request forms, as well as the batch numbers applied to each patient, the patient's weight and body surface area, total quantity of product dispensed in ml and mg. Any discrepancy between the calculated dose and the administered dose and the reason for the discrepancy must be recorded.

7.10. Risks associated with the experimental drugs

Investigators participating in this trial should pay special attention to the contraindications, warnings and precautions for use, as well as possible interactions with other medications specified in the summary of drug product characteristics of the investigational drugs used in this trial: bortezomib, lenalidomide, busulfan, dexamethasone and melphalan. As an example and given its importance: **administering paracetamol in the 72 hours prior to, or to coincide with, administration of busulfan can reduce how effectively the drug is metabolized.**

ADVERSE REACTIONS TO 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 security database contains data for patients with multiple myeloma or B-cell lymphocytic leukemia (B-LLC). Patients were treated with bortezomib as monotherapy, or in combination with dexamethasone.

The adverse effects listed below are classified by organs and systems and by frequency groups. Frequency is defined as: very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ 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 infeciosa, 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
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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*.
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Endocrine disorders

Uncommon:	inadequate secretion of antidiuretic hormone (ADH).
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Metabolic and nutritional disorders

Very common:	loss of appetite, dehydration.
Common:	hypokalemia, hyperglycemia, hypoglycemia, hyponatremia, hypercalcemia.

Uncommon: hyperkalemia, cachexia, hypercalcemia, hypocalcemia, hyponatremia, 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, dysgeusia, 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 ophthalmicus*. 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, hypoacusis 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.
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Skin and subcutaneous tissue disorders

Very common:	rash.
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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, ichthyosis, 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.
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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.

8. DEVELOPMENT OF THE TRIAL AND RESPONSE ASSESSMENT

8.1. Primary and secondary endpoints

The primary efficacy endpoints are:

- Progression-free survival (PFS) after both conditioning regimens.

The secondary efficacy endpoints are:

- Complete response rates after each stage of treatment (induction, autologous transplant and consolidation).
- Sequential negative minimal residual disease (MRD) tests in patients who have achieved complete response after each stage of treatment (induction, autologous transplant and consolidation).
- Overall survival.
- Safety of the combination VRD-GEM in induction and consolidation phases and in both conditioning regimens

8.2. Response assessment

The investigator will carry out basic tests (serum and urine protein studies, calcium and creatinine) that will enable him/her to assess the response to therapy according to the International Myeloma Working Group (IMWG) response criteria (Appendix 7). Serum and urine immunofixation will be used to document CR and bone marrow samples will be referred for MRD analysis.

A response assessment will be carried out on day 1 (\pm 4 days) of each new cycle of induction and consolidation treatment.

9. ADVERSE EVENTS

Safety during the trial will be monitored pursuant to regulations established in Royal Decree 223/2004 on Clinical Trials on recording, evaluating and reporting of adverse events.

The sponsor, through the principle investigator, will evaluate Serious Adverse Events (SAE) using product safety data sheet. It will report, via the CRO, those SAEs that meet the expedited reporting criteria (serious, unexpected and related to the treatments) to the health authorities, with help from the clinical monitor. The sponsor will also be responsible for notifying the competent authorities [AEMPS (Spanish Agency of Medicines and Health Products)], the reference CREC, hospital CREC, competent authorities of the autonomous communities) and the principle investigators of any reportable event which the sponsor shall do via the CRO within the timeframes established by current Spanish legislation (i.e., serious adverse and unexpected events shall be reported a maximum of 15 calendar days after the sponsor becomes aware of the event, and a maximum of seven days if the serious adverse or unexpected reaction has caused the patient's death or put the patient's life at risk).

All Adverse Events (AE) will be recorded in the CRF (non-serious related events and related and unrelated serious events) over the course of the trial (serious events will be recorded from the time the informed consent form is signed) and up to 30 days after the final study procedure. In the case of adverse events, these will continue to be recorded until the AE resolves or medical opinion considers it to be clinically stable.

The reference safety information document in which to attribute the expected or unexpected nature of serious adverse reactions, for the purposes of expediting reporting, will be the Investigator's Brochure for lenalidomide (Revlimid®) and bortezomib (Velcade®), and the summary of product characteristics for busulfan (Busilvex®).

9.1. Minimum required information

9.1.1. Adverse Events

An Adverse Event (AE) is any unintended, untoward or harmful medical event that does not necessarily have a causal relationship with the study drug(s), and which, at any dose, appears or worsens during the course of the trial. It may be a new intercurrent illness, worsening of a concomitant illness, a lesion or other concomitant deterioration in the patient's health, including analytic values (as indicated below), independent of its etiology. Any medical condition that existed prior to treatment with the study drug and that remains unchanged or improves, should not be considered or recorded as an AE. If this medical condition were to worsen, then it should be considered an AE.

Information on non-serious adverse events that the investigator considers to be associated with the study drugs will be recorded on the Adverse Event form in the CRF and will be duly monitored.

Only non-serious AEs the investigator considers to be related to the administration of the drug treatment will be recorded in the CRF.

To the extent possible, each adverse event will also be described according to:

- Its duration (start and stop dates).
- Degree of severity (grade 1, 2, 3, 4 or 5).
- Seriousness of the AE (serious or non-serious).
- Study drug(s) with which there is a suspected causal relationship
- The action(s) taken

Section 9.2 shows examples of degree of severity, relationship to the study drug and actions taken, exactly as they should be recorded in the CRFs.

9.1.2. Serious Adverse Events (SAEs)

Information about all serious adverse events (related or unrelated to the treatment) will be collected and recorded in the Serious Adverse Event form and on the corresponding page of the CRF. The SAE will be reported from the time the informed consent form is signed. In order to guarantee the patient's safety, each serious adverse event must be reported to TFS within 24 hours from the time the investigator becomes aware of the event. A serious adverse event is generally defined as an adverse (untoward) event that:

1. Causes death or threatens the life of the patient
2. Requires or prolongs hospitalization
3. Causes permanent or significant incapacity or disability
4. Causes a genetic anomaly or birth defect
5. Constitutes an important medical event

Important medical events are defined as those events that are not immediately life-threatening or the cause of death, hospitalization or disability, but can put the patient in danger, require medical or surgical intervention to prevent one of the outcomes described above, or can be clinically significant. Medical and scientific judgment should be used to decide whether an AE is considered serious. Infectious agents transmitted via the study medication will also be considered clinically significant SAEs.

Hospitalizations that occur under the following circumstances will not be considered SAEs: if they are scheduled before the patient is included in the study, if they are for treatment purposes, for social reasons, or if they occur in the context of emergency ambulatory care without requiring admittance (unless they meet the previous criteria) or are part of normal treatment or monitoring of the disease under study and not associated with a worsening of the disease.

Pregnancy, in female patients or in the female partners of male patients, although not itself a serious adverse event, should be managed expeditiously in the same way as a SAE. It should be recorded on a specific pregnancy reporting form, and be reported in an expedited manner to Janssen and Celgene, to Actiomed, and to Pierre Fabré where necessary, from the time there is awareness of the event and should be monitored until the end, even if a voluntary or spontaneous interruption occurs. The details of the birth

and the presence or absence of any defect in the fetus or any congenital anomaly should be described.

The development of second primary malignancies will be monitored as events of interest, and should be communicated as serious adverse events regardless of the patient's treatment group. Thus, any second primary malignancies, regardless of their causal relationship with the investigational drug(s) [(study or control drug(s))], that occur at any time during the study, from the time the informed consent form is signed until 30 days after receiving the last dose of the drug. Events related to a second primary malignancy should be reported using a SAE reporting form and should be considered "medically important events" even if they do not meet other seriousness criteria; these events should also be recorded on the corresponding page(s) of the CRF and on patient source documents. At the time the serious adverse event is reported, documentation regarding the diagnosis of the second primary malignancy should be provided (e.g., confirmatory histology or cytology results, x-rays, CAT scan, etc.).

If second primary malignancies occur, they will be examined and reported to the **Celgene Department of Pharmacovigilance** as serious adverse events regardless of: whether or not they meet seriousness criteria; their relationship to the study drug; and whether they have occurred in patients at any time during the study, including patients who:

- a) are currently participating in the trial
- b) have discontinued the study for any reason (including death)
- c) are in the follow-up period; identical duration of safety monitoring in both treatment arms should be guaranteed with respect to SPM so that they are truly comparable. All SPM that occur in trial participants, in both treatment arms, will be recorded for 36 months after the last dose of any of the study drugs has been administered.

9.2. Qualification of an adverse event

The grade of severity of an adverse event provides a qualitative assessment of the scope or intensity of an adverse event, determined by the investigator or reported by the patient. The grade of severity does not reflect the clinical seriousness of the event; rather it describes the degree or scope of the distress or incidence (e.g., severe nausea, mild attack). Nor does it reflect the relationship to the study medication.

Grade of severity of an adverse event

The investigator will assess the severity of AE and SAEs. The severity of adverse events (AEs) will be classified on a scale from 1 to 5 according to the latest version of the National Cancer Institute's (NCI) Common Terminology Criteria for Adverse Events (CTCAE) which can be viewed on the following NCI website: <http://ctep.cancer.gov/reporting/ctc.html>

If a specific event does not appear on the NCI CTCAE toxicity scale, the following table will be used to classify it:

Grade	Definition
1	Mild. The patient reports a sign, symptom or event which, in general, is transient, does not require special treatment and does not limit activities of daily living.
2	Moderate. Discomfort that limits daily living activities but that usually improves with basic therapeutic measures.
3	Severe. Patient incapacitated, and it is not possible to carry out activities of daily living, or significantly effects patient's clinical status and necessitates therapeutic intervention. Hospitalization may or may not be required.
4	Life-threatening. Risk of imminent death that requires hospitalization or clinical intervention.
5	Death.

Relationship of the adverse events and serious adverse events to the study treatment

The relationship between the administration of the study drug and the occurrence of an adverse event is described in one of the following two categories: suspected or not suspected by the investigator.

0= NOT SUSPECTED	A temporary relationship between the clinical event and medication under study which indicates an improbable causal relationship , or the event can be satisfactorily explained by the existence of other drugs, therapeutic interventions or underlying disorders.
1= SUSPECTED	A temporary relationship between the clinical event and the medication under study which indicates a possible causal relationship , where the existence of other drugs, therapeutic interventions or underlying disorders does not sufficiently explain the event observed.

It is only necessary to record on the CRF those non-serious AEs which the investigator believes are related to the administration of the treatment drug, as well as all SAEs whether they are related or not.

Actions to be taken in response to an adverse event

The measures to be taken in response to an adverse event are described using a numeric scale, from 0-5 covering different possible scenarios. One or more should be selected.

0 =	None
1 =	Adjustment/temporary interruption to the study treatment
2 =	Study medication permanently discontinued due to the adverse event
3 =	Administration of concomitant medication
4 =	Administration of non-pharmacological treatment
5 =	Hospitalization/prolonged hospitalization

9.3. Procedures for reporting SAEs from the investigator to the sponsor

Responsibility for reporting

Any Serious Adverse Event (SAE) that occurs from the time the informed consent form is signed, until 30 days after the last dose of study drug is administered or last study procedure is completed, should be reported. The period after interruption of the study drug can be extended if there is a strong suspicion that the drug has not yet been eliminated or if it is suspected that the SAE is related to the study drug, even though the 30 days have passed.

The investigator must report each SAE immediately and complete the SAE reporting form within 24 hours of the time she or he becomes aware of it, even if the event does not appear to be related to the treatment. New information about monitoring of a previously reported serious adverse event should also be reported within the same time frame. If warranted, notification will be sent to investigators in order that all investigators participating in studies using the same medication will be informed of the said SAE.

All SAEs should be monitored until one of the following occurs:

- The event resolves.
- The event stabilizes.
- The event returns to baseline, if a baseline value has been established.
- The event can be attributed to products other than the study medication, or to factors not related to the conduct of the study.
- It is unlikely that more information can be obtained (the trial subject or the

primary care physician refuses to provide additional information, the subject is lost to follow-up after due diligence has been demonstrated with respect to follow-up efforts).

All serious adverse events (SAEs) that have not resolved by the end of the study, or that have not resolved with the patient's withdrawal from the study will be monitored until one of the aforementioned outcomes is achieved.

Any queries about SAEs should be resolved via communication by fax, which follows the same flow of communication as for reporting SAEs.

The death of the patient in a clinical trial, whether expected or not, and whether or not this event is related to the study drug(s), is considered a serious adverse event, reportable within 24 hrs.

The investigator should keep a copy of all information related to the SAE, including correspondence with Trial Form Support (TFS) and the Ethics Committee.

Procedures for the investigator when reporting an SAE

The investigator should complete the Serious Adverse Event (SAE) Reporting Form, preferably in English, or if this is not possible, in Spanish, evaluate the relationship of the event to the study drug, and send the form by fax within 24 hours to Trial Form Support (TFS) (FAX: 91 125 05 51). The original Serious Adverse Event Form, together with the fax confirmation, should be kept with the case report forms at the study site. The monitor/CRO will collect a copy of the SAE form. Responses to queries will follow this line of communication, even if they are received by email, and should be sent by fax at: 91 125 05 51.

SAE monitoring information will be sent to the same person to whom the original Serious Adverse Event Reporting Form was sent, including the date the original report was created. New information will be sent on a new Serious Adverse Event Reporting Form (indicating that it is a follow-up report and the new date). The follow-up information should include whether the event has resolved or continues, if it was treated and how, and if the patient is continuing in the study. The reporting form as well as the fax confirmation page should be filed.

The sponsor (via TFS) will provide Janssen, Celgene and Actiomed, and where necessary, Pierre Fabré Ibérica, S.A, with a copy of all SAE reports preferably on the same day they are received, and in exceptional cases, within 24 hours of the time in

which the event becomes known, independent of the event's relationship to the study treatment and whether or not they are described in the Investigator's Brochure or in the summary of product characteristics. TFS should send the SAE stamped with the date and time they received it to Janssen, Celgene and Actiomed, and where necessary, to Pierre Fabré Ibérica, S.A.

Accidental exposure of healthy individuals to a study drug during handling is reportable to TFS within a maximum of 24 hrs.

9.4. Reporting to Health Authorities and Ethics Committees

The sponsor, through TFS, will report the following to the competent Health Authorities and Ethics Committees:

- All information relating to serious and unexpected adverse events that are related to the study drug and that are fatal or life-threatening, as soon as possible, or within a maximum period of seven days from the time the event is known. The relevant monitoring information for these cases will subsequently be reported within a period of eight days.
- Any other serious or unexpected event where a relationship to the study medication is suspected, as soon as possible but within a maximum of 15 days from the time the investigator becomes aware of the event.

To evaluate the expectedness of a SAE, the Investigator's Brochure on bortezomib (Velcade®) and lenalidomide (Revlimid®) will be used, as well as the summary of product characteristics for dexamethasone, melphalan and busulfan (Busilvex®).

It is the sponsor's responsibility to evaluate serious adverse events. This responsibility may be delegated to a contract research organization (CRO); however ultimate responsibility lies with the sponsor. The investigator, or a CRO hired for this purpose, should evaluate each SAE with respect to its expectedness. If it is an unexpected SAE, it will become a SUSAR and reported accordingly.

9.5. Pregnancy

9.5.1. Women of childbearing potential

All cases of pregnancy should be reported immediately. This includes fetal exposure via the father (the patient is male) or via the mother, and any suspected pregnancy (including positive pregnancy tests regardless of age or disease) in patients undergoing treatment with the investigational drugs from the time the informed consent form is signed and up to 30 days after receiving the last dose of study medication. If the female

patient is taking the investigational drug, the drug should be discontinued immediately and the patient must return all unused medicine to the investigator. Pregnancy, suspected pregnancy or a positive pregnancy test result should be reported immediately to the sponsor, who, through the CRO, will immediately report this to Janssen, Celgene, Actiomed, and if necessary, Pierre Fabré, using the Pregnancy Reporting Form or the SAE Reporting Form (see Appendices) or an equivalent approved form. Accidental exposure to lenalidomide or bortezomib by any pregnant woman (for example, carer or pharmacist) is also an immediately reportable event.

The patient will then be sent to an obstetrician/ gynecologist, preferably one with experience in reproductive toxicity, for subsequent evaluation and counseling.

The investigator will monitor the patient until her pregnancy reaches full-term, and will immediately report the outcome (whether normal or anomalous) to the sponsor.

If the outcome of the pregnancy is anomalous (for example, a spontaneous or therapeutic abortion occurs) the investigator should report this as an AE. If the anomalous outcome meets any of the severity criteria, it should be reported as a SAE using the SAE reporting form or other equivalent authorized form, within 24 hours from the time the investigator becomes aware of the event.

All newborn deaths which take place in the 30 days after birth, regardless of the cause, should be reported as a SAE. As well, the death of a breastfeeding baby outside of the 30 day period, and if the investigator believes the death is related to exposure to the study medication during pregnancy, should also be reported using the SAE reporting form or other equivalent authorized form. This should be done by fax or other appropriate means within 24 hours of the time the investigator becomes aware of the event.

9.5.2. Men

If the female partner of male patient undergoing treatment with the investigational drug becomes pregnant, the male patient receiving treatment must tell the investigator; as well, the pregnant partner will be told to contact her doctor immediately.

If a pregnancy in the female partner of a male patient is reported, the investigator should ask the pregnant woman if she will agree to provide information to the Celgene

Department of Pharmacovigilance, Janssen, and if necessary, to Pierre Fabré, and if she will allow her pregnancy to be monitored until it reaches full term.

The sponsor will immediately inform Celgene, Janssen and, if necessary, Pierre Fabré, through the CRO, of any information related to a pregnancy or suspected pregnancy (including a positive pregnancy test regardless of age), that occurs in the female partner of a male study participant receiving treatment with the investigational drug, or within 30 days after the last dose of study medication is administered.

The sponsor will use the Pregnancy Reporting Form or the SAE Reporting form or an equivalent approved form for this purpose.

All cases of pregnancy in female patients, and in women of childbearing potential who are the partners of male patients participating in the study, while she or he is taking the study drug or in the 30 days after the final dose of the drug is administered, are considered events that are immediately reportable to the sponsor (on its behalf to Trial Form Support), who in turn will report the events to Celgene and Janssen, and where necessary, to Pierre Fabré.

The pregnancy will be monitored until it reaches full term, whether or not a voluntary or spontaneous interruption occurs. The details of the birth, as well as the presence or absence of any defect in the fetus or congenital anomaly, will be noted.

Exposure to lenalidomide during pregnancy should be reported to the sponsor (or to Trial Form Support on its behalf), who will report this to Celgene immediately by telephone (Tel: 630 56 48 73) and subsequently (but no later than 24 hours) to Celgene by email (drugsafety-spain@celgene.com) or fax (at the local Pharmacovigilance fax number: 91 422 90 95). Any exposure to bortezomib should also be reported to Janssen S.A by fax (91 722 85 20), using the Pregnancy Reporting Form, and to Pierre Fabré where necessary. Immediate communication by phone is not required.

If the outcome of the pregnancy meets the criteria that immediately classify it as a SAE [i.e. the outcome is a natural or induced abortion (all congenital anomalies in the aborted fetus will be recorded), a stillborn baby, neonatal death or congenital anomaly (including in an aborted fetus)], the investigator will follow the SAE reporting procedures.

All neonatal deaths that occur within 30 days after birth will be reported as SAEs, regardless of their cause. As well, the death of a breastfeeding baby outside of the 30 day period should be reported to Celgene and to Janssen, and to Pierre Fabré where necessary, if the investigator believes the event is related to exposure to the study drug during the pregnancy. The reporting should take place within 24 hours of the time the investigator is aware of the event. A SAE Reporting Form will be sent to Celgene by email: drugsafety-spain@celgene.com or by fax at: 91 422 90 95, to Janssen by fax on: (91 722 85 20), and to Pierre Fabré where necessary. The form should be stamped by the CRO with the date and time received.

In order to monitor clinical data about the pregnancy, the doctor will request authorization from the pregnant woman, whether she is a study patient or the partner of a study patient, which will be documented by signing the Disclosure of Medical Information form. The form should NOT be sent to the clinical monitor/CRO to ensure the patient's identity is kept confidential. It will be filed at the study site along with the rest of the study documentation.

9.6. Handling product quality complaints with bortezomib (Velcade®)

A product quality complaint (PQC) is defined as any suspected defect in a product that related to its manufacturing, labeling or packaging. For example, there may be dissatisfaction with the identity, quality, expiration date or reliability of a product, including the integrity of the package.

Product quality complaints can have an impact on the safety and efficacy of the product and, as a result, on patient safety. Timely, accurate and complete reporting and analysis of quality complaints during clinical trials is crucial for the protection of study subjects, the investigators and the sponsor. Said reporting is mandated by the World Health Authorities.

Product quality complaints regarding bortezomib (Velcade®) should, like SAEs, be reported within 24 hours, on the corresponding Product Quality Complaint form, by fax to Janssen Cilag S.A. Quality complaints due to logistical problems (the cold chain is broken, transportation...) or with product expiration are outside the scope of this report.

Telephone and fax numbers of contact persons

The telephone and fax numbers of persons responsible for Pharmacovigilance at Actiomed are:

ACTIOMED FARMACOVIGILANCIA S.L.

C/ Coso 103

50001 Zaragoza (Spain)

Tax ID: B50896059

Tel.: (+34) 976 20 44 00

Fax: (+34) 976 20 44 02

e-mail: actiomed@actiomed.com

The date and signature of the principle investigator or that of an authorized co-investigator in his/her staff should appear on all reports.

The product quality complaint form can be signed by the pharmacist in charge of study medication at each site.

10. ETHICAL ASPECTS

10.1. Good clinical practice

The study will be conducted in accordance with the International Conference on Harmonization with respect to good clinical practice and corresponding regulatory requirements. The investigator will be thoroughly familiarized with the correct use of the study drug as described in the protocol and the Investigator's Brochure. Essential clinical documents will be maintained to demonstrate the validity of the study and the integrity of the data collected. The master files should be determined at the beginning of the study, and they should be maintained during the course of the study and stored as per corresponding regulations.

10.2. Ethical considerations

The study will be conducted pursuant to the ethical principles set out in the Declaration of Helsinki (see Appendix 9). The CREC will examine all documentation related to the study for the purpose of protecting the rights, safety and well-being of the patients. The study will only be conducted at sites that have obtained CREC approval. The investigator will deliver the protocol, the Investigator's Brochure, informed consent, marketing materials (if appropriate), written information provided to patients, updates regarding safety, yearly progress reports and any modifications to these documents.

10.3. Patient information and informed consent

Once the trial has been explained in its entirety, informed consent will be obtained in writing from the patient, or his/her legal guardian or representative, before his/her

participation in the trial becomes effective. Informed consent should be obtained and recorded pursuant to the International Conference on Harmonization in relation to good clinical practice and all corresponding regulatory requirements.

10.4. Patient confidentiality

In order to maintain patient confidentiality, patients will be identified using an assigned code in all case report forms, study drug accounting records, reports and communication regarding the study. The investigator will provide access to original medical records to inspectors and the sponsor's potential auditors or designated persons, as well as to regulatory authorities, so they can verify the data collected in the case report forms and audit the data compilation process.

Patient confidentiality will be maintained and no patient's identity will be disclosed to the extent that pertinent regulations and legislation allow.

10.5. Compliance with the protocol

The investigator will conduct the trial in accordance with the protocol provided by the sponsor, once approval or a favorable opinion has been obtained from the CREC and the corresponding regulatory authorities. The protocol should not be modified without the consent of both the investigator and the sponsor. Modifications to the protocol require approval or a favorable opinion in writing from the CREC prior to implementation, unless the modification is necessary to avoid immediate risk to the patients. The CREC can provide, if the regulatory authorities permit, a review and approval or favorable opinion as quickly as possible in order to make minor changes to trials in progress that have been approved or received a favorable opinion from the CREC. The sponsor will present any modifications made to the protocol to the regulatory authorities in accordance with current legislation.

When immediate deviation from the protocol is required to avoid immediate risks to patients, the investigator will contact the sponsor if circumstances permit, to discuss the measures they plan to adopt. Any deviation from the protocol should be recorded in detail on the CRF and in the original documentation.

10.6. Premature end to the trial

This trial may be interrupted prematurely if, in the opinion of the sponsor or the regulatory authorities, there is sufficient reasonable cause to do so. The investigator will receive notification in writing in which the party calling for an end to the trial documents the reasons for it to be discontinued.

Circumstances that justify ending the study include, but are not limited to:

- Unforeseen, considerable or unacceptable risks to the patients have been identified.
- It is not possible to enroll a sufficient number of patients.
- Lack of compliance with the protocol requirements.
- Plans to modify, suspend or discontinue development of the study drug.
- Administrative issues that the sponsor is unable resolve with the health authorities.

10.7. Liability and insurance

The sponsor 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 are in strict compliance with the legal requirements established in Royal Decree 223/2004 regarding Clinical Trials.

11. PRACTICAL CONSIDERATIONS

11.1. Obligations of all participants in the trial

11.1.1. Investigator

The responsibilities of the investigator are specified in article 37 of Royal Decree 223/2004.

The investigator must be in agreement with this protocol and possess thorough knowledge of the properties of the products used in the clinical trial.

The investigator should give the patient information sheet to the patient and assist him or her in understanding the explanations provided therein. It is important that the investigator informs the patient that his or her participation in the study is completely voluntary, and that this will not affect the patient/physician relationship. The investigator should also guarantee the patient that all persons involved in the study will maintain the confidentiality of all patient information.

The principal investigator or one of his collaborators will be responsible for collecting, recording and reporting the data correctly, and will guarantee the immediate reporting of serious adverse or unexpected events within 24 hours to Trial Form Support (by fax at: 91- 125 05 51).

The investigator is responsible for preparing and maintaining accurate, complete medical histories, which are designed to document all observations and other

relevant study data relating to each participant in the trial. All information recorded in the CRFs for this study must be consistent with each patient's original documentation.

It is the responsibility of the investigator to regularly report to the Clinical Research Ethics Committee on the progress of the study; the investigator will be jointly responsible along with the sponsor for producing the clinical trial report.

11.1.2. The monitor

The trial monitor will be responsible for directly monitoring the conduct of the trial, following Good Clinical Practice guidelines. The responsibilities of the monitor are specified in article 36 of Royal Decree 223/2004.

All study data recorded in the original documents will be transcribed onto the CRFs. The study data will be entered into a validated and secure data processing system and back-up copies will be stored. Any changes to the study data will be recorded. During the course of the trial, the monitor will visit the trial sites to verify compliance with the protocol, to compare the CRFs with the patients' individual medical histories, evaluate drug accountability and ensure that the study is being conducted in accordance with the pertinent regulatory requirements. The CRFs will be checked against the original documentation. Medical histories will be verified in such a way that guarantees patient confidentiality. Any instances of data omission or of data that cannot be interpreted will be dealt with by the investigator.

11.1.3. The sponsor

The obligations of the sponsor are specified in article 35 of Royal Decree 223/2004.

The sponsor of the clinical trial is the physical or legal person who has an interest in the trial being conducted. The sponsor signs authorization requests addressed to the CREC and/or the Spanish Medicine Agency (AEM) and takes responsibility for the trial, including its conduct, initiation, and end. The sponsor is also in charge of ensuring compliance with the pertinent legal regulations.

The PETHEMA Foundation assumes the obligations of the sponsor set out in Article 35 of Royal Decree 223/2004, having all of the means and collaborators necessary to wholly guarantee fulfillment of said obligations.

11.2. Auditing

The regulatory authorities, the CREC and the sponsor or designated representative can request access to all original documents, case report forms and any other study

documentation for the purpose of auditing or inspecting the site. The investigator must guarantee direct access to these documents and cooperate at all times in the execution of these activities.

Care will be taken during these procedures to ensure the protection of personal information, in accordance with data protection laws.

11.3. Drug accountability

Drug accountability at the study site is the responsibility of the investigator. The investigator must guarantee that the study drug is used solely in accordance with this protocol. Where permitted, the investigator may choose to transfer some responsibilities related to drug accountability to a pharmacist or other qualified person. The drug accountability records that show the date of delivery of the drug to the study site, the site's inventory, drug dispensation to patients and the return or elimination of the study drug will be stored at the study site. These records will properly document the fact that the dosages specified in the protocol are what are administered to the patients. The accountability records will include dates, quantities, batch and series numbers, expiration dates (if appropriate) and patient numbers.

All drugs that have been returned by patients, are unused or expired will be returned to the person designated by the sponsor, or destroyed at the study site's Pharmacy Service if so authorized. Any of these procedures should be properly documented.

11.4. Custody of records

The investigator will maintain all study records in accordance with Good Clinical Practice as set out in the International Conference on Harmonization and corresponding regulatory requirements.

11.5. Publication of the trial results and use of information

The results of this clinical trial will be presented at scientific conferences and published in scientific journals. The final results of the trial and the manuscript for publication will be sent to Janssen S.A, Celgene and Pierre Fabre Ibérica, S.A., a minimum of 60 days prior to the manuscript being submitted for publication. Janssen S.A, Celgene and Pierre Fabre Ibérica will also be informed of any posters, abstracts or other written or presentation materials related to the trial a minimum of five days before these are submitted.

11.5.1. Basic trial regulations

The principal investigator and/or the HOSPITAL undertake not to use or transfer to third parties, nor distribute and/or publish the results of this trial without prior written consent from the PETHEMA Foundation, sole sponsor of this trial. The following conditions should also be observed:

- a) The results of this trial shall not be published until the conclusion of the trial, or before if both parties agree.
- b) The sponsor shall not cite the names of the investigators without their authorization, except in references to already published work.
- c) The sponsor shall permit the publication of data obtained from this study in scientific journals of recognized prestige, and permit the data to be shared at seminars and conferences within the medical field, as long as the conditions set out in paragraph a) of this section are observed, and the sponsor is allowed to review the final draft of the article within a minimum period of 30 days.

11.5.2. PETHEMA Group conditions for publication

The following guidelines should be observed in any publications derived from PETHEMA studies:

- a) The names of participating sites will be stated and of any persons who participate in the study design, monitoring, analysis of the results and writing the trial report will be listed as authors.
- b) Those in charge of the protocol will also be responsible for reporting the results at PETHEMA meetings and scientific conferences, as well as for writing the articles based on the protocol. The persons in charge of the protocol will also have assistance in the writing of these articles if they deem it necessary.
- c) The final draft of the text may be submitted for review and approval by another member of PETHEMA with demonstrated expertise, so that his/her suggestions and changes can help to improve the quality of the work. This person can appear as co-author at the discretion of the persons in charge of the protocol. If the reviewer is not listed as a co-author, he/she should be mentioned in the acknowledgements section.
- d) Inclusion of the data manager as a co-author is at the discretion of the persons in charge of the protocol. If the data manager is not listed as co-author, s/he should be included in the acknowledgements section.
- e) The statistician (if there is one) can be listed as co-author or appear in the acknowledgements section depending on his/her degree of participation, and at the discretion of the protocol managers.

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- f) The statistician and the data manager will not be included in the calculation to determine the maximum number of authors according to the number of patients included per site.
- g) A maximum number of authors will be determined per each participating site to appear in the article heading. This selection, based on the number of included patients, will be made according to the criteria for cases contributed to the study (as long as evaluation and follow-up can be carried out until the final update), and in accordance with the following regulations:
- Protocols in which less than 200 patients have been recruited: each site will have the right to one author per every 5% of patients included out of the total recruited for the study. There will be a limit of 15 authors for the publication. This restriction will be applied to publications for conferences.
 - Protocols in which 200 or more patients are included: Each site that has included 10 cases will have the right to one author. For every fifteen additional cases, sites will have the right to a second author. In any case, there will be a limit of 25 authors for the publication. This restriction will also be applied to publications for conferences.
- h) If a limit to the number of authors has been specified by the conference organizers or journal, the number will be reduced by the last to meet the authorship criteria. The judgment of the protocol managers will prevail in the event of discrepancies.
- i) The appendix shall list all institutions as well as all persons that have participated in the protocol.

Before submitting the manuscript for publication, a copy will be sent to each author to make any changes they feel are appropriate. If no response is given in the timeframe set by the protocol manager, it will be assumed that the author agrees with the content of the manuscript. Given that there may be a considerable number of authors and that, on occasion, the suggestions may be redundant, contradictory or without substance, the writers of the publication will be responsible for the definitive version.

12. STATISTICAL ANALYSIS

12.1. Estimating the sample size

The sample size has been calculated to achieve a minimum statistical power of 80% with a predefined alpha error of 0.05 for comparison of progression-free survival. A sample of 460 patients is required to achieve the primary objective.

Comparison of BUMEL versus MEL200.

The objective is prolongation of progression-free survival by one year with BUMEL. Assuming a 20% loss of patients during the induction period due to progression, toxicity or death, 368 (184 per arm) of the initial 460 patients will be randomized. This sample will allow us to obtain a statistical power of 80%.

In addition, the sample size will have the same statistical power to compare overall survival (secondary objective #3) and a confidence interval of 5% in estimating the proportion of patients who have achieved complete response with negative MRD (secondary objectives #1 and #2)

12.2. Population for analysis

The efficacy analysis will include all patients that are included in the induction, and in any of the study arms (intention-to-treat analysis). Analysis of the safety of treatment administration will only include those patients who receive at least one dose of treatment.

12.3. Procedures for handling missing, unused and spurious data

All available data on safety and efficacy will be included in the lists and data tables. Values will not be allocated to unavailable data.

Patients treated with the study drugs who do not receive safety related follow-up will not be included in the safety analysis. This is because inclusion of these patients would only lower the percentages of patients with adverse events or laboratory toxicities.

Any spurious or erroneous data will be examined in accordance with standardized data control procedures.

12.4. Statistical methods

Summary tables will be created which will show the number of observations, the mean, standard deviation, the median, the minimum and maximum values for continuous variables, as well as the number and percentage by category for categorical data. Time-to-event data will be summarized using 25th, 50th (median) and 75th percentiles,

in addition to the 95% two-sided confidence intervals and the percentage of excluded observations. The summary categories will be provided for patients treated in each of the treatment arms, induction as well as maintenance. Formal, two-tailed statistical hypothesis tests related to the superiority of one of the induction or maintenance treatment arms over the other two will be carried out using a significance level of 0.05.

The first efficacy analysis will be the response rate once induction, transplantation and consolidation are complete, comparing both treatment groups when applicable. The confidence intervals (limit of 95%) of the response rates will be provided. Relative risk will be calculated in all patients included in the study.

The second efficacy analysis will be the complete response rates once induction transplantation and consolidation are complete, comparing both treatment groups when applicable.

The third efficacy analysis will be PFS, duration of response and OS, overall as well as by treatment groups, keeping in mind different points (diagnostic, transplantation and consolidation).

The fourth efficacy analysis will determine minimal residual disease overall, and by groups when applicable, once induction, transplantation and consolidation are complete.

12.4.1. Efficacy analysis

The disease response categories that will be used for the efficacy analysis are: strict CR, CR, Very Good Partial Response VGPR, PR, stable disease and disease progression. CR determined by flow cytometry will be added.

Survival

- Overall survival: Duration in months from the date induction treatment is initiated to the date of death or last visit. Patients who are lost to follow-up will be censored on the date of the last visit. This analysis will use the Kaplan-Meier method to determine overall survival. Time-to-death data will be analyzed to look for differences between the different treatment groups using a logrank test, with the conclusion that some of the proposed treatment regimens produce a longer overall survival than the other two if the two-sided logrank test is statistically significant at a significance level of $\alpha = 0.05$. Stratification factors will be used in the analysis.
- Duration of response: The duration of response in months will be calculated from the first date there is evidence of a response, to the first date there is evidence

of disease (or relapse if the patient has achieved CR). The disease response will be evaluated using a Kaplan-Meier analysis, adjusted using stratification factors, similar to the analysis of overall survival and progression-free survival. Duration of response will be calculated in the (best) overall response of a patient.

- Progression-free survival (PFS): Progression-free survival will be calculated as the length of time between the initial treatment to the first time disease progression is documented, or death. If disease progression is based on an increase in monoclonal paraprotein levels, the criteria proposed to assess the response would require that an increase in the monoclonal paraprotein level be documented on two consecutive occasions. Therefore, if the second measurement of paraprotein levels confirms disease progression, the PFS will be calculated from the time of randomization to the first time a level of paraprotein is measured that demonstrates disease progression. If the second measurement does not confirm progression, the patient will continue the study treatment until progression is documented. PFS will be censored at the last date at which it was known the patient's disease had not progressed for 1) patients whose disease has not progressed at the time of analysis and 2) patients who have withdrawn from the treatment phase of the study before progression was documented (including those who died for reasons not related to MM). For patients who received another treatment for MM before disease progression or unacceptable toxicity was determined, PFS will be censored at the day before initiation of the new treatment.

Additional efficacy analyses

Descriptive analyses

Descriptive efficacy analyses will consist of evaluating the changes produced from the time of the screening visit, in the following values of clinical importance in MM:

- Serum and/or urine M-protein.
- Percentage of plasma cells in bone marrow aspiration using morphology or flow cytometry
- Analysis of light chains
- Flow cytometry analysis (percentage of plasma cells in S phase and residual disease)
- Cytogenetic analysis using in situ hybridization
- Measuring plasmacytomas of soft tissue and bone using radiological tests.

Co-variate adjustments

To ensure that the conclusions of this study are not overly influenced by the factors present in this study, with very different rates between different treatment groups, additional exploratory analyses will be carried out of time to progression, duration of response, rates of survival and response by selecting a combination of possible prognostic variables (obtained before or during the screening visit), as Cox regression model covariates (for time to progression, duration of response and survival), as well as methods of categorical data modeling such as logistical regression (for response rate). Factors will include:

- Cytogenetic alterations
- Presence of extramedullary disease
- B2-microglobulin
- C-reactive protein
- Type/stage of disease at diagnosis
- Age at diagnosis
- Flow cytometry analysis (percentage of plasma cells in S phase and residual disease).

These analyses will be performed including all of the covariates in the model in order to determine the relative influence of each in the respective efficacy endpoints. The adjusted conclusions of these analyses will help to determine whether there is reason to believe that the relative efficacy of the study treatment can vary as a function of the characteristics that patients present.

12.4.2. Baseline comparisons

The two conditioning regimens will be evaluated in order to establish a descriptive comparison of demographic characteristics and of the screening visit. The data to be evaluated will include at least: age, sex and the components of the evaluation of type and stage of the disease.

Safety analyses

Safety evaluations will depend on the incidence, severity and type of adverse events, as well as clinically significant changes in findings from the patient's physical exams, vital signs and clinical laboratory results. Analyses will be done to determine whether statistically significant differences exist between the two conditioning and maintenance treatment groups, and rates of discontinuation of treatment due to adverse events or toxicity in accordance with clinical laboratory evaluations and rates of hematological toxicity.

All adverse events considered by the investigator to be related to the study medication, and serious adverse events that occur after the first dose of the study drug is administered (bortezomib, lenalidomide or busulfan) and during the 30 days after the last dose of the study drug is administered, will be included in the data lists organized by patient. As well, a table detailing the adverse events in order of maximum grade of severity will also be provided. Deaths, serious adverse events and adverse events that imply discontinuation of the study will be classified in the same way in another table.

12.5. Procedures for reporting deviations from the original statistical plan

All deviations from the original statistical analysis plan will be included in the final clinical trial report.

12.6. Preliminary analysis

A preliminary analysis will be carried out when the first 230 patients have completed the induction treatment, and 200 have completed autologous transplantation.

13. REFERENCES

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APPENDIX 1: LIST OF SITES, CRECs AND PRINCIPLE INVESTIGATORS

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<p>Hospital de Cabueñes Los Prados, 395 Gijón, Asturias - 33394</p>	<p>Dr. María Esther González García Regional CREC of Asturias</p>
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<p>Hospital Son Llátzer Ctra. Manacor, Km.4 Palma de Mallorca - 07198</p>	<p>Dr. Joan Bargay Leonart Regional CREC of the Balearic Islands</p>
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<p>Hospital Universitario de Canarias Ofra, s/n San Cristóbal de La Laguna - 38320</p>	<p>Dr. Miguel Teodoro Hernández García CREC, Hospital Universitario de Canarias</p>
<p>Hospital General de Ciudad Real Tomelloso s/n Ciudad Real - 13005</p>	<p>Dr. Belén Hernández Ruiz CREC, Hospital General de Ciudad Real</p>
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<p>Clínica Universidad de Navarra</p> <p>Av. Pio XII, 36 Pamplona/Iruña - 31008</p>	<p>Dr. Felipe Prósper Cardoso</p> <p>Regional CREC of Navarra</p>
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Hospital Universitario La Fe C/ Bulevar Sur s/n Valencia - 46009	Dr. Javier de la Rubia Comos CREC, Hospital Universitario La Fe
Hospital del Vinalopó C/ Tónico Sansano Mora, 14 Elche - 03293	Dr. Pedro Luis Fernández García CREC, Hospital del Vinalopó y Torrevieja
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* Information relating to the principle investigators at certain hospitals may be pending confirmation.

Appendix 2: REFERENCE CREC

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Appendix 3: SCHEDULE OF VISITS INDUCTION

EVALUATION	TREATMENT PERIOD			PRE-TRANSPLANTATION
	Screening visit	VRD	VRD	A minimum of 4 WKS after COMPLETION of the last cycle
	Days -21 a -1	DAY 1 OF EACH NEW CYCLE	DAY 11 of 4-week cycles	
Informed consent	X			
Medical history	X			
Physical exam	X	X		X
Height and weight	X			
ECOG Performance Status	X	X		X
Electrocardiogram	X			
Hematology	X	X	X	X
Biochemistry	X	X		X
Serology	X			
Pregnancy test ¹	X	X		X
Proteinogram and Igs with immunofixation	X	X ²		X ²
Proteinogram in urine and immunofixation	X	X ²		X ²
Serum free light chains ³	X	X ³		X ³
B2 microglobulin and PCR	X			X
Bone marrow aspiration ⁴	X	X ⁴		X ⁴
Skeletal survey	X			
CAT/MRI/PET ⁵	X			X ⁵
Administration of bisphosphonates		X		
Disease response		X		X
Concomitant medication	X			
Adverse events [from signing of informed consent form]	X ⁶		X	

¹Pregnancy test. See Appendix 10.

²Only serum and urine protein electrophoresis should be carried out in each cycle. If no M-component is detected, serum and urine immunofixation should be performed to confirm complete response.

³Will be carried out at the initiation and at the end of induction and when confirming complete response.

⁴Will be carried out at the initiation and at the end of induction and when confirming complete response.

⁵Additional radiologic tests will be performed if extramedullary plasmacytomas are suspected. Patients with plasmacytomas at diagnosis should be re-evaluated after the third cycle of treatment using the same diagnostic test (CAT, MRI, PET/CT). If after the third cycle the result is negative, it will not be necessary to repeat the test at the end of induction.

⁶Adverse events will be recorded from the time informed consent is signed.

CONSOLIDATION

EVALUATION	CONSOLIDATION			Post-consolidation
	Post-transplantation/ Consolidation ¹	VRD	VRD	END-OF-STUDY VISIT
	+3 months/day 1 of cycle 1	DAY 1 OF CYCLE 2	Day 11 of both consolidation cycles	
Medical history				
Physical exam	X	X		X
Height and weight	X			
ECOG Performance Status	X	X		X
Hematology	X	X	X	X
Biochemistry	X	X		X
Pregnancy test ²	X	X		X
Proteinogram and Igs with immunofixation	X ³	X ³		X ³
Urine proteinogram and immunofixation	X ³	X ³		X ³
Serum free light chains ⁴	X	X ⁴		X ⁴
B2 microglobulin and PCR	X			X
Bone marrow aspiration	X			X
Skeletal survey ⁵	X ⁵			X ⁵
CAT/MRI/PET ⁶	X ⁶			X ⁶
Administration of bisphosphonates	X	X		
Disease response	X	X		X
Concomitant medication	X			
Adverse events	X		X	

¹ It will not be necessary to repeat laboratory analyses on day 1 of cycle 1, as long as these tests have been performed for post-transplant evaluation a maximum of 15 days prior.

² In women of childbearing potential.

³ Immunofixation will be performed to confirm complete response.

⁴ These will be carried out during re-evaluation at 3 months after transplantation and subsequently when confirming complete response.

⁵ Will not be carried out unless there are clinical data to suggest an increase in, or the appearance of, new bone lesions.

⁶ In the case of extramedullary plasmacytomas, the same technique will be used to evaluate the response as was used at diagnosis. If during evaluation after the third cycle or at the end of induction the plasmacytoma has disappeared, it will not be necessary to repeat the diagnostic imaging test.

Appendix 4: ECOG AND KARNOFSKY PERFORMANCE STATUS SCALES

Karnofsky	Description	ECOG
100	Normal, no complaints; no evidence of disease	0
90	Able to carry on normal activity; minor signs or symptoms of disease.	0
80	Normal activity with effort; some signs or symptoms of disease	1
70	Cares for self; unable to carry on normal activity or to do active work.	1
60	Requires occasional assistance, but is able to care for most of his/her personal needs	2
50	Requires considerable assistance and frequent medical care.	2
40	Disabled; requires special care and assistance.	3
30	Severely disabled; admission to hospital is indicated although death not imminent.	3
20	Very sick; hospital admission necessary; active supportive treatment necessary.	4
10	Moribund; fatal processes progressing rapidly.	4
0	Dead.	5

Source: Mor V, Laliberte L, Morris JN, Wiemann M. The Karnofsky Performance Status Scale: an examination of its reliability and validity in a research setting. *Cancer* 1984; 53: 2002-2007.

Appendix 5: FORMULAS USED IN THIS PROTOCOL

- **Body surface area:**

Body surface area should be calculated using a standard nomogram. The following is an example:

$$\text{BSA (m}^2\text{)} = \sqrt{(\text{Height (cm)} \times \text{Weight (kg)} / 3600)^{1/2}}$$

Calculation of volume of VELCADE (ml):

$$\frac{\text{Dose (mg/m}^2\text{)} \times \text{Patient BSA(m}^2\text{)}}{2.5 \text{ mg/mL}}$$

= Total volume of VELCADE to be administered

2.5 mg/mL= Reconstituted concentration for subcutaneous administration

- **Corrected calcium:**

Corrected calcium will be calculated using the following formula, and only in patients whose albumin is outside the normal range at the screening visit:

$$\text{Corrected Ca} = \text{Total Ca} - \text{Albumin} + 4$$

- **Ideal weight**

$$\text{Men} = 50 + 0.9 \times (\text{size in cm} - 152.5)$$

$$\text{Women} = 46 + 0.91 \times (\text{size in cm} - 152.5)$$

- **Adjusted ideal weight**

$$\text{Adjusted ideal weight} = \text{ideal weight} + 0.4 \times (\text{weight} - \text{ideal weight})$$

• **Quantity of busulfan :**

$$\text{Ideal or adjusted ideal weight (Kg)} \times \text{Busulfan dose (mg/Kg)}$$

$$\text{-----} = \text{A ml of Busulfan to be diluted}$$
$$6 \text{ (mg/ml)}$$

• **Quantity of diluent:**

$$(\text{A ml of Busilvex®}) \times (10) = \text{B ml of diluent}$$

Appendix 6: MULTIPLE MYELOMA DIAGNOSTIC CRITERIA

SYMPTOMATIC MM
<ul style="list-style-type: none">• M-protein in serum and/or urine• Presence of clonal plasma cells* in bone marrow or of plasmacytomas• Symptoms derived from organ or tissue impairment (including bone impairment) due to Myeloma [ROTI (Myeloma-Related Organ or Tissue Impairment due to the plasma cell proliferative process)].

* If flow cytometry tests are done, >90% of plasma cells will have a pathological phenotype.

** Some patients may not have symptoms, but will have deterioration in organ function due to myeloma-related impairment.

Symptoms due to Myeloma-Related O rgan or T issue Impairment (ROTI)
<ul style="list-style-type: none">• *Hypercalcemia: Corrected calcium > 11.5 mg/dl• *Renal failure: Creatinine > 2 mg/dl• *Anemia: Hemoglobin 2g/dl below the lower limit of normal, or hemoglobin <10 g/dl• *Bone lesions: lytic lesions or osteoporosis with compression fractures• Other: Hyperviscosity, amyloidosis, recurrent infections (>2 episodes in 1 year)

International Myeloma Working Group. Criteria for the classification of monoclonal gammopathies, multiple myeloma and related disorders: a report of the International Myeloma Working Group. Br J Haematol 2003; 121: 749-757.

APPENDIX 7: IMWG RESPONSE CRITERIA

International uniform response criteria for multiple myeloma. Leukemia 2006; 20:1467-73 6

Response category	Response criteria
Complete Response (CR)	Requires each of the following: <ul style="list-style-type: none"> Negative immunofixation in serum and urine, and Disappearance of any soft tissue plasmacytomas, and ≤ 5% plasma cells in bone marrow
Stringent Complete Response (sCR)²	CR as defined above, plus: <ul style="list-style-type: none"> Normal serum free light chain ratio, and Absence of plasma cells with pathological phenotype in bone marrow; necessary to analyze a minimum of 3000 cells using multi-parametric flow cytometry (using four colors)
Very Good Partial Response (VGPR)¹	<ul style="list-style-type: none"> Serum and urine M-protein measurable by immunofixation, but not electrophoresis, or, Reduction in serum M-protein ≥ 90% plus urine M-protein <100 mg in 24 hr-urine
Partial Response (PR)	<ul style="list-style-type: none"> Reduction in serum M-protein ≥50% and in 24hr-urine > 90% or <200 mg in 24-hr urine If serum and urine M-protein is unmeasurable, a decrease ≥50% in the difference between levels of involved and uninvolved serum free light chain levels is required If serum and urine M-protein, and serum free light chains are unmeasurable, a decrease of ≥50% in plasma cell infiltration in bone marrow (as long as the baseline infiltration is ≥30%) In addition to the above criteria, if present at diagnosis, a ≥50% reduction in the size of soft tissue plasmacytomas is required
Stable Disease (SD)	<ul style="list-style-type: none"> Does not meet the criteria of CR, sCR, VGPR or PR or disease progression
Progressive Disease (PD)³	A ≥25% increase in the lowest level obtained for one or more of the following parameters: <ul style="list-style-type: none"> Serum M-protein (the absolute increase ≥ 0.5 g/dl required) and/or Urine M-protein (the absolute increase ≥ 200 mg in 24 hr-urine required) and/or For patients with unmeasurable levels of serum and urine M-protein: a >25% increase in the difference of involved and uninvolved serum light chain levels (absolute increase >10 mg/L required) A ≥25% increase in plasma cell infiltration in bone marrow (a ≥ 10% absolute increase required) Appearance of new bone lesions or soft tissue plasmacytomas or increase in the size of existing lesions or plasmacytomas. Appearance of hypercalcemia (serum corrected calcium >11.5 mg/dl) attributable exclusively to myeloma

All response categories (CR, sCR, VGPR, PR) require two consecutive assessments made at any time before any new treatment is initiated; CR, PR and SD require evidence that no new bone lesions have appeared if radiographic studies were carried out. Radiological studies are not necessary to establish the above response criteria. Confirmation by repeating bone marrow studies is not needed.

¹To code CR and VGPR in accordance with current criteria, in patients in which the disease is measurable only by serum free light chains: CR in these patients requires a normal ratio of serum free light chains of between 0.26-1.65, in addition to the above-mentioned

criteria. VGPR is defined as a >90% decrease between the levels of involved and involved serum free light chains.

² Stringent CR has been updated and reflects the need for multiparameter flow cytometry as the technique of choice over immunofluorescence or immunohistochemistry.

³ Progression measured by levels of serum or urine M-protein requires confirmation

Criteria to initiate a new line of treatment:

- Clinical or biological relapse as per the IMWG criteria stated earlier in the section 'progressive disease', or
- Significant increase in the paraprotein or monoclonal component in the absence of data on clinical/biological relapse, if the monoclonal protein doubles over two consecutive measurements taken at least two months apart; or if there is an increase in the absolute values of monoclonal protein of 1g/dl, or 500 mg of proteinuria in 24hr urine, or 20 mg/dl of involved serum free light chain (plus an abnormal ratio of serum free light chains), in two consecutive measurements taken at least two months apart.

APPENDIX 8: CENTRALIZATION OF SAMPLES

Three reference laboratories have been established (Hospital Clínico Universitario de Salamanca, Hospital 12 de Octubre de Madrid and Hospital La Fe de Valencia). The number of hospitals could increase depending on how enrolment develops.

Distribution. Initially, the hospitals in the Castilla-Leon Autonomous Region will send their samples to Hospital Clínico de Salamanca. Hospitals in the Madrid Autonomous Region will send theirs to the Hematology Unit at Hospital 12 de Octubre, while hospitals in the Autonomous Region of Valencia will send their samples to Hospital La Fe. All other participating sites can select which of the three reference hospitals they prefer to send to, but it must always be to the same hospital.

Samples. 10 ml of serum (serum bank), 8 ml of bone marrow in EDTA (CMF and DNA) and 5 ml of bone marrow in lithium-heparin (cytogenetic). Samples will be shipped at room temperature, less than 24 hours after collection.

Identification of samples. Patient number, Protocol code, time of disease (diagnosis, post-induction, 3 months from transplant, end-of-study visit and at any time to confirm complete response), shipping hospital and contact physician with telephone number.

Time of shipping. Various sets of samples are required: at the time of diagnosis, at the start and end of induction, at 3 months from transplant, at the end of the two consolidation cycles, and at any time to confirm complete response.

Transportation and contacts

Containers. Containers appropriate for the trial will be sent by PETHEMA to the list of participating hospitals. Any errors in distribution or a lack of supply can be resolved by requesting containers from the PETHEMA secretary in Madrid, Rocío Aguirre, by email: pethema@pethema.es, or by leaving a voicemail at this number: 915040259. The following mobile number: 629853789 may be used for urgent requests only.

Business hours. Samples will be accepted during arrival times from Monday to Thursday, and until 10:00 am on Friday (this means that **samples must be taken between Monday and Thursday, never on Friday, Saturday or Sunday**). Please arrange for your samples to arrive before 10:00 am (at each destination site, check with the courier). You must call to arrange delivery outside of these hours.

Transportation: The PETHEMA Foundation will cover the cost of transportation, using the company **MRW**. To request transport, the operator will need a subscriber number and the Protocol code for this trial.

Agencia MRW 2615 (Castilla 47. 28039- Madrid)

Telephone number: (valid throughout Spain) 91 534 19 24

PETHEMA Foundation (Registration no. 15018)

Protocol code: GEM2012MENOS65

Destinations:

Salamanca: Unidad de Inmunopatología, Servicio de Hematología. Hospital Clínico Universitario. Pº San Vicente 58-182. 37007-Salamanca. Tel: 923291384 and 923291375. Fax: 923294624. E-mail: sanmigiz@guqu.usal.es

Madrid: Unidad de Biología Molecular, Dr. Montalbán / Dr. Lahuerta / Dr. Martínez López Servicio de Hematología. Hospital 12 de Octubre. Avda. de Córdoba s/n. 28041-Madrid Tel: 91 390 80 00-Ext. 1027/1771; Fax: 91 390 85 10. E-mail: mmontalban.hdoc@salud.madrid.org

Valencia: Servicio de Hematología. Hospital La Fe. Lourdes Cordon/Dr. Amparo Sempere. Avda Campanar 21. 46009 Valencia. Tel: 963 862 700 E-mail: lou.cordon@gmail.com/semper_amp@gva.es.

APPENDIX 9: DECLARATION OF HELSINKI

Ethical principles for medical investigations involving human subjects

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964
and amended by the:

- 29th WMA General Assembly, Tokyo, Japan, October 1975
- 35th WMA General Assembly, Venice, Italy, October 1983
- 41st WMA General Assembly, Hong Kong, September 1989
- 48th WMA General Assembly, Somerset West, South Africa, October 1996
- 52nd WMA General Assembly, Edinburgh, Scotland, October 2000
- 53rd WMA General Assembly, Washington, DC, USA, October 2002
(Note of Clarification on paragraph 29 added)
- 55th WMA General Assembly, Tokyo, Japan, October 2004
(Note of Clarification on Paragraph 30 added)
- 59th WMA General Assembly, Seoul, Korea, October 2008

A. INTRODUCTION

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.

The Declaration is intended to be read as a whole and each of its constituent paragraphs should not be applied without consideration of all other relevant paragraphs.

2. Although the Declaration is addressed primarily to physicians, the WMA encourages other participants in medical research involving human subjects to adopt these principles

3. It is the duty of the physician to promote and safeguard the health of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfillment of this duty.

4. The Declaration of Geneva of the WMA binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act in the patient's best interest when providing medical care."

5. Medical progress is based on research that ultimately must include studies involving human subjects. Populations that are underrepresented in medical research should be provided appropriate access to participation in research.

6. In medical research involving human subjects, the well-being of the individual research subject must take precedence over all other interests.

7. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best current interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

8. In medical practice and in medical research, most interventions involve risks and burdens.

9. Medical research is subject to ethical standards that promote respect for all human subjects and protect their health and rights. Some research populations are particularly vulnerable and need special protection. These include those who cannot give or refuse consent for themselves and those who may be vulnerable to coercion or undue influence.

10. Physicians should consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

B. PRINCIPLES FOR ALL MEDICAL RESEARCH

11. It is the duty of physicians who participate in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects.

12. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

13. Appropriate caution must be exercised in the conduct of medical research that may harm the environment.

14. The design and performance of each research study involving human subjects must be clearly described in a research protocol. The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest, incentives for subjects and provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study. The protocol should describe arrangements for post-study access by study subjects to interventions identified as beneficial in the study or access to other appropriate care or benefits.

15. The research protocol must be submitted for consideration, comment, guidance and approval to a research ethics committee before the study begins. This committee must be independent of the researcher, the sponsor and any other undue influence. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration. The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No change to the protocol may be made without consideration and approval by the committee.

16. Medical research involving human subjects must be conducted only by individuals with the appropriate scientific training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health-care professional. The responsibility for the protection of research subjects must always rest with the physician or other health care professional and never the research subjects, even though they have given consent.

17. Medical research involving a disadvantaged or vulnerable population or community is only justified if the research is responsive to the health needs and priorities of this population or community and if there is a reasonable likelihood that this population or community stands to benefit from the results of the research.

18. Every medical research study involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and communities involved in the research in comparison with foreseeable benefits to them and to other individuals or communities affected by the condition under investigation.

19. Every clinical trial must be registered in a publicly accessible database before recruitment of the first subject.

20. Physicians may not participate in a research study involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians must immediately stop a study when the risks are found to outweigh the potential benefits or when there is conclusive proof of positive and beneficial results.

21. Medical research involving human subjects may only be conducted if the importance of the objective outweighs the inherent risks and burdens to the research subjects.

22. Participation by competent individuals as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no competent individual may be enrolled in a research study unless he or she freely agrees.

23. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information and to minimize the impact of the study on their physical, mental and social integrity.

24. In medical research involving competent human subjects, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information. After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

25. For medical research using identifiable human material or data, physicians must normally seek consent for the collection, analysis, storage and/or reuse. There may be situations where consent would be impossible or impractical to obtain for such research or would pose a threat to the validity of the research. In such situations the research may be done only after consideration and approval of a research ethics committee.

26. When seeking informed consent for participation in a research study the physician should be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent should be sought by an appropriately qualified individual who is completely independent of this relationship.

27. For a potential research subject who is incompetent, the physician must seek informed consent from the legally authorized representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the population represented by the potential subject, the research cannot instead be performed with competent persons, and the research entails only minimal risk and minimal burden.

28. When a potential research subject who is deemed incompetent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorized representative. The potential subject's dissent should be respected.

29. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research population. In such circumstances the physician should seek informed consent from the legally authorized representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research should be obtained as soon as possible from the subject or a legally authorized representative.

30. Authors, editors and publishers all have ethical obligations with regard to the publication of the results of research. Authors have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. They should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results should be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest should be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

31. The physician may combine medical research with medical care only to the extent that the research is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.

32. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best current proven intervention, except in the following circumstances:

- The use of placebo, or no treatment, is acceptable in studies where no current proven intervention exists; or
- Where for compelling and scientifically sound methodological reasons the use of placebo is necessary to determine the efficacy or safety of an intervention and the patients who receive placebo or no treatment will not be subject to any risk of serious or irreversible harm. Extreme care must be taken to avoid abuse of this option.

33. At the conclusion of the study, patients entered into the study are entitled to be informed about the outcome of the study and to share any benefits that result from it, for example, access to interventions identified as beneficial in the study or to other appropriate care or benefits.

34. The physician must fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never interfere with the patient-physician relationship.

35. In the treatment of a patient, where proven interventions do not exist or have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorized representative, may use an unproven intervention if in the physician's judgment it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, this intervention should be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information should be recorded and, where appropriate, made publicly available.

Source:

World Medical Association, 2008. World Medical Association. Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects.

<http://www.wma.net/en/30publications/10policies/b3/index.html> (Accessed May 30, 2013.)

APPENDIX 10: PREGNANCY PREVENTION PROGRAM (PPP) - LENALIDOMIDE

Pregnancy Risk Minimization Program with Lenalidomide in Clinical Trials Conducted by Celgene

Appendix 10 applies to all patients that receive treatment with Lenalidomide. This Appendix includes the following documentation related to the Pregnancy Risk Minimization Program:

The Risks of Fetal Exposure to Lenalidomide, Pregnancy Test Guidelines and Acceptable Contraceptive Methods;

- 1) The Risks of Fetal Exposure to Lenalidomide, Pregnancy Test Guidelines and Acceptable Contraceptive Methods
- 2) Education and Counseling on Lenalidomide
- 3) Lenalidomide Fact Sheet

1. The Risks of Fetal Exposure to Lenalidomide, Acceptable Contraceptive Methods and the Pregnancy Test Guidelines provide the following information:

- Risks associated with fetal exposure to lenalidomide
- Definition of a woman of childbearing potential
- Pregnancy test requirements for patients of childbearing potential who receive lenalidomide.
- Acceptable contraceptive methods for women of childbearing potential as well as male patients who receive lenalidomide during the study
- Counseling requirements on contraceptive precautions and the possible risks of fetal exposure to lenalidomide for all patients in the study who receive lenalidomide

2. The Education and Counseling about Lenalidomide Document should be completed and signed by an appropriately trained healthcare professional or by the Investigator at the participating site, before dispensing lenalidomide for treatment. A copy of this document will be kept with the patient's medical records.

3. The Lenalidomide Fact Sheet will be distributed to each patient who receives treatment with lenalidomide. The patient should read this document before beginning treatment.

1. The Risks of Fetal Exposure to Lenalidomide, Pregnancy Test Guidelines and Acceptable Contraceptive Methods

Risks Associated with Pregnancy

Lenalidomide is structurally related to thalidomide. Thalidomide is a known teratogenic substance that causes severe, life-threatening birth defects. An embryo-fetal development study conducted with primates has shown that lenalidomide produces deformities in the offspring of females who received the drug during pregnancy. The teratogenic effects of lenalidomide cannot be ruled out in humans, and therefore a plan should be put in place to avoid pregnancy.

Criteria for females of childbearing potential (FCBP)

This protocol defines a woman of childbearing potential as a sexually mature female who: 1) has not undergone a hysterectomy or bilateral salpingo-oophorectomy or who 2) is not naturally post-

menopausal (amenorrhea resulting from oncological treatment does not rule out reproductive potential) for at least 24 consecutive months (i.e., having menstruated at any time during the previous 24 months).

Counseling

Lenalidomide is contraindicated in women of childbearing potential unless they meet the following criteria (that is, all women of childbearing potential should be advised about the following risks and requirements before taking part in a study with lenalidomide):

- The patient understands the potential teratogenic risks to the unborn baby.
- The patient understands the need to use effective contraceptive methods continuously during the four weeks prior to beginning the study, throughout the study, during dose interruptions and for three months after treatment has finished.
- The patient is able to comply with effective contraceptive measures.
- The patient has been informed of and understands the possible consequences of pregnancy and the need to report any risk of pregnancy immediately to the study physician.
- The patient understands the need to begin treatment as soon as the drug is dispensed after receiving a negative pregnancy test result.
- The patient understands and accepts the need to undergo frequent pregnancy tests as established in this protocol.
- The patient confirms in writing that she understands the dangers and necessary precautions associated with taking lenalidomide.
- The investigator must guarantee that women of childbearing potential:
- Comply with the conditions for minimizing the risk of pregnancy, including confirmation that the patient has an acceptable level of understanding
- The patient confirms in writing that she is aware of the above-mentioned requirements.

Lenalidomide is contraindicated in women who ARE NOT of childbearing potential, unless they meet the following criteria (in other words, all women who ARE NOT of childbearing potential must be advised of the following risks and conditions before beginning treatment with lenalidomide):

- The patient confirms in writing that she understands the risks and precautions associated with the use of lenalidomide.

Traces of lenalidomide have been found in semen. Male patients who take lenalidomide must meet the following conditions (that is, all men must be advised of the following risks and requirements before beginning treatment with lenalidomide):

The patient understands of the potential teratogenic risk if they have sexual contact with a woman of childbearing potential.

The patient understands the need to use condoms, even if he has had a vasectomy, when engaging in sexual activity with a woman of childbearing potential.

Contraception

Females of childbearing potential (FCBP) who enroll in this trial must commit to using two reliable methods of contraception simultaneously, or practice total abstinence from heterosexual sexual contact, during the following periods in this study: 1) for at least 28 days before initiation of treatment with the drug 2) while participating in the study 3) during dose interruptions and 4) for at least three months after treatment has stopped.

The two acceptable contraceptive methods must include one highly effective and one other effective method (barrier-type). If necessary, FCBPs should be sent to a healthcare professional trained in contraceptive counseling. Following are examples of highly-effective and additional effective methods of contraception:

- Highly-effective methods:
 - Intrauterine device (IUD)
 - Hormones (birth control pills, injections, implants)
 - Tubal ligation
 - Vasectomized partner

- Additional effective methods:
 - Male condoms
 - Diaphragms
 - Cervical cap

Due to the increased risk of venous thromboembolism in patients with multiple myeloma taking lenalidomide and dexamethasone, concomitant use of combined oral contraception is not recommended. If a patient is currently using combined oral contraception, she should substitute one of these for one of the effective birth control methods mentioned above. The risk of venous thromboembolism lasts for four to six weeks after treatment has stopped when using combined oral contraception. The effectiveness of steroidal contraceptives can be reduced when receiving concomitant treatment with dexamethasone.

Implants and levonorgestrel-releasing intrauterine systems are associated with an increased risk of infection at the time of insertion and with irregular vaginal bleeding. The use of an antibiotic prophylactic, especially in patients with neutropenia, should be considered in these cases.

Pregnancy tests

All women of childbearing potential, including those who commit to total abstinence, must undergo medically-supervised pregnancy tests with a minimum sensitivity of 25 mIU/mL, as detailed below.

Before beginning treatment with the study drug

Female patients:

All WCPB must have two negative pregnancy tests (with a sensitivity of at least 25 mIU/mL) before taking lenalidomide. The first pregnancy test should be performed 10-14 days prior to initiation of treatment with lenalidomide, and the second test in the 24 hours prior to initiation of

treatment. The patient cannot receive treatment with the study drug until the investigator has verified that the results of these pregnancy tests are negative.

Male patients:

While participating in the study, male patients must practice total abstinence, or agree to use condoms when engaging in sexual activity with women of childbearing potential, during dose interruptions, and for at least three months after treatment with the study drug has stopped, even if they have undergone a successful vasectomy.

During participation in the study and for 28 days following the end of treatment with the study drug

Female patients:

- All WCPB with regular menstrual cycles or who have no menstrual cycles agree to undergo pregnancy tests during the first 28 days of their participation in the study, every 28 days thereafter throughout the study, after cessation of the study treatment, and at 28 days after treatment has finished. If the patient's menstrual cycles are irregular, pregnancy tests should be carried out once a week during the first 28 days, then every 14 days over the course of study, at the time treatment with the study drug has stopped, and at 14 and 28 days thereafter.
- The investigator should confirm at each visit that the WCBP is continuing to use two reliable methods of contraception.
- Counseling as to the precautions surrounding pregnancy and potential risks of fetal exposure to the study drug should be given at least every 28 days.
- If a patient becomes pregnant or receives a positive pregnancy test result, treatment with lenalidomide must be stopped immediately.
- Pregnancy tests and counseling should be given if a patient misses a menstrual period, or if her pregnancy test or menstrual bleeding is abnormal. The study drug should be stopped during this evaluation.
- Women should agree not to breastfeed while participating in the study, and for at least 28 days after treatment with the study drug has stopped.

Male patients:

- Counseling on the need for condom use while engaging in sexual activity with women of childbearing potential and the possible risks of fetal exposure should be take place a minimum of every 28 days.
- Any pregnancy or positive pregnancy test result that occurs in the partner of a patient participating in the study, must be reported to the investigator immediately.

Additional precautions

- Patients should be aware that can never give the study drug to anyone else, and that they will have to return any unused capsules to the study physician once treatment has finished.
- Patients must not donate blood during treatment with lenalidomide and for at least 28 days after treatment has stopped.
- Male patients must not donate blood, semen or sperm during treatment with lenalidomide and for at least 28 days after treatment has stopped.
- During each cycle, only the quantity of lenalidomide needed for that treatment cycle will be dispensed.

2. Guidelines on Counseling and Education about Lenalidomide

To be completed before dispensing each dose of lenalidomide.

Protocol code: _____

Patient number: (Printed): _____

Date of Birth: ____/____/____ (day/month/year)

(Mark the corresponding box to indicate the risk category)

Female

If the patient is female, mark:

WCBP (woman of childbearing potential): a sexually mature female who: 1) has not undergone a hysterectomy (surgical removal of the uterus) or bilateral salpingo-oophorectomy (surgical removal of both ovaries) or who 2) has not been naturally post-menopausal (amenorrhea resulting from oncological treatment does not rule out reproductive potential) for at least 24 consecutive months (i.e. a woman who has menstruated at some point during the previous 24 months).

NOT a WCBP

Male

Do not dispense lenalidomide if:

- The patient is pregnant.
- Pregnancy tests were not carried out on the WCPB.
- The patient states that she has not used TWO reliable forms of contraception (except in cases where the patient is practicing total abstinence), for at least 28 days before treatment with lenalidomide, during dose interruptions and for three months after treatment has stopped.

WCPB:

1. I have verified that the requested pregnancy tests are negative.
2. I have counseled the WCPB on the following:
 - Potential harm to the fetus: If lenalidomide is taken during pregnancy, it can cause congenital birth defects or the death of the fetus. Women are advised to avoid becoming pregnant while taking lenalidomide. The potential teratogenic risks of lenalidomide in humans cannot be ruled out. WCPB must commit to not become pregnant while taking lenalidomide.
 - The use of TWO reliable contraceptive methods simultaneously, or total abstinence from heterosexual sexual activity [for at least three months before, during dose interruptions, and for 28 days after treatment with lenalidomide has stopped].
 - Compliance with contraceptive advice, even if the patient is amenorrheic.
 - Use of one highly effective contraceptive method and one additional contraceptive method SIMULTANEOUSLY. Following are examples of highly effective and additional effective methods of contraception:
 - Highly effective:
 - Intrauterine device (IUD)
 - Hormonal (birth control pills, injections, implants)
 - Tubal ligation
 - Vasectomized partner
 - Other effective methods:
 - Male condoms
 - Diaphragms
 - Cervical cap
 - Pregnancy tests before and during treatment, including if the patient agrees not to engage in heterosexual sexual activity. Two pregnancy tests will be performed before the study drug is administered: the first in the 10-14 day period before initiating treatment with lenalidomide, and the second within 24 hours prior to the start of treatment.
 - Frequency of pregnancy tests:
 - Weekly during the first 28 days of the study, and one test every 28 days while the patient is participating in the study if menstrual cycles are regular, or every 14 days if menstrual cycles are irregular.
 - If the patient misses a menstrual period or experiences abnormal menstrual bleeding.
 - When the patient leaves the study, and at 28 days after treatment with the study

drug has finished if menstrual cycles are regular. If cycles are irregular, pregnancy tests should be carried out at the end of the study, and at 14 and 28 days after the study treatment has finished.

- In the case of pregnancy, lenalidomide should be discontinued immediately and the study physician informed as soon as possible.
- NEVER share lenalidomide with anyone.
- Do not donate blood while taking lenalidomide, and for 28 days after treatment has stopped.
- Agree not to breastfeed while participating in the study and for at least 28 days after treatment has stopped.
- Do not break, chew or open lenalidomide capsules.
- Return any unused capsules to the investigator.

3. Provide the patient with a copy of the Lenalidomide Fact Sheet

WOMEN NOT OF CHILDBEARING POTENTIAL (WHO HAVE BEEN NATURALLY MENOPAUSAL FOR AT LEAST 24 CONSECUTIVE MONTHS, HAD A HYSTERCTOMY OR BILATERAL SALPINGO-OOPHORECTOMY):

1. I have counseled the female patient NOT of childbearing potential about the following:
 - The potential harm to the fetus (See section 2 on WCPB)
 - NEVER to share lenalidomide with anyone
 - Not to donate blood while taking lenalidomide, or for 28 days after treatment has stopped.
 - No to break, chew or open the lenalidomide capsules
 - To return any unused capsules to the investigator
2. I have provided the patient with the Lenalidomide Fact Sheet

MEN:

1. I have counseled the male patient about the following:
 - Potential damage to the fetus (see section 2 on WCPB).

Committing to total abstinence, or to using condoms while engaging in sexual relationships with women of childbearing potential (even if the patient has had a vasectomy), while taking lenalidomide, during dose interruptions, and for at least 28 days after treatment with lenalidomide has stopped.

- Male patients should inform their study physician if their partner becomes pregnant, and female partners of male patients taking lenalidomide should be advised to call their doctor immediately if they become pregnant.

-
- NEVER to share lenalidomide with anyone.
 - Not to donate blood, semen, or sperm while taking lenalidomide, or for 28 days after the drug treatment has finished.
 - Not to break, chew or open the lenalidomide capsules.
 - To return any unused capsules to the investigator.

2. I have provided the patient with the Lenalidomide Fact Sheet.

Name of the investigator/trained healthcare professional (please print): _____
(circle the one that applies)

Signature of the investigator/trained healthcare professional: _____
(circle the one that applies)

Date: ____/____/____

****Keep a copy of the Counseling and Education Guidelines with the patient's medical records****

3. Lenalidomide Fact Sheet

FOR PATIENTS ENROLED IN CLINICAL TRIALS

Please read the Lenalidomide Fact Sheet before taking Lenalidomide and each time you receive a new supply, as it may include new information. This Fact Sheet does not replace the informed consent to participate in the clinical study, nor conversations with the study physician or your family doctor about your medical condition and treatment.

What is the most important information I should know about lenalidomide?

1. Lenalidomide can cause congenital defects (birth defects in babies) or the death of the fetus. Lenalidomide is a drug similar to thalidomide. Thalidomide is known to cause life-threatening congenital defects in the fetus. Lenalidomide has not been tested in pregnant females, but it can also cause congenital defects. The preliminary findings of a study carried out in monkeys appear to indicate that lenalidomide causes congenital defects in the offspring of female monkeys that received the drug during pregnancy.

If you are a woman who can become pregnant:

- **Do not take lenalidomide if you are pregnant or are planning to become pregnant.**
- **You should practice total abstinence or use two reliable and effective methods of contraception simultaneously:**
 - During the 28 days before beginning lenalidomide
 - While taking lenalidomide
 - During dose interruption
 - And for three months after lenalidomide treatment has stopped.
- **You must undergo pregnancy tests on the following dates:**
 - During the 10-14 days before receiving the first dose of lenalidomide, and again in the 24 hours prior to receiving the first dose
 - Weekly during the first 28 days
 - Every 28 days after the first month, or every 14 days if you have irregular

menstrual periods.

- If you miss a menstrual period or experience abnormal bleeding
- Twenty-eight days after the last dose of lenalidomide is administered (or at 14 and 28 days after the last dose if your menstrual periods are irregular)
- **Stop taking lenalidomide if you become pregnant while receiving treatment with this drug**
- **If at any time during the study you believe you may be pregnant, you must discontinue treatment with lenalidomide immediately and inform the study physician. The physician will report any cases of pregnancy to the sponsor and to Celgene.**
- **Agree not to breastfeed while taking lenalidomide.**
- **The study physician can tell you where you can obtain contraceptive counseling.**

If you are a woman not of childbearing potential:

In order to guarantee the fetus is not exposed to lenalidomide, the study physician will confirm that you are not of childbearing potential.

If you are a man:

Traces of lenalidomide have been detected in human semen. The risk to the fetus of a woman of childbearing capacity whose partner is taking lenalidomide is currently unknown.

- Male patients (including those who have undergone a vasectomy) should practice total abstinence or should use a condom during sexual activity with women who are pregnant or who can become pregnant:
 - While taking lenalidomide
 - During dose interruptions
- For three months after treatment with lenalidomide has stopped
- **Male patients cannot donate sperm while taking lenalidomide, or for 28 days after treatment with lenalidomide has stopped.**
- **If at any time during the study you think your partner may be pregnant, you should inform the study physician immediately. The study physician will report all cases of pregnancy to the sponsor and to Celgene. Call your doctor immediately if your partner becomes pregnant.**

1. Restrictions with sharing medication and donating blood while taking lenalidomide:

- **Do not share lenalidomide with others. Keep the drug out of reach of children and never share it with another person.**
- **Do not donate blood** while taking lenalidomide, or for 28 days after treatment with the

drug has stopped.

- **Do not break, chew or open lenalidomide capsules.**
- Each supply of lenalidomide will only be enough to last 28 days.
- Return any unused capsules to the study physician.
- More information will be provided on the informed consent form. You can ask your doctor for any additional information you may need.

APPENDIX 11: SERIOUS ADVERSE EVENT REPORTING FORM

PLEASE FAX TO +34 91 125 05 51 WITHIN 24 HOURS

Protocol code: GEM2012MENOS65		Patient Number: _____		Site: _____			
Investigator Information			Patient Information				
Date of Report: _____ Day Month Year		Report type: <input type="checkbox"/> Initial <input type="checkbox"/> Follow-up <input type="checkbox"/> Final	Date of birth: ____/____/____ Day Month Year		Race: <input type="checkbox"/> Caucasian <input type="checkbox"/> Black <input type="checkbox"/> Asian <input type="checkbox"/> Other		
Date of Initial Report: ____/____/____ Day Month Year			Gender: <input type="checkbox"/> Male <input type="checkbox"/> Female	Medication (Randomization) No:			
Date the investigator's staff became aware: ____/____/____ Day Month Year			Principal Investigator's Name:				
Principal Investigator's Address:		Tel () _____		Height: ____ cm / or ____ in			
		Fax () _____		Weight: ____ Kg / or ____ in			
		Email: _____					
Study Drug Information (_____)							
Indication for use:		Indication diagnosis date: ____/____/____ Day Month Year		Regimen:			
Study drug name 1: BORTEZOMIB		First dose: ____/____/____ Day Month Year	Last dose prior to event: ____/____/____ Day Month Year	and Cycle ____, Day ____ (Oncology only)	Dose (in mg):	Route:	Lot:
Study drug name 2: LENALIDOMIDE		First dose: ____/____/____ Day Month Year	Last dose prior to event: ____/____/____ Day Month Year	and Cycle ____, Day ____ (Oncology only)	Dose (in mg):	Route:	Lot:
Study drug name 3: DEXAMETHASONE		First dose: ____/____/____ Day Month Year	Last dose prior to event: ____/____/____ Day Month Year	and Cycle ____, Day ____ (Oncology only)	Dose (in mg):	Route:	Lot:
Study drug name 4: MELPHALAN		First dose: ____/____/____ Day Month Year	Last dose prior to event: ____/____/____ Day Month Year	and Cycle ____, Day ____ (Oncology only)	Dose (in mg):	Route:	Lot:
Study drug name 5: BUSULFAN		First dose: ____/____/____ Day Month Year	Last dose prior to event: ____/____/____ Day Month Year	and Cycle ____, Day ____ (Oncology only)	Dose (in mg):	Route:	Lot:
Please attach copies of the following completed CRF pages (if relevant)							
<ul style="list-style-type: none"> • Medical History • History of Therapy and Events Related to Disease Under Study • Concomitant Medication 							
Relevant Laboratory and Diagnostic Tests (Please provide relevant data below and attach copies of reports, if available)							
Test	Date			Value/Units	Results		
	Day	Month	Year				
	____	____	____				
	____	____	____				
	____	____	____				
	____	____	____				

Study contact completing form		Principal Investigator	
Initials	Date	Initials	Date

Serious Adverse Event Form

Page 1 of 4

Protocol code: GEM2012MENOS65		Patient Number: _____		Site: _____	
Action taken with study drug 1: BORTEZOMIB (check all that apply)					
<input type="checkbox"/> Dose continued unchanged					
<input type="checkbox"/> Dose/regimen reduced		Date decreased: ____/____/____ Day Month Year		New Dose: _____	
<input type="checkbox"/> Dose/regimen increased		Date increased: ____/____/____ Day Month Year		New Dose: _____	
<input type="checkbox"/> Dose/regimen temporarily withheld					
		Date withheld: ____/____/____ Day Month Year			
<input type="checkbox"/> Discontinued permanently due to this Adverse Event				Date of discontinuation: ____/____/____ Day Month Year	
<input type="checkbox"/> Patient no longer receiving study drug (explain the reason in narrative)				Date of last dose: ____/____/____ Day Month Year	
<input type="checkbox"/> Not applicable					
Relationship:		Assessment – The SAE is probably associated with:			
<input type="checkbox"/> Non related <input type="checkbox"/> Unlikely <input type="checkbox"/> Possible <input type="checkbox"/> Probable <input type="checkbox"/> Definite		<input type="checkbox"/> Another drug/combination therapy drug. Please specify _____ <input type="checkbox"/> Another condition (e.g. condition under study, intercurrent illness). Please specify _____ <input type="checkbox"/> Protocol design or procedures (but not to study drug). Please specify _____			
Action taken with study drug 2: LENALIDOMIDE (check all that apply)					
<input type="checkbox"/> Dose continued unchanged					
<input type="checkbox"/> Dose/regimen reduced		Date decreased: ____/____/____ Day Month Year		New Dose: _____	
<input type="checkbox"/> Dose/regimen increased		Date increased: ____/____/____ Day Month Year		New Dose: _____	
<input type="checkbox"/> Dose/regimen temporarily withheld					
		Date withheld: ____/____/____ Day Month Year			
<input type="checkbox"/> Discontinued permanently due to this Adverse Event				Date of discontinuation: ____/____/____ Day Month Year	
<input type="checkbox"/> Patient no longer receiving study drug (explain the reason in narrative)				Date of last dose: ____/____/____ Day Month Year	
<input type="checkbox"/> Not applicable					
Relationship:		Assessment – The SAE is probably associated with:			
<input type="checkbox"/> Non related <input type="checkbox"/> Unlikely <input type="checkbox"/> Possible <input type="checkbox"/> Probable <input type="checkbox"/> Definite		<input type="checkbox"/> Another drug/combination therapy drug. Please specify _____ <input type="checkbox"/> Another condition (e.g. condition under study, intercurrent illness). Please specify _____ <input type="checkbox"/> Protocol design or procedures (but not to study drug). Please specify _____			
Action taken with study drug 3: DEXAMETHASONE (check all that apply)					
<input type="checkbox"/> Dose continued unchanged					
<input type="checkbox"/> Dose/regimen reduced		Date decreased: ____/____/____ Day Month Year		New Dose: _____	
<input type="checkbox"/> Dose/regimen increased		Date increased: ____/____/____ Day Month Year		New Dose: _____	
<input type="checkbox"/> Dose/regimen temporarily held					
		Date held: ____/____/____ Day Month Year			
<input type="checkbox"/> Discontinued permanently due to this Adverse Event				Date of discontinuation: ____/____/____ Day Month Year	
<input type="checkbox"/> Patient no longer receive study drug (explain the reason in narrative)				Date of last dose: ____/____/____ Day Month Year	
<input type="checkbox"/> Not applicable					
Relationship:		Assessment – The SAE is probably associated with:			
<input type="checkbox"/> Non related <input type="checkbox"/> Unlikely <input type="checkbox"/> Possible <input type="checkbox"/> Probable <input type="checkbox"/> Definite		<input type="checkbox"/> Another drug/combination therapy drug. Please specify _____ <input type="checkbox"/> Another condition (e.g. condition under study, intercurrent illness). Please specify _____ <input type="checkbox"/> Protocol design or procedures (but not to study drug). Please specify _____			

Study contact completing form _____ Principal Investigator _____
Initials Date Initials Date
Serious Adverse Event Form Page 2 of 4

PLEASE FAX TO +34 91 125 05 51 WITHIN 24 HOURS

Protocol code: GEM2012MENOS65	Patient Number: _____	Site: _____
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Action taken with study drug 4: MELPHALAN (check all that apply)

<input type="checkbox"/> Dose continued unchanged		
<input type="checkbox"/> Dose/regimen reduced	Date decreased: ____/____/____ Day Month Year	New Dose: _____
<input type="checkbox"/> Dose/regimen increased	Date increased: ____/____/____ Day Month Year	New Dose: _____
<input type="checkbox"/> Dose/regimen temporarily withheld	Date withheld: ____/____/____ Day Month Year	
<input type="checkbox"/> Discontinued permanently due to this Adverse Event		Date of discontinuation: ____/____/____ Day Month Year
<input type="checkbox"/> Patient no longer receiving study drug (explain the reason in narrative)		Date of last dose: ____/____/____ Day Month Year
<input type="checkbox"/> Not applicable		

Relationship:	Assessment – The SAE is probably associated with:
<input type="checkbox"/> Non related <input type="checkbox"/> Unlikely <input type="checkbox"/> Possible <input type="checkbox"/> Probable <input type="checkbox"/> Definite	<input type="checkbox"/> Another drug/combination therapy drug. Please specify _____ <input type="checkbox"/> Another condition (e.g. condition under study, intercurrent illness). Please specify _____ <input type="checkbox"/> Protocol design or procedures (but not to study drug). Please specify _____

Action taken with study drug 5: BUSULFAN (check all that apply)

<input type="checkbox"/> Dose continued unchanged		
<input type="checkbox"/> Dose/regimen reduced	Date decreased: ____/____/____ Day Month Year	New Dose: _____
<input type="checkbox"/> Dose/regimen increased	Date increased: ____/____/____ Day Month Year	New Dose: _____
<input type="checkbox"/> Dose/regimen temporarily withheld	Date held: ____/____/____ Day Month Year	
<input type="checkbox"/> Discontinued permanently due to this Adverse Event		Date of discontinuation: ____/____/____ Day Month Year
<input type="checkbox"/> Patient no longer receiving study drug (explain the reason in narrative)		Date of last dose: ____/____/____ Day Month Year
<input type="checkbox"/> Not applicable		

Relationship:	Assessment – The SAE is probably associated with:
<input type="checkbox"/> Non related <input type="checkbox"/> Unlikely <input type="checkbox"/> Possible <input type="checkbox"/> Probable <input type="checkbox"/> Definite	<input type="checkbox"/> Another drug/combination therapy drug. Please specify _____ <input type="checkbox"/> Another condition (e.g. condition under study, intercurrent illness). Please specify _____ <input type="checkbox"/> Protocol design or procedures (but not to study drug). Please specify _____

Adverse Event Information

ADVERSE EVENT (Diagnostic term): _____	AE onset date: ____/____/____ Day Month Year	AE became serious: ____/____/____ Day Month Year
Seriousness Criteria (check all that apply): <input type="checkbox"/> Death <input type="checkbox"/> Life threatening <input type="checkbox"/> Hospitalization/prolonged hospitalization <input type="checkbox"/> Persistent or significant disability/incapacity <input type="checkbox"/> Congenital anomaly/birth defect <input type="checkbox"/> Important medical event	Maximum severity <input type="checkbox"/> Grade 1/Mild <input type="checkbox"/> Grade 2/Moderate <input type="checkbox"/> Grade 3/Severe <input type="checkbox"/> Grade 4/Life-threatening	Did AE (s) resolve after stopping study drug? <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NA
		Did AE (s) reappear after reintroducing study drug? <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NA

Serious Adverse Event Form

Page 3 of 4

Description of Adverse Event(s)
<p>Please provide a brief narrative description of the SAE (presenting symptoms, clinical course, treatment etc.) <u>Attach additional pages</u> <u>e.g. hospital discharge summary if available.</u></p>

Status of SAE at time of this report		
<table style="width: 100%; border: none;"> <tr> <td style="width: 50%; vertical-align: top;"> <input type="checkbox"/> Fatal <input type="checkbox"/> Completely resolved: <u> / / </u> DD MM YYYY </td> <td style="width: 50%; vertical-align: top;"> <input type="checkbox"/> Not completely resolved <input type="checkbox"/> ongoing and unchanged <input type="checkbox"/> ongoing with increased severity <input type="checkbox"/> ongoing with decreased severity </td> </tr> </table>	<input type="checkbox"/> Fatal <input type="checkbox"/> Completely resolved: <u> / / </u> DD MM YYYY	<input type="checkbox"/> Not completely resolved <input type="checkbox"/> ongoing and unchanged <input type="checkbox"/> ongoing with increased severity <input type="checkbox"/> ongoing with decreased severity
<input type="checkbox"/> Fatal <input type="checkbox"/> Completely resolved: <u> / / </u> DD MM YYYY	<input type="checkbox"/> Not completely resolved <input type="checkbox"/> ongoing and unchanged <input type="checkbox"/> ongoing with increased severity <input type="checkbox"/> ongoing with decreased severity	

Death Information	
<p>Date of death: <u> / / </u> DD MM YYYY</p> <p>Autopsy performed?</p> <p><input type="checkbox"/> Yes <input type="checkbox"/> No</p> <p>Autopsy report attached?</p> <p><input type="checkbox"/> Yes <input type="checkbox"/> No</p> <p>Death certificate attached?</p> <p><input type="checkbox"/> Yes <input type="checkbox"/> No</p>	<p>Cause of death per (specify):</p> <p><input type="checkbox"/> Autopsy Report _____</p> <p><input type="checkbox"/> Death Certificate _____</p> <p><input type="checkbox"/> Other _____</p>

 Name of study contact completing form (printed)
 Date:

 Signature of study contact completing form

 Principal investigator printed name
 Date

 Principal investigator signature

APPENDIX 12: PREGNANCY REPORTING FORM FOR SUBJECTS INCLUDED IN THE TRIAL

Study Code: GEM2012MENOS65

Study Site:

Subject No:

Subject Initials:

Country:

Investigational Product(s)

Therapy start date:
(yy-mmm-dd)

Therapy stop date:
(yy-mmm-dd)

Date of last menstruation:
(yy-mmm-dd)

Date of expected delivery:
(yy-mmm-dd)

Investigator's signature: _____

Date:
(yy-mmm-dd) _____

Keep the original of this form in the Investigator's file and a copy in the CRF. Please fax to TFS Trial Form Support Drug Safety, Fax No +34 91 125 05 51

Infant Follow up

Pregnancy result (mark with X)

Live birth	Elective abortion	Spontaneous abortion	Stillbirth	Unknown

Please fill in a SAE form in case of any spontaneous abortion, stillbirth, birth defect/congenital anomaly, death, or other serious infant condition.

Infant delivery date (yy-mmm-dd)

Condition of infant
Normal Abnormal*

* If abnormal, please comment

Comments:

Investigator's signature: _____

Date:
(yy-mmm-dd)

Printed name

Appendix 13: PRODUCT QUALITY COMPLAINT FORM

Form no.:206.01_version 1.0

PLEASE SEND TO FAX No: 91 722 85 20 WITHIN 24 HORAS	PRODUCT QUALITY COMPLAINT FORM (PQC)
---	--------------------------------------

Information about how the Product Quality Complaint was received (Complete fields in white)

Protocol code:	GEM2012MENOS65	Name of investigator:	
Date PQC received by Janssen:	To be completed by Janssen	Initial notification:	<input type="checkbox"/>
PQC received by at Janssen:		Follow-up notification:	<input type="checkbox"/>
Country in which PQC occurred:		SPAIN	

Source of information about the PQC

Name and profession of the person who discovered the PQC:		Phone number:	
<input type="checkbox"/> Doctor <input type="checkbox"/> Nurse <input type="checkbox"/> Pharmacist <input type="checkbox"/> Other _____			
City		Investigator Fax	
Country	SPAIN	Date on which the investigation team became aware of the PQC:	

Product Quality Complaint Information (PQC)

Does the PQC affect more than one kit/box of medication?	<input type="checkbox"/> Yes <input type="checkbox"/> No	If yes, list the numbers of kits/boxes:	
Was the defective drug/product administered to the patient?	<input type="checkbox"/> Yes <input type="checkbox"/> No	Kit 1:	
Patient's date of birth (if drug was administered)		Kit 2:	
Was a SAE associated with the PQC?		Kit 3:	
<input type="checkbox"/> Yes <input type="checkbox"/> No	If yes, indicate which SAE occurred (if applicable)		
SAE No. (if Janssen, BRM No.):		To be completed by Janssen	
Drug(s)	Pharmaceutical form, dose	Lot No.	Expiration date:
1.	1.	1.	1.
2.	2.	2.	2.
Date drug treatment initiated:	End date	Time initiated (hh:mm)	Time stopped
1.	1.		
2.	2.		

Form, No.:206.01_version 1.0

PLEASE FAX TO: 91 722 85 20 WITHIN 24 HOURS	PRODUCT QUALITY COMPLAINT FORM (PQC)
Description of the Product Quality Complaint	
Additional comments:	

Definition:

Product Quality Complaint (PQC): is any written, oral or electronic communication which claims there is a fault with the identity, quality, quantity, durability, reliability, security, effectiveness or function of a pharmaceutical product after its distribution.

A complaint is any indication of a fault with the product that leads to it not meeting the expectations of the user due to quality. A complaint may include an adverse reaction, or harm associated with use of the pharmaceutical product. It may include the design, packaging, packaging material, appearance or marketing of a product.

WARNING: Any incidents that are the result of logistical problems should be excluded from the above definition and should not be reported (e.g. "COLD CHAIN IS BROKEN").