11 February 2015
EMA/130972/2015
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Revlimid

International non-proprietary name: lenalidomide

Procedure No. EMEA/H/C/000717/X/0073/G

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

AMT	antimyeloma therapy
ASCT	autologous stem cell transplant
CR	Complete response
EBMT	European Group for Blood and Marrow Transplantation
ECOG	Eastern Cooperative Oncology Group
FCBP	Female of child bearing potential
IA	Interim analysis
IHD	ischaemic heart disease
IR	incidence rate
MDS	myelodysplastic syndromes
MAH	marketing authorisation holder
MI	myocardial infarction
MM	multiple myeloma
NA	not applicable
NDMM	newly diagnosed multiple myeloma
NMSC	non melanoma skin cancer
OLEP	open-label extension phase
ORR	overall response rate
OS	overall survival
PD	progressive disease
PFS	progression free survival
PFS2	progression free survival on next line therapy
PY	person-years
RD	lenalidomide plus standard-dose dexamethasone
Rd	lenalidomide plus low-dose dexamethasone until PD
Rd18	lenalidomide plus low-dose dexamethasone during 18cycles
RDI	relative dose intensity
SCT	stem-cell transplantation
SPC	Summary of product characteristics

SPM	second primary malignancies
TEAE	Treatment emergent adverse event
TNE	Transplant non eligible
TTF	Time to treatment failure
TTP	time to progression
VGPR	Very good partial response

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Celgene Europe Ltd. submitted on 28 February 2014 an application for a group of variations consisting of an extension application and a Type II variation to the European Medicines Agency (EMA) for Revlimid in accordance with Article 7(2)b of Commission Regulation (EC) No 1234/2008.

Lenalidomide was designated as an orphan medicinal product EU/3/03/177 on 12 December 2003 in the following indication: Treatment of multiple myeloma.

The applicant applied for the following indication in Multiple myeloma:

Continuous treatment of adult patients with previously untreated multiple myeloma who are not eligible for transplant.

Information on Paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) EMEA/494387/2008 on the granting of a class waiver.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did submit a critical report addressing the possible similarity with authorised orphan medicinal products.

Scientific Advice

The applicant received Scientific Advice/Protocol Assistance from the CHMP on 01/06/2001. The Scientific Advice/Protocol Assistance pertained to clinical aspects of the dossier.

1.2. Manufacturers

Manufacturers responsible for batch release

Celgene Europe Limited
1 Longwalk Road
Stockley Park
Uxbridge
UB11 1DB
UNITED KINGDOM

Penn Pharmaceutical Services Ltd.

23-24 Tafarnaubach Industrial Estate
Tredegar, Gwent NP2 3AA
South Wales
United Kingdom

1.3. Steps taken for the assessment of the product

Rapporteur: Pierre Demolis

Co-Rapporteur: Filip Joshephson

Submission date:	28 February 2014
Start of procedure:	26 March 2014
Rapporteur's first Assessment Report circulated to all CHMP members on:	2 July 2014
Co-Rapporteur's first Assessment Report circulated to all CHMP members on:	17 June 2014
PRAC RMP Rapporteur Assessment Report adopted by PRAC on:	10 July 2014
The consolidated List of Questions for the applicant adopted by CHMP on:	24 July 2014
The applicant submitted the responses to the CHMP consolidated List of Questions on:	17 October 2014
Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions on:	26 November 2014
PRAC RMP Rapporteur Assessment Report adopted by PRAC on:	4 December 2014
Rapporteurs circulated the final Joint Assessment Report on the applicant's responses to the List of Questions on:	12 December 2014
CHMP adoption of similarity report of Revlimid with Thalidomide Celgene and Imnovid	18 December 2014
CHMP opinion:	18 December 2014
CHMP revised opinion adopted by written procedure*:	11 February 2015

* A revised opinion was adopted by the CHMP in order to correct a discrepancy between the indication and the posology section in the SmPC. Reference to age which was initially included in section 4.2 "Posology and method of administration" was deleted to reflect the recommended indication. For clarity regarding the use of lenalidomide in combination, a reference to section 4.2, where the combination therapy is described, was also added to the indication.

2. Scientific discussion

2.1. Introduction

Multiple myeloma is a B-cell neoplasm that stems from the malignant transformation of plasma cells in the bone marrow and is characterised by the accumulation of clonal plasma cells in the bone marrow (Boyd, 2012; Palumbo, 2011).

Multiple myeloma (MM) accounts for about 10% of haematologic malignancies (Mateos, 2014). It is a disease of the elderly (San Miguel, 2013), with an overall median age at manifestation of approximately 70 years (Mateos, 2014). In Europe, 38,900 new cases of MM and 24,300 deaths due to MM were estimated in 2012 (Ferlay, 2013).

The prognosis of patients with MM depends on a variety of factors at time of diagnosis: tumour burden factors (disease stage and extramedullary disease), patient-related factors (eg, age, performance status [PS], and renal function), tumour biology status, and light chain and IgA disease (Mikhael, 2013; NCCN, 2013; Rajkumar, 2005; Reece, 2005). A large heterogeneity in the natural course of the disease is observed; some patients present with highly refractory disease, whereas others may be disease free for up to 15 years after initial therapy (Avet-Loiseau, 2013).

Clinical complications of progressive MM include recurrent infections, cytopenias, renal failure, hyperviscosity syndrome, hypercalcaemia, bone pain, and pathologic fractures (Munshi, 2012).

For patients with newly diagnosed multiple myeloma (NDMM), the choice of initial therapy is affected by the patient's age, health, and ability to undergo high-dose chemotherapy (HDC) with autologous stem-cell transplantation (ASCT). Patients with NDMM who are not eligible for ASCT (i.e., transplant-non eligible [TNE] patients) typically receive standard conventional treatment. Approximately 60% of patients with NDMM in Europe are ineligible for ASCT (Kantar Health, 2013). The TNE population constitutes a heterogeneous patient group, encompassing fit elderly patients as well as those young and elderly patients with comorbidities or older than 75 years deemed frail elderly, for whom treatment goals and strategies differ vastly (Ludwig, 2012; Palumbo, 2014).

The standard primary therapy for non-transplant candidates includes bortezomib and thalidomide. Other regimens included into NDMM treatment guidelines are the combination of Melphalan and Prednisone (MP) with either thalidomide (MPT) or bortezomib (MPB) (NCCN, 2013).

The applicant requested the approval for the following indication:

Revlimid is indicated for the continuous treatment of adult patients with previously untreated multiple myeloma who are not eligible for transplant.

The CHMP agreed on the following indication wording:

Revlimid is indicated for the treatment of adult patients with previously untreated multiple myeloma who are not eligible for transplant (see section 4.2).

The lenalidomide mechanism of action includes anti-neoplastic, anti-angiogenic, pro-erythropoietic, and immunomodulatory properties. Specifically, lenalidomide inhibits proliferation of certain haematopoietic tumour cells (including MM plasma tumour cells and those with deletions of chromosome 5), enhances T cell- and Natural Killer (NK) cell-mediated immunity and increases the number of NK T cells, inhibits angiogenesis by blocking the migration and adhesion of endothelial cells and the formation of microvessels, augments foetal haemoglobin production by CD34+ haematopoietic stem cells, and inhibits production of pro-inflammatory cytokines (e.g., TNF-α and IL 6) by monocytes. In MDS Del (5q), lenalidomide was shown to selectively inhibit the abnormal clone by increasing the apoptosis of Del (5q) cells. Lenalidomide binds directly to cereblon, a component of a cullin ring E3 ubiquitin ligase enzyme complex that includes deoxyribonucleic acid (DNA) damage-binding protein 1(DDB1), cullin 4 (CUL4), and regulator of cullins 1 (Roc1). In the presence of lenalidomide, cereblon binds substrate proteins Aiolos and Ikaros which are lymphoid transcriptional factors, leading to their ubiquitination and subsequent degradation resulting in cytotoxic and immunomodulatory effects (SmPC section 5.1).

For the combination of lenalidomide with dexamethasone until disease progression in patients who are not eligible for transplant the recommended starting dose of lenalidomide is 25 mg orally once daily on days 1-21 of repeated 28-day cycles. The recommended dose of dexamethasone is 40 mg orally once daily on days 1, 8, 15 and 22 of repeated 28-day cycles. Patients may continue lenalidomide and dexamethasone therapy until disease

progression or intolerance. Dosing is continued or modified based upon clinical and laboratory findings (see section 4.4). For patients ≥ 75 years of age, the starting dose of dexamethasone is 20 mg/day on Days 1, 8, 15 and 22 of each 28-day treatment cycle. The recommended dose of lenalidomide for patients suffering from moderate renal impairment is 10 mg once daily (SmPC section 4.2).

For the combination of lenalidomide with melphalan and prednisone followed by maintenance monotherapy in patients who are not eligible for transplant the recommended starting dose is lenalidomide 10 mg/day orally on days 1-21 of repeated 28-day cycles for up to 9 cycles, melphalan 0.18 mg/kg orally on days 1-4 of repeated 28 day cycles, prednisone 2 mg/kg orally on days 1-4 of repeated 28-day cycles. Patients who complete 9 cycles or who are unable to complete the combination therapy due to intolerance are treated with lenalidomide alone,10 mg/day orally on days 1-21 of repeated 28-day cycles given until disease progression. Dosing is continued or modified based upon clinical and laboratory findings (SmPC section 4.2).

2.2. Quality aspects

2.2.1. Introduction

An additional strength of hard capsules, containing 20 mg of lenalidomide as active substance, is being introduced with this extension application. Currently authorised hard capsules contain 2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg or 25 mg of lenalidomide as active substance.

Other ingredients are: for the capsule contents: lactose anhydrous, cellulose microcrystalline, croscarmellose sodium, magnesium stearate; for the capsule shell: gelatin, titanium dioxide (E171), indigo carmine (E132), yellow iron oxide (E172); for the printing ink: shellac, propylene glycol, black iron oxide (E172) and potassium hydroxide.

The additional strength is available in polyvinylchloride (PVC) / polychlorotrifluoroethylene (PCTFE) / aluminium foil blisters, the same container closure system as the one used in the authorised strengths.

2.2.2. Active Substance

No new information with regard to the active substance has been provided with this extension application. Reference is made to the already authorised information.

2.2.3. Finished Medicinal Product

Description of the product and pharmaceutical development

The aim of pharmaceutical development was to develop an immediate release hard capsule containing 20 mg of lenalidomide as active substance, in order to account for posology requirements. The pharmaceutical development was initially done on 2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg and 25 mg strengths which have been authorised since 2007. The development of the new 20 mg strength was based on the authorised dossier of the existing authorised strengths.

The qualitative composition of the 20 mg strength is identical to authorised strengths. All excipients are well-known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards, except gelatin

capsules and printing ink, for which additional information on compliance with EU legislation was provided. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC.

The quantitative composition is not dose proportional between different strengths as minor adjustments in several excipient ratios were made in order to improve the manufacturing process of 20 mg capsules.

A bioequivalence study was performed showing bioequivalence between 4 x 5 mg strength (reference) treatment and 20 mg strength (test) treatment. The formulation used during bioequivalence and clinical study is the same that is used for marketing. Comparative dissolution data between the 20 mg biobatch and 5 mg strength was provided. For both batches, all tablets were ⩾85% dissolved at 15 minutes.

The discriminatory power of the dissolution method has been demonstrated. Considering the nature of line extension (addition of a new strength within a validated range of strengths, with minor differences in quantitative composition), the validation data submitted was considered sufficient.

Manufacturing process development for the 20 mg strength was based on manufacturing process of already authorised strengths, which all share similar batch size, manufacturing equipment and manufacturing process.

The primary packaging is polyvinylchloride (PVC) / polychlorotrifluoroethylene (PCTFE) / aluminium foil blisters, the same as for previously authorised strengths. The material complies with Ph.Eur and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The finished product is manufactured by two manufacturers, which are the same as for authorised strengths. The manufacturing process is based on the already authorised process which is principally the same for both manufacturers and consists of two main steps: dry blending and filling of the capsules. The process is considered to be a standard manufacturing process.

Major steps of the manufacturing process have been validated by a number of studies. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for standard manufacturing process and hard capsules.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form and are the same as for existing strengths, except for appearance. They are: appearance (visual observation), identification (HPLC, UV), assay (HPLC), related impurities (HPLC), dissolution (HPLC), uniformity of dosage units by content uniformity (HPLC) and microbial limits (Ph. Eur.).

The analytical methods have been updated to include 20 mg strength, and additional validation for key parameters was carried out to demonstrate the appropriateness of methods for control of finished product.

Batch analysis results are provided for three commercial scale batches from each of the manufacturing sites confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

Stability data of three commercial scale batches from each of the manufacturing sites of 20 mg hard capsules stored under long term conditions for 12 months at 25 ºC / 60% RH and for up to 6 months under accelerated conditions at 40 ºC / 75% RH according to the ICH guidelines were provided. The batches of are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested for: appearance (visual observation), assay (HPLC), related impurities (HPLC) and dissolution (HPLC). The analytical procedures used are stability indicating.

Based on available stability data, the shelf-life and storage conditions as stated in the SmPC are acceptable.

Adventitious agents

Gelatine obtained from bovine sources is used in the product. Valid TSE CEP from the suppliers of the gelatine used in the manufacture is provided.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Quality Development

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on TSE safety.

2.2.6. Recommendations for future quality development

Not applicable.

2.3. Non-clinical aspects

2.3.1. Pharmacology

Primary pharmacodynamic studies

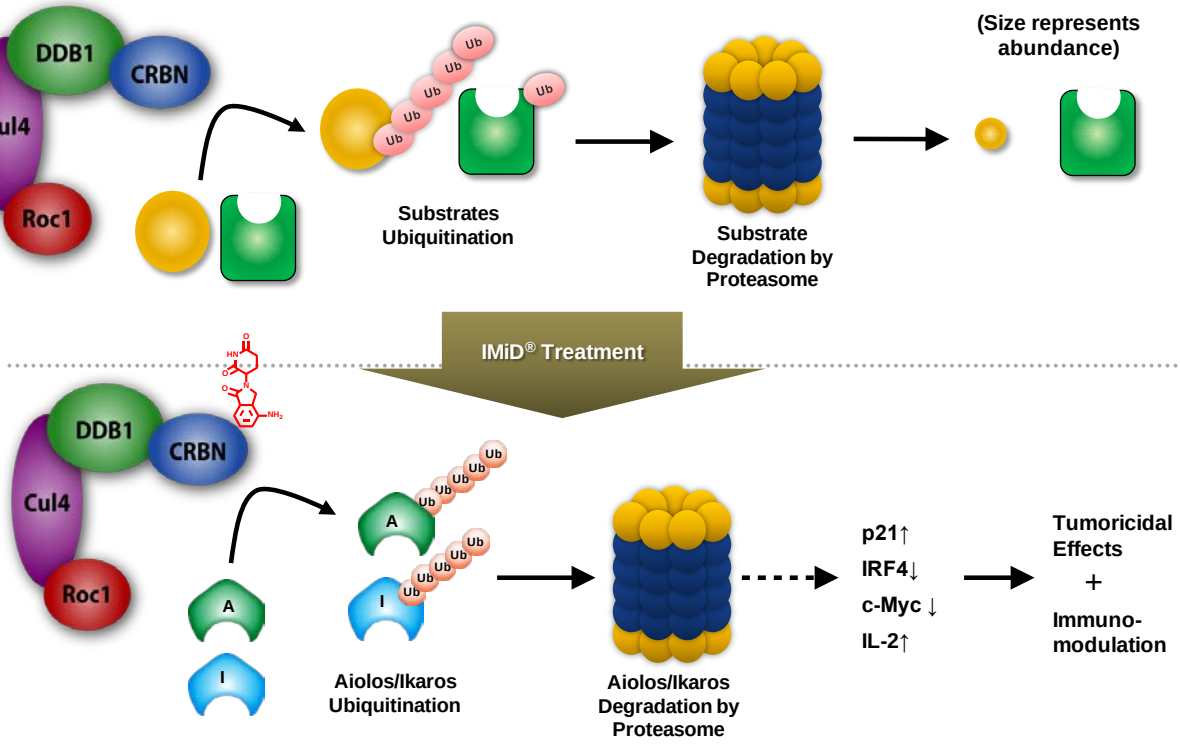
The applicant has summarised recent studies, elucidating the mechanism of action of lenalidomide.

A number of cellular activities, some of which were described in the original MAA, have been identified such as:

- Effects on the cell cycle such as G0/G1 arrest associated with the upregulation of the cyclin-dependent kinase (CDK) inhibitor p21WAF-1.
- Downregulation of the expression of interferon regulatory factor 4 (IRF4) in both MM cell lines and bone marrow samples from lenalidomide-treated MM patients. IRF4 is considered particularly important for MM cell growth and survival.
- Modulation of Rho guanosine-5'-triphosphate binding and hydrolysing enzymes (GTPases)
- Decreased anti-apoptotic proteins such as Bcl-2 and translation checkpoint proteins such as eIFE4
- Inhibition of proliferation and induction of apoptosis in a range of MM cells, attributed to the induction of tumour suppressor gene expression and caspase 8 activation.
- In MM cells, enhanced activity of Egr1, a zinc-finger transcription factor which directly regulates multiple tumour suppressor genes including p53 and p21.

Lenalidomide's pleiotropic activities on a range of cell types including MM cells and immune effector cells suggest modulation of multiple molecular pathways. A common molecular mediator in various cell types that is proximal to the downstream modulation of multiple signaling pathways involved in the inhibition of proliferation, induction of apoptosis in tumour cells, and in the activation of immune effector cells was identified as cereblon (CRBN), a protein required for the teratogenic effects of thalidomide in zebrafish and chicken embryos (Ito, 2010).

Figure 1. Proposed Mechanism of Action of Lenalidomide in Multiple Myeloma



CRBN = cereblon; CUL4 = cullin 4; DDB1 = deoxyribonucleic acid damage-binding protein 1; IRF4 = interferon regulatory factor 4; IL-2 = interleukin-2; Roc1 = regulator of cullins 1.
Cartoon illustrates how cereblon-containing E3 ligase functions in tumor cell without IMiDs (top panel) and in presence of an IMiDs compound such as lenalidomide (bottom panel). Engagement of an IMiDs compound is proposed to alter substrate specificity of cereblon leading to alteration of the balance of protein homeostasis resulting in ultimate biological effects. In the presence of lenalidomide, cereblon binds substrate proteins Aiolos and Ikaros which are lymphoid transcriptional factors, leading to their ubiquitination and subsequent degradation resulting in tumoricidal and immunomodulatory effects.
Source: Gandhi, 2014; Kronke, 2014; Lopez-Girona, 2011; Lopez-Girona, 2012; Lu, 2014.

Cereblon forms an ubiquitin E3 ligase complex with deoxyribonucleic acid damage-binding protein 1 (DDB1), cullin 4 (CUL4) and protein Roc1, and thalidomide treatment has been shown to modulate the ubiquitin ligase activity of the complex. E3 ubiquitin ligases are responsible for the ply-ubiquitination of a variety of substrate proteins which marks them for destruction in the proteasome. Using independent biochemical methods, lenalidomide was shown to bind to the CRBN-DDB1 complex, with an approximately 10-fold higher affinity than thalidomide. In myeloma cells, CRBN expression is linked to the efficacy of lenalidomide and CRBN expression decreases concurrently with the decrease in efficacy of lenalidomide. Using multiple small interfering ribonucleic acids (siRNAs) to silence the expression of CRBN in U266B1 cells resulted in the absence of CRBN protein and marked abrogation of lenalidomide induced delay of cell cycle progression. In addition, using lentiviral vectors, U266B1 cell lines were produced with either 60% or 75% less expression of CRBN and showed that relative to the parental cell line these cells were gene dose-dependently less responsive to inhibition of proliferation by lenalidomide. Moreover, gene profile changes by lenalidomide were reversed in the presence of CRBN siRNAs. In particular, induction of p21WAF1 cyclin-dependent kinase inhibitor protein was prevented in the absence of the expression of CRBN. Similar results on different myeloma cell lines and using multiple CRBN siRNAs, confirmed

the critical role of CRBN in the antiproliferative response of MM cells to lenalidomide. In fact, CRBN expression decreases concomitantly with the acquisition of lenalidomide resistance in H929 myeloma cells. Similar independent studies have also confirmed the importance of CRBN in mediating the anti-proliferative activity of lenalidomide in MM cells.

Importantly, when CRBN expression was reduced in activated human T cells using CRBN siRNAs lenalidomide's effect on the induction of IL-2 and TNF-α were reduced by ~60% suggesting that CRBN is also important in the immunomodulatory activity of lenalidomide on T cells. Whether CRBN has a role in the enhancement by lenalidomide of immune synapse formation between tumour and T or NK effector cells, or activation of NK cells for direct and antibody-mediated cellular cytotoxicity remains to be elucidated.

The direct tumour cytotoxic effects of lenalidomide have been linked to actin polymerisation and relocalisation of membrane proteins leading to cytoskeletal reorganisation, cell cycle arrest, and alterations in gene expression. The mechanisms associated with lenalidomide-induced stress fiber formation include upregulation of the RhoA GTPase. These cytoskeletal effects of lenalidomide have been shown to be associated with restoration of immune synapse formation and T cell activation. Lenalidomid treatment produced the polarisation of antigen-presenting proteins such as cluster of differentiation (CD) 1c and the increase of co-stimulatory molecules, such as CD54. These effects correlated with increased antigen presentation properties of tumour cells. These results suggest that regulation of cytoskeleton dynamics may constitute a key mechanism of lenalidomide activity on tumour and effector cells via immunological synapse formation and this activity is mediated by CRBN and Rho GTPases and is one of the earliest cellular effects of lenalidomide.

The role of CRBN in the activity of lymphoma has also been evaluated, although not to the extent as in MM. Studies have shown that CRBN mediates the toxic effect of lenalidomide in ABC type DLBCL, and is required to maintain the IRF4 levels, as was shown in MM. Also, expression levels of CRBN correlated with the inhibitory effect of lenalidomide on the viability of AML and MDS cell lines. In the LP-1 MM cell line, the combination of lenalidomide and Dex synergistically induced expression of CRBN while inhibiting MM cell proliferation.

Secondary pharmacodynamic studies

No new key secondary pharmacodynamic data have been submitted.

Safety pharmacology programme

No new safety pharmacology studies have been submitted (data not shown).

Pharmacodynamic drug interactions

No new specific pharmacodynamic drug interactions studies have been submitted (data not shown).

2.3.2. Toxicology

No additional toxicity studies have been submitted (data not shown).

2.3.3. Ecotoxicity / environmental risk assessment

No ERA has been submitted (see discussion on non-clinical aspects).

2.3.4. Discussion on non-clinical aspects

Lenalidomide binds directly to cereblon, a component of a cullin ring E3 ubiquitin ligase enzyme complex that includes deoxyribonucleic acid (DNA) damage-binding protein 1(DDB1), cullin 4 (CUL4), and regulator of cullins 1 (Roc1). In the presence of lenalidomide, cereblon binds substrate proteins Aiolos and Ikaros which are lymphoid transcriptional factors, leading to their ubiquitination and subsequent degradation resulting in cytoxic and immunomodulatory effects. Section 5.1 of the SmPC has been updated to reflect it.

Further to the CHMPs' request the applicant has presented a comprehensive discussion on the potential use of cereblon expression as a biomarker for clinical efficacy. Whereas the data (not shown) indeed suggested the possible value of cereblon expression as a biomarker, they also pointed to several limitations which currently would not allow an immediate use in the clinical setting. It was agreed with the applicant that at this time, the value of cereblon as a predictive biomarker is unknown.

As part of the EMEA/H/C/000717/II/56 procedure which was an extension of indication in the treatment of patients with transfusion dependent anaemia due to low- or intermediate-1- risk myelodysplastic syndromes associated with a deletion 5q cytogenetic abnormality with or without other cytogenetic abnormalities (MDS del5q) for Revlimid, an Environmental Risk Assessment (ERA) was provided. This ERA covered the MDS population and the Multiple Myeloma (MM) overall population regardless of the stage of the disease. The assessment of this report concluded that Revlimid is considered to pose a negligible risk to the environment. The CHMP have previously assessed the impact on the environment for the newly diagnosed multiple myeloma population indication seeking in this dossier, therefore an ERA is not required for this application.

2.3.5. Conclusion on the non-clinical aspects

The non-clinical data submitted by the MAH support the sought indication.

2.4. Clinical aspects

2.4.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Type of Study	Study Identifier; Location of Study Report	Primary Objective(s) of Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis; Eligibility Criteria	Duration of Treatment	Study Status; Type of Report
Comparative Bioavailability (BA) and Bioequivalence (BE)	CC-5013-BE-005 5.3.1.2	To investigate the BE of a single oral dose of 20 mg lenalidomide administered as a 20 mg capsule (test) relative to four 5-mg capsules (reference) formulation in healthy male subjects.	Phase 1, open-label, single-dose, randomized, two-way crossover Subjects were randomized to 1 of 2 treatment sequences: AB or BA.	Treatment A (Test Formulation): 1 x 20-mg capsule of lenalidomide PO Treatment B (Reference Formulation): 4 x 5-mg capsules of lenalidomide PO	28 (N = 14 per sequence)	Healthy subjects; male, 18-55 years of age	Subjects received a single dose of test or reference formulation on Day 1, followed by a washout period of 5 to 7 days, and then a single dose of test or reference formulation.	Completed; full report
Bioanalytical and Analytical Methods for Human Studies	CC-5013-DMPK-011 5.3.1.4	To provide full validation of a LC-MS/MS method for the quantification of lenalidomide in human plasma. (Protocol Amendment 5 extended the freezer storage and freeze thaw cycle stabilities)	In vitro Freezer storage stability of lenalidomide in human plasma evaluated at ≤ -80°C at 2 concentrations (15 and 750 ng/mL)	(^{13}C)-lenalidomide; in vitro	NA	Human plasma	NA	Completed; full amended final report (Protocol Amendment 5; issued 21Dec2012)
Controlled, Pertinent to Claimed Indication Main studies (Data Cutoff: 30 Apr 2013)	CC-5013-MM-015 5.3.5.1	To determine the efficacy of lenalidomide plus melphalan and prednisone (MPR) compared to placebo plus melphalan and prednisone (MPp) in subjects with NDMM who were ≥ 65 years of age.	Phase 3, multicenter, randomized, double-blind, placebo-controlled, 3-arm parallel group study Subjects randomized (1:1:1) to 3 arms: 1. MPR induction plus R maintenance (MPR+R) 2. MPR induction plus placebo maintenance (MPR+p) 3. MPp induction plus placebo maintenance (MPp+p) Stratified by age (≤ 75, > 75 years) and ISS stage (stages I-II, stage III).	Melphalan (M), prednisone (P), lenalidomide (R), placebo (p) Induction Therapy (first 9 cycles): **MP** (M 0.18 mg/kg + P 2 mg/kg) PO QD on Days 1-4 and **R** (10 mg) or **p** PO QD on Days 1-21 Maintenance Therapy: **R** (10 mg) (Arm MPR+R) or **p** (Arms MPR+p and MPp+p) PO QD on Days 1-21 of 28-day cycles from Cycle 10 until progressive disease (PD).	459 randomized (450 planned) Arm MPR+R = 152 Arm MPR+p = 153 Arm MPp+p = 154	Subjects with symptomatic NDMM as defined in protocol; ≥ 65 years of age	Induction therapy (maximum of nine 28-day cycles) plus maintenance (28-day cycles) until PD occurred, until subject permanently discontinued R/p treatment, or up to the time when all subjects had been followed for at least 5 years from randomization or had died. Open-label extension phase: optional for subjects after PD.	Ongoing; full report issued 30Oct2013 (data cutoff 30Apr2013)

Controlled, Pertinent to Claimed Indication Main Studies (Data Cutoff: 24 May 2013)	CC-5013-MM-020 (IFM 07-01) 5.3.5.1	To compare the efficacy of lenalidomide plus low-dose dexamethasone (Rd) given until PD to that of melphalan, prednisone, and thalidomide (MPT) given for twelve 42-day cycles.	Phase 3, multicenter, randomized, open-label, 3-arm study Subjects were randomized (1:1:1) to 3 arms: 1. Rd until PD 2. Rd up to 18 cycles (Rd18) 3. MPT up to 12 cycles Stratified by age (≤ 75, > 75 years), ISS stage (stages I-II, stage III), and country.	Lenalidomide (R), dexamethasone (d), melphalan (M), prednisone (P), thalidomide (T) **Rd**: **R** 25 mg PO QD on Days 1-21 plus **d** 40 mg PO QD on Days 1, 8, 15, and 22 of 28-day cycle **MPT**: **M** 0.25 mg/kg PO QD and **P** 2 mg/kg PO QD on Days 1-4, plus **T** 200 mg PO QD on Days 1-42 of 42-day cycle Starting doses above were adjusted for age (>75 years) and/or renal function, per protocol.	1623 randomized (1590 planned) Arm Rd = 535 Arm Rd18 = 541 Arm MPT = 547	Subjects with symptomatic NDMM as defined in protocol; subjects had measurable M-protein, and were ≥ 65 years of age or not candidates for SCT	Arm Rd: 28-day cycles until PD Arm Rd18: Rd up to eighteen 28-day cycles (72 weeks) Arm MPT: up to twelve 42-day cycles (72 weeks)	Ongoing; full report issued 23Dec2013 (data cutoff 24May2013)

Type of Study	**Study Identifier; Location of Study Report**	**Primary Objective(s) of Study**	**Study Design and Type of Control**	**Test Product(s); Dosage Regimen; Route of Administration**	**Number of Subjects**	**Healthy Subjects or Diagnosis; Eligibility Criteria**	**Duration of Treatment**	**Study Status; Type of Report**
Other Study Reports (Supportive studies)	SWOG S0232 5.3.5.4	To compare the effects of treatment with lenalidomide plus dexamethasone with those of placebo plus dexamethasone on progression-free survival (PFS) in subjects with previously untreated MM.	Phase 3, multicenter, randomized, double-blind, parallel-group, placebo-controlled study Subjects were randomized (1:1) to 2 arms: 1. R/D 2. Placebo/D Induction using standard dexamethasone with lenalidomide or with placebo, followed by maintenance with same until PD occurred or subject discontinued treatment for another reason. Stratified by ISS stage (stage I, stage II, stage III) and Zubrod performance status (0 and 1, 2 and 3).	Lenalidomide (R), standard dexamethasone (D), placebo Induction: 3 cycles x 35-days **R** 25 mg or **placebo** PO QD on Days 1-28, plus **D** 40 mg PO QD on Days 1-4, 9-12, and 17-20 Maintenance: 28-day cycles **R** 25 mg or **placebo** PO QD on Days 1-21, plus **D** 40 mg PO QD on Days 1-4 and 15-18	198 randomized (500 planned) R/D = 100 Placebo/D = 98	Subjects with previously untreated NDMM who were not immediately undergoing ASCT and had measureable M-protein; age ≥ 18 years, Zubrod performance status of 0-3 and adequate bone marrow, liver, and renal function	Until PD occurred or subject withdrew for another reason	Completed; full report

2.4.2. Pharmacokinetics

This grouped application includes a type II variation and a line extension.

- A type II variation to add the following indication: Revlimid is indicated for the continuous treatment of adult patients with previously untreated multiple myeloma who are not eligible for transplant.
- A line extension application to add the following strength: 20 mg (21 capsules pack).

The new strength is 20 mg and the already approved strengths are 2.5, 5, 7.5, 10, 15 and 25 mg. To support the application of the new strength, the applicant has submitted one oral single-dose bioequivalence study (CC-5013-BE-005) in the fasted state with the 20 mg capsule (test) formulation relative to 4 x 5 mg capsules (reference).

The applied strength, 20 mg, contains the same excipients as the already approved strengths, 2.5, 5, 7.5, 10, 15 and 25 mg, but the composition is not quantitatively proportional with the other strengths. The 5 mg strength was selected as the reference since 5 mg capsule formulation is the same formulation as the 10 mg capsule and since 5 mg capsules were used as the reference standard in previous bioequivalence studies and keeping the same reference standard maintained consistency when making comparisons across all formulations.

The clinical part of the study was conducted between 1st December 2008 and 5th January 2009.The analytical part of the study was conducted between 19th December 2008 and 15th January 2009.

Study design: The study was a randomised, single oral dose, 2-way crossover study conducted in 28 healthy male volunteers under fasting conditions. After an overnight fast one capsule of 20 mg of test or four capsules of 5 mg of reference was administered together with 240 ml of water. Fasting continued until 4 hours after drug administration. Water was allowed ad libitum until 1 hour pre-dose and beginning 4 hours after drug administration. Blood-samples were collected pre-dose and at 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 6, 9, 12, 16 and 24 hours after drug administration. The study periods were separated by a wash-out period of 5 to 7 days.

Test and reference products: Test product: Lenalidomide, 20 mg, capsule, manufactured by Norwich Pharmaceuticals, batch No. 07B0026, expiry date: July 2010. Reference product: Lenalidomide, 5 mg, capsule, manufactured by Norwich Pharmaceuticals, batch No. 07B0043, expiry date: July 2010.

Population studied: A total of 28 adult healthy male volunteers, aged 18-52 years were enrolled. There were no drop-outs during the study. All subjects (N=28) completed both study periods and were included in the pharmacokinetic analysis.

Analytical methods

Concentrations of lenalidomide in plasma were determined by a validated liquid chromatography-tandem mass spectrometry (LC/MS/MS) method. The lower limit of quantitation for lenalidomide in human plasma was 5 ng/mL, with linearity demonstrable to 1000 ng/mL. The inter-day precision range, based upon CV% of QC samples, was 1.8% to 3.3%. The inter-day accuracy range, based upon percent relative error (RE%) at QC levels, was -0.8 to 2.1%. A total of 68 human plasma samples (~8% of the study samples) were reanalysed to assess incurred sample reproducibility for the assay. The % difference between 2 measurements (original as the reference and reanalysis) of all the reanalysis samples was within ±15%.

Results

The results are presented in Table 1.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range) for lenalidomide, n=28.

Treatment	AUC_{0-t} ng*h/ml	C_{max} ng/ml	t_{max} h
Test	1059 ± 165	330 ± 77	0.89 (0.50-3.00)
Reference	1037 ± 160	321 ± 90	0.75 (0.50-2.50)
*Ratio (90% CI)	102.07 (99.77-104.41)	103.68 (96.57-111.31)	-

AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours

C_{max} maximum plasma concentration

t_{max} time for maximum plasma concentration

**calculated based on ln-transformed data*

Special populations

A meta-analysis (CSR CC-5013- MCL-001-PK) pooled data from 7 clinical studies (CDC-501-001, CDC-501-002, CC-5013-MM-021, CC-5013-MM-017, CC-5013-MCL-001, CC-5013-PK-001, and CC-5013-PK-002) with a total of 147 patients who received monotherapy with oral lenalidomide (5 to 50 mg) in single- and/or multiple-dose regimens has been submitted.

117 of these patients had haematologic malignancies such RRMM (68 patients), MDS and mantle cell lymphoma (MCL), 30 were non-cancer patients with various degrees of renal impairment. The study showed that creatinine clearance is the only important and statistically significant predictor of apparent lenalidomide clearance, while age, weight, race, sex, and mild hepatic impairment do not affect the clearance of lenalidomide.

2.4.3. Pharmacodynamics

No new clinical pharmacology studies have been submitted.

2.4.4. Discussion on clinical pharmacology

This application includes the addition of the 20 mg strength. The 20-mg formulation has been developed to ease administration in NDMM the recommending starting dose being 25 mg once daily (one 20 mg capsule plus one 5 mg capsule). It is also useful for NDMM patients older than 75 years of age for whom starting dose is 20 mg. The rationale for this line extension is endorsed.

A bioequivalence study (CC-5013-BE-005) compared 20 mg capsule formulation with 5 mg capsules.

Lenalidomide 1 x 20-mg capsule is bioequivalent to lenalidomide 4 x 5-mg capsules. Based on the new data for the 20-mg capsule strength, the in vitro and in vivo biopharmaceutical evidence for the approved capsules strengths submitted with the NDMM application in 2010, and the linear pharmacokinetics of lenalidomide, the

20-mg lenalidomide capsules are interchangeable with the corresponding number of the approved lenalidomide capsule strengths (2.5-, 5-, 7.5-, 10-, 15-, and 25-mg capsules) to achieve the same exposure at a given dose.

The 20-mg formulation is part of treatments used in the pivotal study MM-020 but it is not used in the MM-015 study.

2.4.5. Conclusions on clinical pharmacology

Based on these results, Revlimid 20 mg capsule and Revlimid 5 mg capsule are bioequivalent under fasting conditions when both products are administered at the same dose (20 mg).

2.5. Clinical efficacy

2.5.1. Dose response study

ECOG E4A03

Study ECOG E4A03 defined the selection of the Rd dose regimen for Study MM-020. It was an open-label, randomised, multicenter, Phase 3 (non-inferiority) study to evaluate the response rate and toxicity of lenalidomide plus standard-dose dexamethasone (RD) *versus* lenalidomide plus low-dose dexamethasone (Rd) in patients with NDMM and to determine whether lenalidomide plus low-dose dexamethasone had a similar response rate with lower toxicity. The study was sponsored by the Eastern Cooperative Oncology Group (ECOG) with 445 subjects enrolled in US centres.

This study was initiated on 26 October 2004 and was suspended by its DMC on 27 March 2007 after preliminary study results of this study suggested improved survival for Rd-treated patients compared with RD-treated patients. Subsequently, patients on RD treatment were to cross over to Rd treatment.

A total of 445 eligible patients were registered/randomised to the study in a 1:1 ratio to 2 treatment arms:

- RD (n = 223): lenalidomide (25 mg per day, Days 1 to 21 every 28 days) plus standard dexamethasone (40 mg/day on Days 1 to 4, 9 to 12, and 17 to 20 every 28 days)
- Rd (n = 222): lenalidomide (25 mg per day, Days 1 to 21 every 28 days) plus low-dose dexamethasone (40 mg/day on Days 1, 8, 15, and 22 every 28 days)

After 4 cycles patients could continue treatment on the protocol or withdraw from the study for any reason. All patients were given aspirin 325 mg/day on Days 1 to 28 of each cycle during treatment with either lenalidomide and dexamethasone regimen (i.e., RD or Rd) unless they were being treated with alternate prophylaxis (either low molecular weight heparin or warfarin).

The primary endpoint was to compare the response rate (by the end of the first 4 cycles) between RD and Rd treatment arm by independent review. The overall response rate (CR + nCR + PR) in the first 4 cycles at the time of the data cut-off date (27 March 2007) was 77% (172/223) in Arm RD and 64% (143/222) in Arm Rd (p = 0.004, Fisher's exact test). The overall response during treatment was 80% (179/223) in Arm RD and 68% (151/222) in Arm Rd (p = 0.004; Fisher's exact test).Time to progression had not been reached for either treatment arms (78 weeks event free 51.04% in RD vs 58.31% in Rd; p = 0.418, unstratified log rank test of survival curve difference between treatment arms; HR = 1.18, 95% CI: 0.79-1.76). Median Progression-free survival was 84.1 weeks in RD and NE in Rd (p = 0.135, unstratified log rank test; HR = 1.32, 95% CI:

0.92-1.90). Among the responders the proportion of subjects who continued to respond at the time of analysis was 73% in Arm RD and 80% in Arm Rd. Median Overall Survival (OS, defined as the number of weeks between registration/randomisation and death) had not been reached for either treatment arm. As of the data release cut-off, 17 of the 222 patients (8%) in Arm Rd and 43 of the 223 patients (19%) in Arm RD had died.

2.5.2. Main studies

- **CC-5013-MM-015**

This was a phase III, multicentre, randomised, double-blind, placebo-controlled, 3-arm parallel group study designed to determine the efficacy and safety of lenalidomide in combination with melphalan and prednisone *versus* placebo plus melphalan and prednisone in subjects with newly diagnosed multiple myeloma who are 65 years of age or older.

Methods

Study Participants

Patients were required to fulfil all of the following inclusion criteria:

1. Must understand and voluntarily sign an informed consent form

2. Age equal to or greater than 65 years at the time of signing the informed consent

3. Newly diagnosed, symptomatic MM as defined by the 3 criteria below (Durie, 2003):

- MM diagnostic criteria (all 3 required);

- Monoclonal plasma cells in the bone marrow ≥ 10% and/or presence of a biopsy proven plasmacytoma

- Monoclonal protein present in the serum and/or urine

- Myeloma-related organ dysfunction (at least one of the following;[C] Calcium elevation in the blood (serum calcium > 10.5 mg/dL or upper limit of normal [ULN]); [R] Renal insufficiency (serum creatinine > 2 mg/dL); [A] Anaemia (haemoglobin < 10 g/dL or 2 g < laboratory normal); [B] Lytic bone lesions or osteoporosis

AND have measurable disease by protein electrophoresis analyses as defined by the following:

- Immunoglobulin (Ig) G multiple myeloma: Serum monoclonal paraprotein (M-protein) level ≥1.0 g/dL or urine M-protein level ≥200 mg/24 hours

- IgA multiple myeloma: Serum M-protein level ≥0.5 g/dL or urine M-protein level ≥200 mg/24 hours

- IgM multiple myeloma (IgM M-protein plus lytic bone disease documented by skeletal survey plain films): Serum M-protein level ≥ 1.0 g/dL or urine M-protein level ≥ 200 mg/24hours

- IgD multiple myeloma: Serum M-protein level ≥0.05 g/dL or urine M-protein level ≥200 mg/24 hours

- Light chain multiple myeloma: Serum M-protein level ≥1.0 g/dL or urine M-protein level ≥200 mg/24 hours

4. Karnofsky performance status ≥60%

5. Able to adhere to the study visit schedule and other protocol requirements

6. Women of child bearing potential (FCBP) must:

- Have a negative medically supervised pregnancy test before start of study therapy. She must agree to ongoing pregnancy testing during the study, and after end of study therapy (refer to details in appendices of the protocol in Appendix 16.1.1). This applies even if the patient practices complete and continued sexual abstinence.

- Either commit to continued abstinence from heterosexual intercourse (which must be reviewed on a monthly basis) or agree to use, and be able to comply with, effective contraception without interruption, 28 days before starting study drug, during the study therapy (including dose interruptions), and for 28 days after discontinuation of study therapy

7. Male patients must:

- Agree to use a condom during sexual contact with a WCBP, even if they have had a vasectomy, throughout study drug therapy, during any dose interruption and after cessation of study therapy

- Agree to not donate semen during study drug therapy and for a period after end of study drug therapy

8. All patients must:

- Have an understanding that the study drug could have had a potential teratogenic risk.

- Agree to abstain from donating blood while taking study drug therapy and following discontinuation of study drug therapy.

- Agree not to share study medication with another person.

- All patients must have been counselled about pregnancy precautions and risks of foetal exposure.

Any of the following was regarded as a criterion for exclusion from the trial:

1. Previous treatment with AMT (did not include radiotherapy, bisphosphonates, or a single short course of steroid [i.e., less than or equal to the equivalent of dexamethasone 40 mg/day for 4 days; such a short course of steroid treatment must not have been given within 28 days of randomisation])

2. Any serious medical condition, including the presence of laboratory abnormalities, which places the patient at an unacceptable risk if he or she participated in this study or confounds experimental the ability to interpret data from the study

3. Pregnant or lactating females

4. Radiotherapy within 14 days (2 weeks) of randomisation

5. Plasmapheresis within 28 days (4 weeks) of randomisation.

6. Any of the following laboratory abnormalities:

- Absolute neutrophil count (ANC) < 1,500/µL (1.5×10^9/L)

- Platelet count < 75,000/μL (75.10^9/L) for patients in whom < 50% of bone marrow nucleated cells are plasma cells; but platelet count <30,000/μL for patients in whom $\geq$ 50% of bone marrow nucleated cells are plasma cells

- Haemoglobin < 8.0 g/dL (80 g/L)

- Serum creatinine > 2.5 mg/dL (221 μmol/L)

- Serum aspartate aminotransferase (AST/SGOT) or alanine aminotransferase (ALT/SGPT) > 3.0 x ULN

7. Prior history of malignancies, other than MM, unless the patient had been free of the disease for ≥ 3 years. Exceptions included the following: Basal cell carcinoma of the skin; Squamous cell carcinoma of the skin; Carcinoma in situ of the cervix; Carcinoma in situ of the breast; Incidental histological finding of prostate cancer (Tumour, Node, Metastasis [TNM] stage of T1a or T1b)

8. Neuropathy of ≥ Grade 2 severity

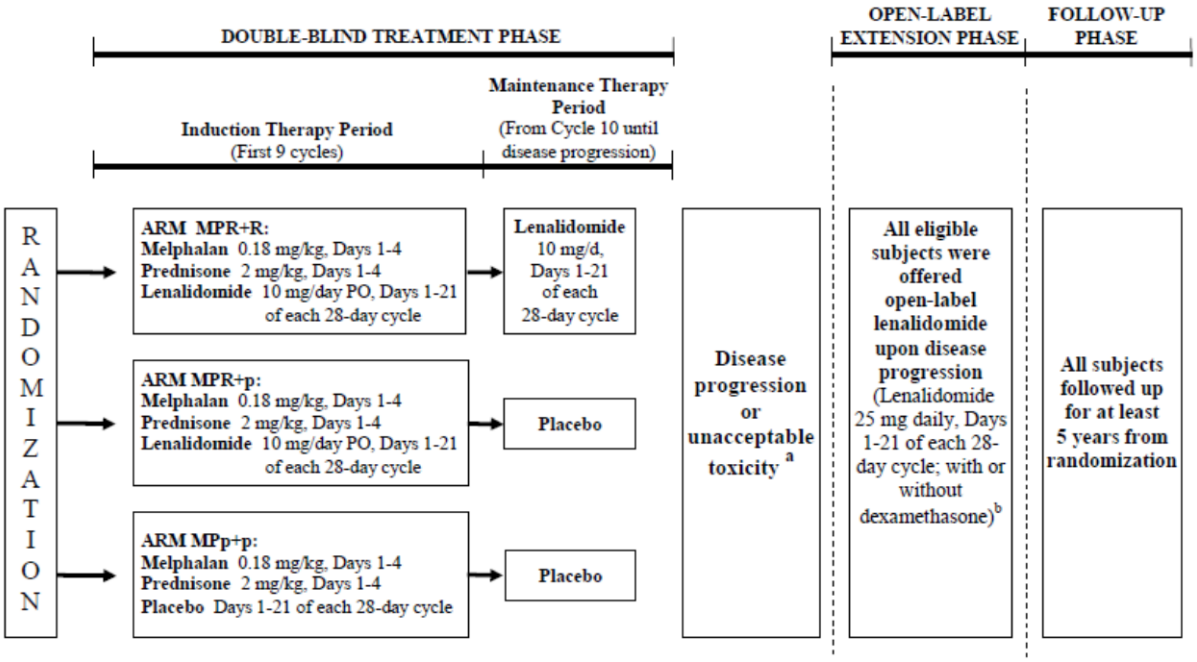
9. Known human immunodeficiency virus (HIV) positivity or active infectious hepatitis, Type A, B, or C

Treatments

This study consisted of 3 phases for each study patient: a double-blind treatment phase, an open-label extension phase (OLEP), and a follow-up phase.

The overall study design and dosing regimens prior to unblinding are presented in the figure 2.

Figure 2. Design of Study MM-015



Eligible patients were randomised (1:1:1) to 1 of 3 treatment arms:

- Induction therapy with MPR (up to 9 cycles) followed by maintenance therapy with single-agent lenalidomide (herein referred to as Arm MPR+R)
- Induction therapy with MPR (up to 9 cycles) followed by maintenance therapy with placebo (herein referred to as Arm MPR+p)
- Induction therapy with MP plus placebo (up to 9 cycles) followed by maintenance therapy with placebo (herein referred to as Arm MPp+p).

Additional treatment periods for which various drug exposure measures were summarised are defined as follows:

- Open-Label Extension Phase: for subjects who progress and opt to receive open-label treatment (second line treatment lenalidomide +- dexamethasone), from the first dose date of the open-label cycle to the end date of the last cycle on open-label treatment.
- Follow-Up Phase: for subjects who have no other phases or treatment periods remaining and enter the follow-up phase, from the start of the follow-up visits to the date of total study discontinuation (no further follow-up on the study).

Treatment Duration

The first dose date of lenalidomide/placebo, melphalan, or prednisone, whichever is earlier, was considered the start date of the overall study treatment. For each cycle, the lenalidomide/placebo start date was considered the cycle start date and the day before that (after the 1st cycle) was considered the end day of the previous cycle. The end date of the last cycle was calculated as the start date of last treatment cycle plus 27 days, unless subject discontinues study or dies before the end of the last cycle, in which case the end date of the last cycle was the treatment discontinuation date or the death date. The overall study treatment end date was the same as the end date of the last cycle of the last study drug.

A patient who developed PD during the treatment period (induction + maintenance) decided whether or not to enter the OLEP within 28 days (4 weeks) of PD. After the 11 May 2010 unblinding, patients in MPR+p and MPp+p arm discontinued placebo and underwent observation until disease progression. Those who progressed during this observation could have entered the OLEP.

The dose of melphalan and prednisone was dependent on the patient's weight. Rounding of these doses was necessary. Rounding of melphalan was done to the nearest 2 mg; rounding of prednisone was to the nearest 1 mg with the cut off at 0.5 mg.

Objectives

The primary objective was to determine the efficacy of melphalan/prednisone/lenalidomide (MPR) compared with placebo plus MP in subjects with NDMM who are 65 years of age or older.

The secondary objective was to assess the safety of MPR compared with placebo plus MP in subjects with NDMM who are 65 years of age or older.

Outcomes/endpoints

The primary endpoint was progression-free survival (defined as the time between randomization and disease progression per investigator assessment based on the [EBMT/IBMTR/ABMTR] response criteria, or death on study, whichever occurred earlier).

Secondary endpoints included: Overall survival (defined as time from randomization to death due to any cause); Time to progression (TTP) (defined as the time between randomization and disease progression based on the [EBMT/IBMTR/ABMTR] response criteria) ; Duration of response (defined as from the time when the response criteria are first met for CR or VGPR or PR until the first date the response criteria are met for PD or until the subject dies from any cause, whichever occurs first); Time to response (time to myeloma response defined as the time from randomization to the time the response criteria for CR or VGPR or PR are first met); Time to second-line antimyeloma treatment (defined as time from randomization to the start of another anti-myeloma therapy); PFS2 (defined as the time from randomization to the start date of third-line AMT or death from any cause); Safety (adverse events [type, frequency, and severity of AEs, and relationship of AEs to study drug],

laboratory abnormalities, and hospitalizations); Quality of life (QoL): (EORTC QLQ-C30) and QoL Questionnaire for Patients with Multiple Myeloma (QLQ-MY24) Module); Performance status (Karnofsky scale); Exploratory assessment on cytogenetic abnormalities; Exploratory biomarker studies.

Sample size

This study was designed to have 2 interim analyses performed according to the statistical analysis plan (SAP); the first interim analysis to occur when approximately 148 patients across all 3 treatment arms developed disease progression or died during the double-blind treatment (i.e., 50% information for the primary endpoint of 296 PFS events) and the second interim analysis when approximately 207 patients across all 3 treatment arms developed disease progression or died (i.e., 70% information for the primary endpoint of PFS).

As the primary analysis for the study was to compare PFS between Arms MPR+R and MPp+p, a 50% improvement in median TTP, from 15 months in Arm MPp+p to 22.5 months in Arm MPR+R, was considered clinically relevant. Therefore a total of 450 patients (150 in each arm) were to be enrolled, with accrual of about 38 patients per month for 12 months. Full information necessary for a log-rank test to have 80% power to detect the targeted treatment effect would be achieved when 197 patients from Arms MPR+R and MPp+p had progressed or died (approximately 296 events from the 3 arms).

Based on prior clinical experience, the median survival in Arm MPp+p was projected at 36 months, while the median survival for Arm MPR+R was estimated at 54 months. With 273 death events across all treatment arms the study could detect this 50% improvement in median OS with 78% of power.

Randomisation

Subjects who are eligible for the study will be randomised to 1 of the 3 double blind treatment groups according to the following two stratification factors: age (≤ 75 vs > 75years) and ISS (stages 1 or 2 vs stage 3).

Blinding (masking)

This was a double-blind study.

Statistical methods

The primary efficacy analyses for all endpoints were performed based on the intent-to-treat (ITT) population. For the primary analysis, the comparison of PFS between MPR+R and MPp+p using the unstratified log rank test, the overall two-sided significance level was 5%. This 5% was to be spread over 3 analyses (two interim analyses and one final analysis) by an O'Brien-Fleming alpha spending function (DeMets, 1994). The statistical significance of efficacy was to be claimed if the p-value was less than or equal to the significance level as calculated based on the specified alpha spending function and the observed number of events.

To account for the stratified randomisation, a log-rank test stratified by the two strata used in the randomisation (age and ISS score) was to be performed as a secondary analysis for PFS, in addition to the unstratified analysis described above.

Recruitment

The first patient was randomised on 1 February 2007, and the last patient was randomised on 19 September 2008.

The study was conducted in Europe, Australia, and Israel. Patients were randomised at 82 sites (70 in Europe, 8 in Australia, and 4 in Israel).

Conduct of the study

The protocol was amended 5 times. The major changes are described below:

Amendment 4 required that SPMs be treated as SAEs and reported throughout the study duration, including the survival follow-up phase and added a central review of all haematologic SPMs.

Amendment 5 mandated submission of diagnostic reports (eg, pathology reports) from tumour biopsy samples collected at the SPM diagnosis to Celgene or a designee for secondary confirmation and added the collection of samples for exploratory biomarker studies to assess patients for possible molecular risk factors and to examine whether there is any correlation of molecular and genetic risk factors with the potential development of SPMs during and after lenalidomide treatment.

Major protocol violations noted in the study were grouped into 6 categories reported in Table 2.

Table 2. Number (%) of subjects with major protocol violations; ITT Population (Study MM-015)

Type of Protocol Violation	MPR+R (N = 152) n (%)	MPR+p (N = 153) n (%)	MPp+p (N = 154) n (%)	Total (N = 459) n (%)
Subjects With ≥ 1 Major Protocol Violation	18 (11.8)	16 (10.5)	13 (8.4)	47 (10.2)
Type of violation[a]:				
Safety plan not followed	8 (5.3)	13 (8.5)	5 (3.2)	26 (5.7)
Deviation from inclusion criteria	7 (4.6)	4 (2.6)	3 (1.9)	14 (3.1)
Deviation from exclusion criteria	1 (0.7)	0	3 (1.9)	4 (0.9)
Incorrect medication kit dispensed	1 (0.7)[b]	0	2 (1.3)[c]	3 (0.7)
Incorrect dose of medication dispensed	1 (0.7)[d]	0	0	1 (0.2)
Missed multiple doses	1 (0.7)	0	0	1 (0.2)

GCSF = granulocyte colony-stimulating factor; ITT = intent to treat; M = melphalan; p = placebo; P = prednisone; R = lenalidomide; SAE = serious adverse event; SPM = second primary malignancy.
[a] Each subject could have had more than 1 violation.
Data cutoff date = 30 Apr 2013

Baseline data

The baseline demographics and disease characteristics are presented in tables 3 and 4 respectively.

Table 3. Demographic Characteristics (ITT Population) (Study MM-015)

Characteristic		MPR+R (N = 152)	MPR+p (N = 153)	MPp+p (N = 154)
Age (years)	N	152	153	154
	Mean	72.0	72.1	72.0
	SD	5.33	5.20	5.26
	Median	71	71	72
	Min, Max	65, 87	65, 86	65, 91
Age Distribution, n (%)	≤ 75 years	116 (76.3)	116 (75.8)	116 (75.3)
(Stratification Factor)	> 75 years	36 (23.7)	37 (24.2)	38 (24.7)
Sex, n (%)	Male	71 (46.7)	82 (53.6)	75 (48.7)
	Female	81 (53.3)	71 (46.4)	79 (51.3)
Race, n (%)	White	151 (99.3)	151 (98.7)	151 (98.1)
	Black	1 (0.7)	0	0
	Hispanic	0	0	1 (0.6)
	Other	0	2 (1.3)	2 (1.3)

Table 4. Baseline Disease-related Characteristics (ITT Population) (Study MM-015)

Characteristic		MPR+R (N = 152)	MPR+p (N = 153)	MPp+p (N = 154)
ISS Stage, n (%)	I	28 (18.4)	32 (20.9)	28 (18.2)
(Stratification Factor)	II	50 (32.9)	47 (30.7)	48 (31.2)
	III	74 (48.7)	74 (48.4)	78 (50.6)
Karnofsky Performance Status, n (%) [a]	60%	13 (8.6)	16 (10.5)	11 (7.1)
	70%	40 (26.3)	20 (13.1)	22 (14.3)
	80%	37 (24.3)	54 (35.3)	43 (27.9)
	90%	40 (26.3)	40 (26.1)	51 (33.1)
	100%	21 (13.8)	23 (15.0)	27 (17.5)
	Missing	1 (0.7)	0	0
Del 17p	No	46 (30.3)	52 (34.0)	51 (33.1)
	Yes	6 (3.9)	6 (3.9)	7 (4.5)
	Missing / Not evaluable	100 (65.8)	95 (62.1)	96 (62.3)
Del 13q	No	50 (32.9)	59 (38.6)	55 (35.7)
	Yes	38 (25.0)	45 (29.4)	38 (24.7)
	Missing / Not evaluable	64 (42.1)	49 (32.0)	61 (39.6)
t (14;16)	No	3 (2.0)	7 (4.6)	9 (5.8)
	Yes	0	1 (0.7)	0
	Missing / Not evaluable	149 (98.0)	145 (94.8)	145 (94.2)
t (4;14)	No	9 (5.9)	13 (8.5)	12 (7.8)
	Yes	6 (3.9)	2 (1.3)	3 (1.9)
	Missing / Not evaluable	137 (90.1)	138 (90.2)	139 (90.3)
Bone Marrow (% Plasma Cells)	N	150	152	152
	Mean	39.7	39.3	37.9
	SD	24.83	25.01	23.66
	Median	35.0	38.5	35.0
	Min, Max	0.0, 100.0	0.0, 100.0	0.0, 100.0
Creatinine Clearance, n (%)	≥ 60 mL/min	72 (47.4)	83 (54.2)	77 (50.0)
	< 60 mL/min	78 (51.3)	69 (45.1)	76 (49.4)
	Missing	2 (1.3)	1 (0.7)	1 (0.6)
β2-microglobulin, n (%)	> 5.5 mg/L	74 (48.7)	78 (51.0)	67 (43.5)
	≤ 5.5 mg/L	77 (50.7)	75 (49.0)	87 (56.5)
	Missing	1 (0.7)	0	0
Hemoglobin	< 10 g/dL	50 (32.9)	56 (36.6)	51 (33.1)
	≥ 10 g/dL	99 (65.1)	96 (62.7)	100 (64.9)
	Missing	3 (2.0)	1 (0.7)	3 (1.9)
Albumin, n (%)	> 35 g/L	87 (57.2)	82 (53.6)	81 (52.6)
	≤ 35 g/L	63 (41.4)	70 (45.8)	72 (46.8)
	Missing	2 (1.3)	1 (0.7)	1 (0.6)
C-reactive Protein, n (%)	> 4 mg/L	64 (42.1)	56 (36.6)	64 (41.6)
	≤ 4 mg/L	84 (55.3)	93 (60.8)	89 (57.8)
	Missing	4 (2.6)	4 (2.6)	1 (0.6)
Multiple Myeloma Subtype, n (%)	IgA	39 (25.7)	38 (24.8)	33 (21.4)
	Other	108 (71.1)	112 (73.2)	116 (75.3)
	Missing	5 (3.3)	3 (2.0)	5 (3.2)

IgA = immunoglobulin A; ISS = International Staging System; ITT = intent to treat; M = melphalan; max = maximum; min = minimum; p = placebo; P = prednisone; R = lenalidomide; SD = standard deviation.

[a] For Karnofsky performance scale, $p < 0.1$ for the comparison between Arms MPR+R and MPp+p, and Arms MPR+R and MPR+p are based on a pooled t-test comparing the 2 treatment arms.

Numbers analysed

Table 5 summarises the number of subjects who were included in the ITT, efficacy-evaluable, per-protocol, and safety populations as of the 30 Apr 2013 data cut-off date.

Table 5. Analysis sets (Study MM-015)

Analysis Set	MPR+R n (%)	MPR+p n (%)	MPp+p n (%)	Total n (%)
Intent-to-treat Population[a]	152 (100.0)	153 (100.0)	154 (100.0)	459 (100.0)
Safety Population[b]	150 (98.7)	152 (99.3)	153 (99.4)	455 (99.1)
Efficacy-evaluable Population[c]	136 (89.5)	141 (92.2)	139 (90.3)	416 (90.6)
Per-protocol Population[d]	125 (82.2)	130 (85.0)	130 (84.4)	385 (83.9)

M = melphalan; p = placebo; P = prednisone; R = lenalidomide.
[a] The intent-to-treat population includes all randomized subjects.
[b] The safety population includes all subjects who took at least 1 dose of study drug.
[c] The efficacy-evaluable population includes all randomized subjects who have met eligibility criteria, had measurable disease at baseline, received at least 1 dose of the study drug, and had at least 1 valid postbaseline myeloma response assessment.
[d] The per protocol population includes those subjects in the efficacy-evaluable population who had no major protocol violations.
Data cutoff date = 30 Apr 2013

The intent-to-treat (ITT) population is defined as all subjects who are randomised, independent of whether they received study treatment or not.

The safety population is defined as all randomised subjects who receive at least 1 dose of the study treatment (either lenalidomide/placebo or melphalan or prednisone).

The efficacy evaluable (EE) population is defined as ITT subjects who have met eligibility criteria, had measurable disease at baseline, received at least 1 dose of the study treatment, and had at least 1 valid post-baseline myeloma response assessment.

The per protocol (PP) population is defined as ITT subjects who have met eligibility criteria, had measurable disease at baseline, received at least 1 dose of the study treatment, had at least 1 valid post baseline myeloma response assessment, and without any major protocol violation.

Outcomes and estimation

Primary endpoint: Progression free survival (Investigator Assessment)

The updated efficacy results in terms of the primary endpoint of Progression free survival (cut-off date 30 April 2013), based on the investigator assessment, are summarised in Table 6 and Figure 3.

Table 6. Progression-free Survival Based on Investigator Assessment (ITT population) (Study MM-015)

	Statistic	MPR+R (N = 152)	MPR+p (N = 153)	MPp+p (N = 154)
Progressed/Died	n (%)	70 (46.1)	101 (66.0)	121 (78.6)
Progressed	n (%)	58 (38.2)	97 (63.4)	112 (72.7)
Died	n (%)	12 (7.9)	4 (2.6)	9 (5.8)
Censored	n (%)	82 (53.9)	52 (34.0)	33 (21.4)
PFS time (months)	Median [a]	27.4	14.3	13.1
	(95% CI) [b]	(21.25, 35.03)	(13.19, 15.69)	(12.01, 14.77)
	9 months event-free (SE) %	87.80 (2.88)	85.51 (3.09)	78.59 (3.48)
	12 months event-free (SE) %	79.27 (3.75)	69.14 (4.20)	60.19 (4.29)
	24 months event-free (SE) %	53.85 (4.99)	24.41 (4.23)	17.47 (3.44)
	36 months event-free (SE) %	38.95 (5.04)	9.92 (3.02)	5.99 (2.22)
	48 months event-free (SE) %	29.38 (4.95)	7.44 (2.73)	4.99 (2.06)

Comparison between treatment arms:	Hazard Rate Ratio HR [95% CI] [c]	Log-rank Test p-value [d]
MPR+R versus MPp+p	0.371 (0.274, 0.503)	< 0.001
MPR+R versus MPR+p	0.474 (0.347, 0.647)	< 0.001
MPR+p versus MPp+p	0.776 (0.595, 1.012)	0.059

CI = confidence interval; HR = hazard ratio; ITT = intent to treat; M = melphalan; p = placebo; P = prednisone; PFS = progression-free survival; R = lenalidomide; SE = standard error.

[a] The median is based on Kaplan-Meier estimate.

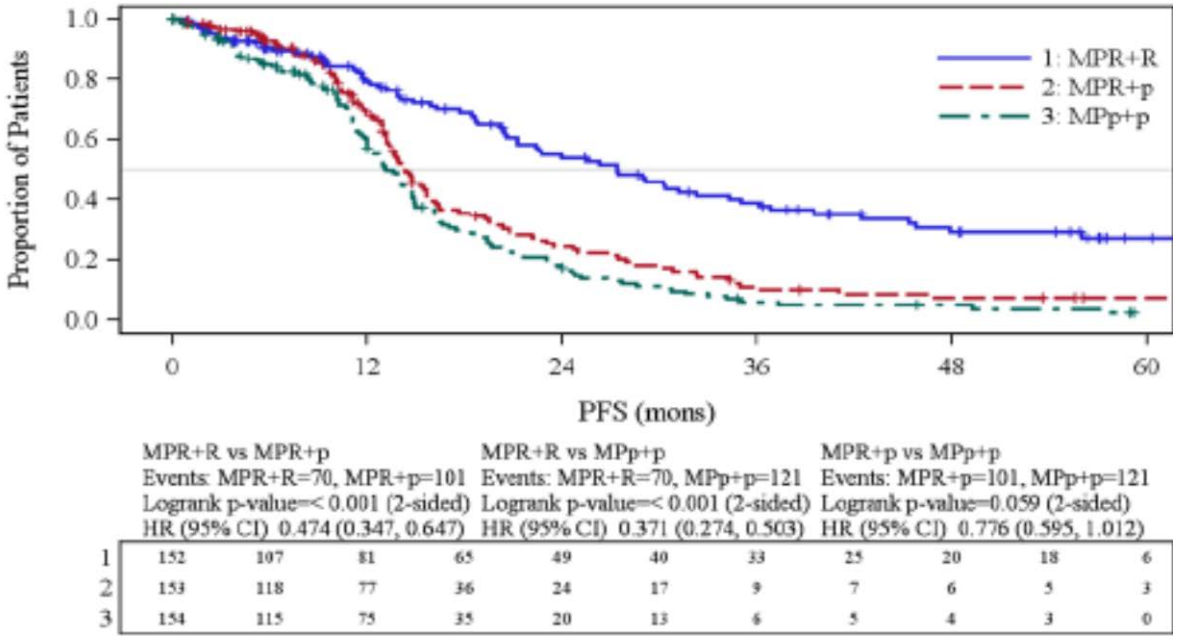
[b] 95% CIs about the median PFS time.

[c] Based on a proportional hazards model comparing the hazard functions associated with 2 treatment arms.

[d] The p-value is based on unstratified log-rank test of Kaplan-Meier curve differences between the treatment arms.

Data cutoff date = 30 Apr 2013

Figure 3. Kaplan-Meier Estimate of Progression-free Survival for All Treatment Arms (Investigator Assessment) for All Subjects (ITT Population) (Study MM-015)



Key Secondary endpoints

Progression-free Survival on Next-line Therapy (PFS2)

The efficacy results in terms of the secondary endpoint of PFS2 (cut-off date 30 April 2013) are summarised in Table 7 and Figure 4.

Table 7. Progression-free Survival on Next-line Therapy (PFS2) Based on Investigator Assessment (ITT Population)

	Statistic	MPR+R (N = 152)	MPR+p (N = 153)	MPp+p (N = 154)
PFS2 event	n (%)	97 (63.8)	109 (71.2)	121 (78.6)
3rd line therapy	n (%)	57 (37.5)	69 (45.1)	88 (57.1)
Died	n (%)	40 (26.3)	40 (26.1)	33 (21.4)
Censored	n (%)	55 (36.2)	44 (28.8)	33 (21.4)
PFS2 time (months)	Median [a]	39.7	27.8	28.8
	(95% CI) [b]	(29.24, 48.39)	(23.06, 33.13)	(24.28, 33.78)
	9 months event-free (SE) %	89.81 (2.50)	89.88 (2.48)	86.13 (2.81)
	12 months event-free (SE) %	85.63 (2.90)	85.76 (2.88)	84.12 (2.97)
	24 months event-free (SE) %	70.64 (3.82)	57.01 (4.13)	58.50 (4.04)
	36 months event-free (SE) %	52.45 (4.23)	40.00 (4.11)	40.62 (4.05)
	48 months event-free (SE) %	42.07 (4.20)	31.28 (3.91)	27.41 (3.70)
	60 months event-free (SE) %	29.27 (4.07)	23.79 (3.74)	16.94 (3.20)

Comparison between treatment arms:	Hazard Rate Ratio HR [95% CI] [c]	Log-rank Test p-value [d]
MPR+R versus MPp+p	0.701 (0.536, 0.916)	0.009
MPR+R versus MPR+p	0.773 (0.588, 1.017)	0.065
MPR+p versus MPp+p	0.916 (0.707, 1.187)	0.505

CI = confidence interval; HR = hazard ratio; ITT = intent to treat; M = melphalan; p = placebo; P = prednisone; PFS2 = progression-free survival on next-line therapy; R = lenalidomide; SE = standard error.

[a] The median is based on Kaplan-Meier estimate.

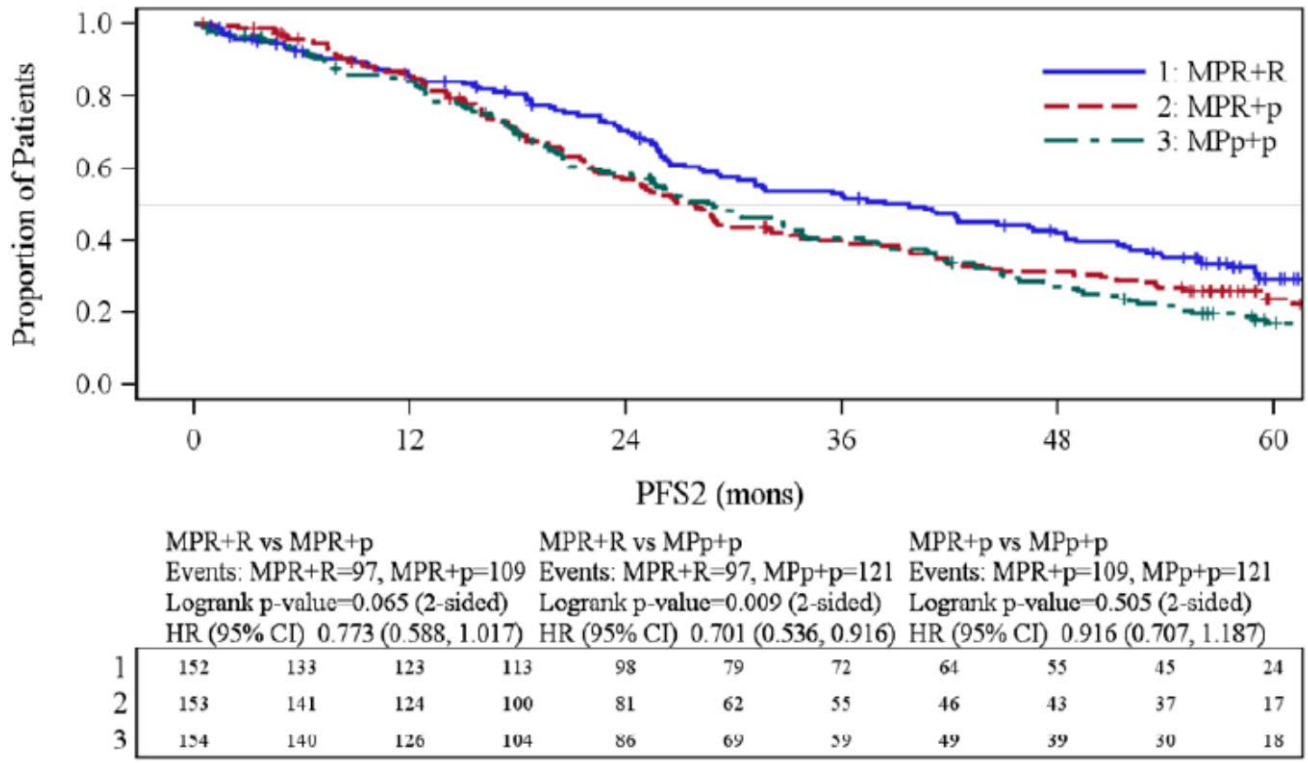
[b] 95% CIs about the median overall time to PFS2.

[c] Based on a proportional hazards model comparing the hazard functions associated with 2 treatment arms.

[d] The p-value is based on unstratified log-rank test of Kaplan-Meier curve differences between the treatment arms.

Data cutoff date = 30 Apr 2013

Figure 4. Kaplan-Meier Estimate of Progression-free Survival on Next-line Therapy Based on Investigator Assessment (ITT Population)



Overall Survival

The efficacy results in terms of the secondary endpoint of Overall survival (cut-off date 30 April 2013) are summarised in Table 8 and Figure 5.

Table 8. Overall Survival for All Subjects (ITT Population) (Study MM-015)

	Statistic	MPR+R (N = 152)	MPR+p (N = 153)	MPp+p (N = 154)
OS				
Died	n (%)	76 (50.0)	84 (54.9)	85 (55.2)
Censored	n (%)	76 (50.0)	69 (45.1)	69 (44.8)
OS time (months)	Median[a]	55.9	51.9	53.9
	[95% CI][b]	(49.11, 67.50)	(43.06, 60.63)	(47.34, 64.24)
	12 months event-free (SE) %	91.18 (2.34)	91.88 (2.25)	90.77 (2.35)
	24 months event-free (SE) %	81.94 (3.21)	74.40 (3.64)	77.97 (3.39)
	36 months event-free (SE) %	68.75 (3.92)	62.25 (4.07)	64.98 (3.92)
	48 months event-free (SE) %	59.65 (4.19)	55.01 (4.19)	57.38 (4.08)
	60 months event-free (SE) %	47.32 (4.39)	42.54 (4.28)	44.42 (4.22)

Comparison between treatment arms:	Hazard Rate Ratio HR [95% CI][c]	Log-rank Test p-value[d]	Wilcoxon p-value[e]
MPR+R versus MPp+p	0.948 (0.696, 1.292)	0.736	0.668
MPR+R versus MPR+p	0.882 (0.647, 1.203)	0.428	0.404
MPR+p versus MPp+p	1.069 (0.790, 1.445)	0.667	0.684

CI = confidence interval; HR = hazard ratio; ITT = intent to treat; M = melphalan; NE = not evaluable; OS = overall survival; p = placebo; P = prednisone; R = lenalidomide; SE = standard error.

[a] The median is based on Kaplan-Meier estimate.

[b] 95% CIs about the median OS time.

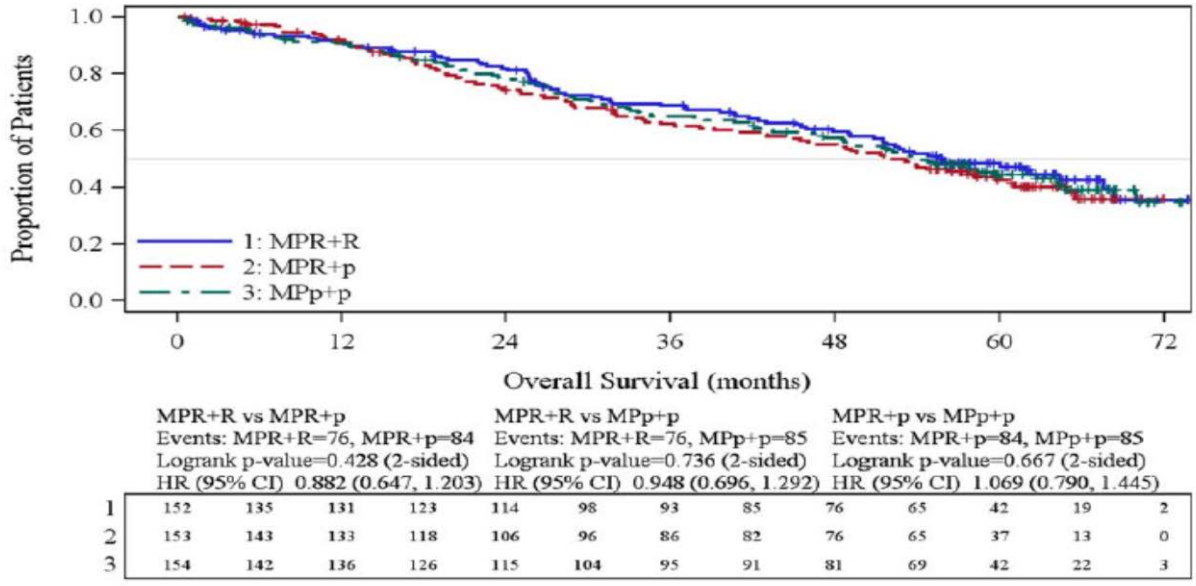
[c] Based on a proportional hazards model comparing the hazard functions associated with the indicated treatment arms.

[d] The p-value is based on the unstratified log-rank test of the Kaplan-Meier curve differences between the indicated treatment arms.

[e] The p-value is based on the differences between the indicated treatment arms.

Data cutoff date = 30 Apr 2013

Figure 5. Kaplan-Meier Estimate of Overall Survival for All 3 Treatment (ITT Population) (Study MM-015)



CI = confidence interval; HR = hazard ratio; ITT = intent to treat; M = melphalan; OS = overall survival; p = placebo; P = prednisone; R = lenalidomide.

Data cutoff date = 30 Apr 2013

Response Rates

Table 9. Myeloma Response Rates During the Treatment Period Based on Best Response Assessments by Investigators (ITT Population) (Study MM-015)

	MPR+R (N = 152) n (%)	MPR+p (N = 153) n (%)	MPp+p (N = 154) n (%)
Response			
CR or PR	120 (78.9)	116 (75.8)	84 (54.5)
Best Overall Response[a]			
Complete Response (CR)	30 (19.7)	17 (11.1)	9 (5.8)
Partial Response (PR)	90 (59.2)	99 (64.7)	75 (48.7)
Stable Disease (SD)	24 (15.8)	31 (20.3)	63 (40.9)
Progressive Disease (PD)	0	2 (1.3)	0
Response Not Evaluable (NE)[b]	8 (5.3)	4 (2.6)	7 (4.5)
Dichotomized response			
CR or PR	120 (78.9)	116 (75.8)	84 (54.5)
SD, PD, or NE	32 (21.1)	37 (24.2)	70 (45.5)

	Dichotomized Response	
Comparison between treatment arms:	**p-value** [c]	**Odds Ratio [95% CI]**
MPR+R versus MPp+p	< 0.001	3.13 [1.89, 5.17]
MPR+R versus MPR+p	0.584	1.20 [0.70, 2.05]
MPR+p versus MPp+p	< 0.001	2.61 [1.60, 4.25]

CI = confidence interval; ITT = intent to treat; M = melphalan; NE = not evaluable; p = placebo; P = prednisone; R = lenalidomide.

[a] Response is the best assessment of response during the treatment period (induction and maintencance) of the study (for definitions of each response category, refer to Section 9.5.1.1.4).

[b] Including subjects who did not have any response assessment data, or whose only assessment was response not evaluable.

[c] Probability from Fisher Exact test for the indicated comparison between treatment arms.

Data cutoff date = 30 Apr 2013

Duration of Myeloma Response

Table 10. Myeloma Response Rates During the Treatment Period Based on Best Response Assessments by Investigators (ITT Population) (Study MM-015)

	MPR+R (N = 152) n (%)	MPR+p (N = 153) n (%)	MPp+p (N = 154) n (%)
Response			
CR or PR	120 (78.9)	116 (75.8)	84 (54.5)
Best Overall Response[a]			
Complete Response (CR)	30 (19.7)	17 (11.1)	9 (5.8)
Partial Response (PR)	90 (59.2)	99 (64.7)	75 (48.7)
Stable Disease (SD)	24 (15.8)	31 (20.3)	63 (40.9)
Progressive Disease (PD)	0	2 (1.3)	0
Response Not Evaluable (NE)[b]	8 (5.3)	4 (2.6)	7 (4.5)
Dichotomized response			
CR or PR	120 (78.9)	116 (75.8)	84 (54.5)
SD, PD, or NE	32 (21.1)	37 (24.2)	70 (45.5)

	Dichotomized Response	
Comparison between treatment arms:	**p-value** [c]	**Odds Ratio [95% CI]**
MPR+R versus MPp+p	< 0.001	3.13 [1.89, 5.17]
MPR+R versus MPR+p	0.584	1.20 [0.70, 2.05]
MPR+p versus MPp+p	< 0.001	2.61 [1.60, 4.25]

CI = confidence interval; ITT = intent to treat; M = melphalan; NE = not evaluable; p = placebo; P = prednisone; R = lenalidomide.

[a] Response is the best assessment of response during the treatment period (induction and maintencance) of the study (for definitions of each response category, refer to Section 9.5.1.1.4).

[b] Including subjects who did not have any response assessment data, or whose only assessment was response not evaluable.

[c] Probability from Fisher Exact test for the indicated comparison between treatment arms.

Data cutoff date = 30 Apr 2013

Duration of response

The median duration of response was longest in Arm MPR+R (26.5 months) compared to Arms MPR+p (12.4 months) and MPp+p (12.0 months). Among the responders, the median duration of response was notably longer in subjects treated with MPR+R compared with those treated with MPp+p ($p < 0.001$, log-rank test; HR = 0.370; 95% CI = 0.259-0.529). Based on the KM estimates, more than half (55%) of the responders in Arm MPR+R had responses lasting at least 2 years compared to 16% of subjects in Arm MPp+p. After 3 years, the estimates for a 3-year duration of response were 38% of subjects in Arm MPR+R and 7% of subjects in Arm MPp+p (data not shown).

Ancillary analyses

N/A

Supportive studies

- **Study CC-5013-MM-020**

Methods

Study CC-5013-MM-020 was a Phase III, Randomised, Open-Label, 3-Arm Study To Determine the Efficacy and Safety of Lenalidomide (Revlimid) Plus Low-Dose Dexamethasone When Given Until Progressive Disease or for 18 Four-Week Cycles *Versus* the Combination of Melphalan, Prednisone, and Thalidomide Given for 12 Six-Week Cycles in Subjects with Previously Untreated Multiple Myeloma Who Are Either 65 Years of Age or Older or Not Candidates for Stem Cell Transplantation.

Study Participants

The study included ≥65-year-old patients (or, if younger than 65 years of age, not eligible for SCT) with newly diagnosed, symptomatic and measurable (by protein electrophoresis analyses) multiple myeloma. All the 3 following diagnostic criteria were required for MM: monoclonal plasma cells in the bone marrow ≥ 10% and/or presence of a biopsy proven plasmacytoma, monoclonal protein present in the serum and/or urine, myeloma-related organ dysfunction ECOG performance status had to be 0, 1, or 2.

Subjects with previous treatment with AMT, prior history of malignancies other than MM (unless the patient had been free of the disease for ≥ 3 years) and/or the following laboratory abnormalities were excluded: absolute neutrophil count (ANC) <1.0 x 109/L; platelet count < 50 x 109/L; serum SGOT/AST or SGPT/ALT > 3.0 x upper limit of normal (ULN); renal failure requiring dialysis; peripheral neuropathy >grade 2; severe co-morbidity.

Treatments

Eligible patients were randomised (1:1:1) to 1 of 3 treatment arms:

- Arm Rd, Revlimid (R 25 mg PO QD on Days 1 to 21) + dexamethasone (d 40 mg PO QD on Days 1, 8, 15, and 22) given in 28-day cycles until documentation of PD;
- Arm Rd18, Revlimid (Rd 25 mg PO QD on Days 1 to 21) + dexamethasone (d 40 mg PO QD on Days 1, 8, 15, and 22) given in 28-day cycles for up to 18 cycles;
- Arm MPT, Melphalan (0.25 mg/kg PO QD) + Prednisone (2 mg/kg PO QD on Days 1-4) + Thalidomide (200 mg PO QD on Days 1-42) given in 42-day cycles for up to 12 cycles until PD or intolerable toxicity.

Initial dose and regimen for Rd and Rd18 were adjusted according to age and renal function: patients >75 years received a dexamethasone dose of 20 mg once daily on Days 1, 8, 15, and 22 of each 28-day cycle. The initial dose of melphalan and thalidomide was adjusted according to age (patients >75 years received a reduced starting dose). The initial dose of melphalan also was adjusted for bone marrow reserve and renal function; patients with reduced absolute neutrophil count and/or, platelet count received a reduced starting dose of melphalan.

Patients received prophylactic anticoagulation during the study.

Objectives

The primary objective of the study was to compare the efficacy of Rd given until PD to that of MPT given for twelve 42-day cycles. The secondary objectives were to compare the efficacy of Rd given for eighteen 28-day cycles (Rd18) to that of MPT given for twelve 42-day cycles, to assess the safety of Rd *versus* that of MPT and to assess the safety and efficacy of Rd therapy given until PD *versus* the safety and efficacy of Rd given for eighteen 28-day cycles.

Outcomes / endpoints

The primary study endpoint was Progression-free survival (PFS), defined as the time from randomisation to the first documentation of disease progression based on the IMWG criteria or death, due to any cause, during the study up to the end of the PFS follow-up phase.

Secondary endpoints included: Overall survival (OS), defined as time from randomisation to death due to any cause (final analysis to be performed when all patients had been followed for at least 5 years from randomisation or lost to follow-up); Myeloma response rate (CR, VGPR, PR, and overall response using IMWG criteria); Duration of response, measured from time of initial response to confirmed disease progression using the IMWG criteria; Time to response, defined as time from randomisation to the first documented objective response; Safety (adverse events [type, frequency, and severity of AEs, and relationship of AEs to study drug], laboratory abnormalities, and hospitalisations); Time to treatment failure, defined as a composite endpoint measuring time from randomisation to discontinuation of study treatment for any reason (including disease progression, treatment toxicity, start of another antimyeloma treatment, and death); Time to second-line antimyeloma treatment, defined as the time from randomisation to the first day the patient received the first salvage (second-line) antimyeloma treatment; Best response achieved to second-line antimyeloma treatment; Relationship of cytogenetic findings in the malignant myeloma clone at baseline to clinical outcomes; Quality of life (EORTC QLQ-C30, QLQ-MY20 module, and the descriptive system of the EQ-5D; Pharmaco-economic/clinical benefit including hospitalisation; Improvement in CRAB criteria; Progression-free survival on next-line therapy (PFS2), after Amendment no.3, defined as the time from randomisation to second objective PD, start of third-line therapy, or death from any cause, whichever occurred first.

Sample size

The primary analysis for the study was to compare PFS between Arm Rd and Arm MPT. An improvement in median PFS of 25%, e.g., from 24 months for Arm MPT to 30 months for Arm Rd, was considered clinically relevant. Therefore a total of approximately 1590 patients (530 in each arm) were enrolled, with accrual of about 67 patients per month for 24 months. With a 24-month accrual period and 36-month follow-up after the study closed to accrual, 530 patients in each treatment arm would have 80% power to detect a hazard rate ratio of 1.25 using a 2-sided log-rank test with overall significance level of 0.05 and significance level of 0.049 for the final analysis (adjusted for one interim analysis).

Randomisation

Patients were randomised (1:1:1) to 1 of 3 treatment arms: Treatment Arm A (Rd), Treatment Arm B (Rd18) and Treatment Arm C (MPT). Patients were stratified at randomisation by age (≤ 75 vs > 75 years), stage according to the International Staging System (Stages I or II vs Stage III), and country.

Blinding (masking)

This was an open-label study.

Statistical methods

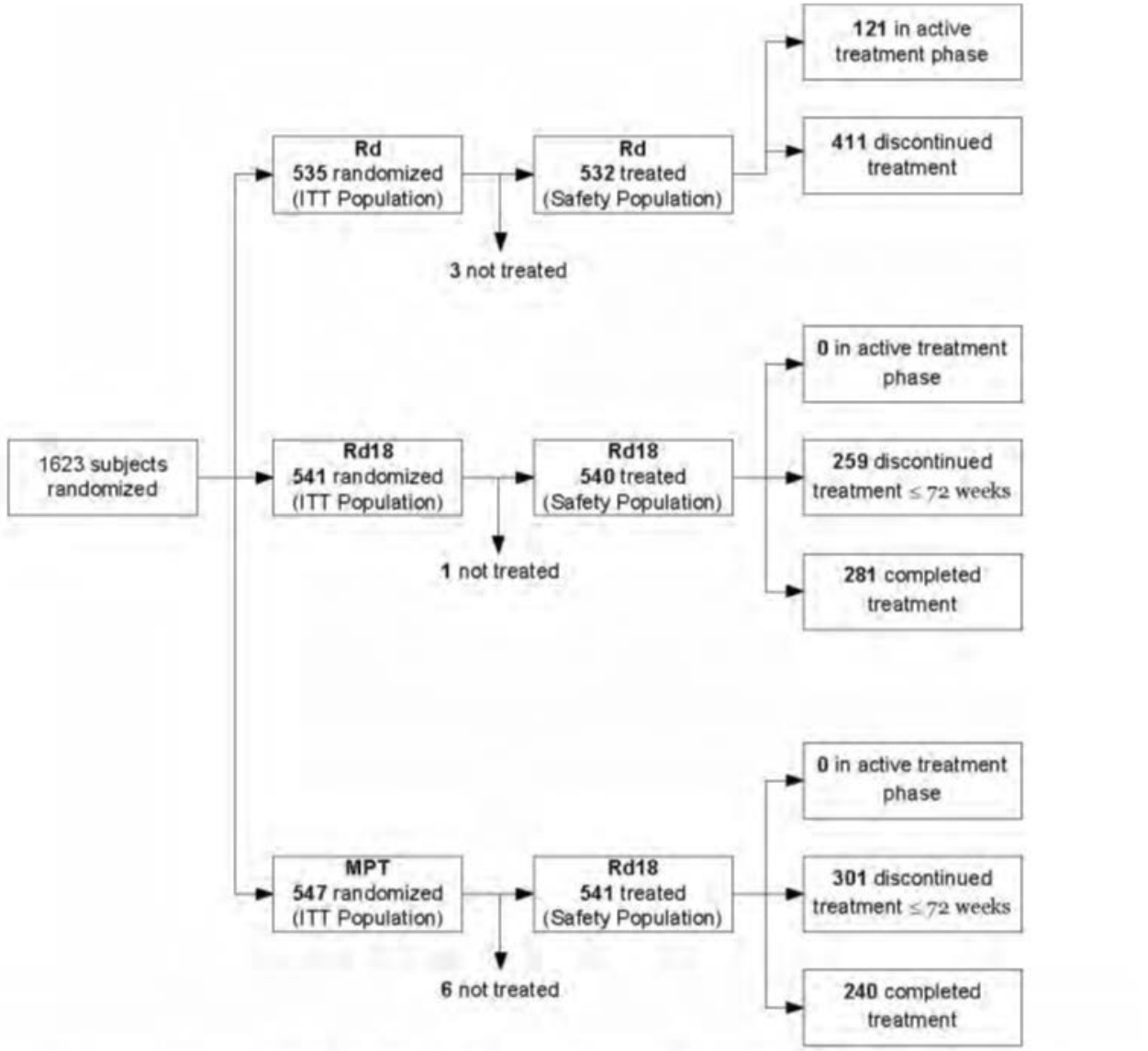
The intent-to-treat (ITT) population was used for the primary efficacy analysis. For the efficacy analysis of all endpoints, the primary comparison was between Rd and MPT, and the secondary comparisons were between Rd and Rd18, and between Rd18 and MPT. Also as a secondary analysis, Rd and Rd18 were combined and compared with MPT on the efficacy endpoints. The sample size and power calculation were based on the primary comparison, Rd *versus* MPT, for the primary endpoint, PFS. The Kaplan-Meier (KM) method was used to estimate the survival distribution functions for each treatment arm. The median PFS along with the 2-sided 95% confidence interval (CI) for the median was estimated. In addition, the event rates at specific time points (e.g., 26, 52, 78, and 104 weeks) were computed, along with the standard errors (Greenwood's formula [Klein, 2003]). The plots of survival curves using the KM method were presented. A Cox proportional hazards model was used to estimate hazard rate (risk) ratio along with 95% CIs.

For the primary analysis, the comparison of PFS between Rd and MPT using unstratified log-rank test, the overall 2-sided significance level was 5%. This 5% was spread over two analyses (one interim analysis and one final analysis) by an O' Brien-Fleming alpha spending function (DeMets, 1994). The significance of efficacy was claimed if the p-value was less than or equal to the significance level as calculated based on the specified alpha spending function and the observed number of events. To account for the stratified randomisation, a log-rank test stratified by the 3 strata used in the randomisation was performed as a secondary analysis for PFS, in addition to the unstratified analysis described above.

Exploratory analysis, based on a Cox proportional hazards model, were conducted for PFS and OS in order to assess the demographic and prognostic factors that most affected treatment outcome, and to adjust the treatment comparisons for these variables. A preliminary univariate Cox regression analysis was used to select the subset of relevant factors for inclusion in a multivariate model. Individual variables significant at the p = 0.20 level in the univariate model were selected for multivariate analysis. The variables to be evaluated included age, sex, baseline ISS score, baseline ECOG performance status, and other relevant baseline characteristics such as cytogenetic abnormalities. Subsequently, corresponding subgroup analyses may be performed for PFS and OS. Logistic regression may be used in an exploratory manner (in a way as described above for time to-event variables) to assess the effects of risk factors on response rates.

Results

Participant flow



d = low-dose dexamethasone; ITT = intent-to-treat; M = melphalan; P = prednisone; R = lenalidomide; T = thalidomide

Recruitment

The first patient was randomised on 29 Aug 2008, and the last patient was randomised on 10 Mar 2011. Subjects were enrolled from 246 sites: 165 in Europe, 23 in Asia, 39 in North America and 19 in the Pacific.

Conduct of the study

The protocol was amended 4 times. The major changes are described below:

Amendment No. 3 introduced in the protocol systematic, prospective collection of data of PD after second-line (PFS2: Progression-free Survival on next-line therapy). It also required that SPMs be treated as SAEs and

reported throughout the study duration from the time of signing the ICD to the time all patients were followed for at least 5 years from randomization or had died

Amendment No. 4 included mandatory submission of samples and corresponding reports from screening and the SPM diagnosis for patients who developed haematologic SPMs (including AML, ALL, CLL, MDS, or myeloproliferative disorders). For these haematologic SPMs, samples and reports were to be sent to an independent central reviewer for confirmation. It also included optional collection of additional samples for exploratory biomarker studies. The purpose of the optional sample collection was to assess the mechanism of action of lenalidomide, to perform exploratory analyses to identify possible markers that correlate with response to lenalidomide, and additional studies to identify genetic aberrations possibly related to the development of SPMs in patients treated with lenalidomide.

Protocol violations of the study are shown in Table 11.

Table 11. Summary of Protocol Violations; ITT Population (Study MM-020)

Statistics	Rd (N=535) n (%)	Rd18 (N=541) n (%)	MPT (N=547) n (%)	Total (N=1623) n (%)
Number of subjects with at least one protocol violation	168 (31.4)	169 (31.2)	209 (38.2)	546 (33.6)
Entered study but subject did not satisfy entry criteria	10 (1.9)	10 (1.8)	16 (2.9)	36 (2.2)
Informed Consent, ie, failure to obtain informed consent (no documentary evidence) or obtaining consent after study procedures have been performed	2 (0.4)	0 (0.0)	2 (0.4)	4 (0.2)
Eligibility and Entry Criteria, ie, subject enrolled violates inclusion/exclusion criteria	9 (1.7)	10 (1.8)	14 (2.6)	33 (2.0)
Developed study drug withdrawal criteria but were not withdrawn from treatment	15 (2.8)	14 (2.6)	3 (0.5)	32 (2.0)
Developed disease progression, not withdrawn	15 (2.8)	14 (2.6)	3 (0.5)	32 (2.0)
Received wrong treatment or incorrect dose	52 (9.7)	50 (9.2)	106 (19.4)	208 (12.8)
Missed one or more doses for reasons outside of per protocol dose modification rules	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.1)
Received the incorrect dose at any time for any reason	31 (5.8)	20 (3.7)	37 (6.8)	88 (5.4)
Received a treatment other than the drug they were randomized to receive for more than one cycle	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.1)
Dispensed and/or dosed with incorrect supply of study medication	0 (0.0)	1 (0.2)	12 (2.2)	13 (0.8)
Began study medication cycle despite DLT	25 (4.7)	30 (5.5)	71 (13.0)	126 (7.8)
Rest period following drug dosing too short	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.1)
Received an excluded concomitant medication and/or therapy	7 (1.3)	8 (1.5)	15 (2.7)	30 (1.8)
Subject received prohibited concomitant medication/treatment	7 (1.3)	8 (1.5)	15 (2.7)	30 (1.8)
Missing visit or assessment	43 (8.0)	32 (5.9)	43 (7.9)	118 (7.3)
Missing safety assessment	25 (4.7)	16 (3.0)	31 (5.7)	72 (4.4)
Missing efficacy assessment	16 (3.0)	14 (2.6)	9 (1.6)	39 (2.4)
Visit not done	4 (0.7)	1 (0.2)	3 (0.5)	8 (0.5)
Visit Schedule Criteria	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.1)
Efficacy Criteria	4 (0.7)	0 (0.0)	0 (0.0)	4 (0.2)
Out of window visit or assessment	2 (0.4)	5 (0.9)	2 (0.4)	9 (0.6)
Visit Schedule Criteria	1 (0.2)	1 (0.2)	1 (0.2)	3 (0.2)
Efficacy Criteria	1 (0.2)	3 (0.6)	0 (0.0)	4 (0.2)
Safety Criteria	0 (0.0)	1 (0.2)	1 (0.2)	2 (0.1)
Other	67 (12.5)	87 (16.1)	71 (13.0)	225 (13.9)
Deliberate and/or routinely repeated non-compliance with the protocol, GCP or regulations by study personnel	3 (0.6)	5 (0.9)	5 (0.9)	13 (0.8)
Missing source documentation or significant source verification shows source does not match clinical data entered into eCRF	3 (0.6)	2 (0.4)	2 (0.4)	7 (0.4)
Failure to report serious adverse events or SUSARs in accordance with regulations	26 (4.9)	39 (7.2)	33 (6.0)	98 (6.0)
Delayed signatures on revised / current version of informed consent form	8 (1.5)	11 (2.0)	7 (1.3)	26 (1.6)
Lenalidomide/thalidomide documents signed late or documents not completed and/or signed	0 (0.0)	1 (0.2)	1 (0.2)	2 (0.1)
Antithrombotic medication not prescribed/taken	23 (4.3)	29 (5.4)	26 (4.8)	78 (4.8)
Incorrect version of Informed Consent Form used	5 (0.9)	1 (0.2)	0 (0.0)	6 (0.4)
Optional assessments issue	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.1)
Other Informed Consent issues	1 (0.2)	4 (0.7)	1 (0.2)	6 (0.4)

d = low-dose dexamethasone; DLT = dose-limiting toxicity; eCRF = electronic case report form; GCP = Good Clinical Practices; ITT = intent-to-treat; M = melphalan; P = prednisone; R = lenalidomide; SD = standard deviation; SUSAR = Suspected Unexpected Serious Adverse Reaction T = thalidomide.
Data cutoff date = 24 May 2013.

Baseline data

Baseline demographic characteristics and disease characteristics are summarised in Table 12 and Table 13.

Table 12. Demographic and Baseline characteristics; ITT Population (Study MM-020)

Trial:	Study MM-020		
Trial Start (First Subject Randomized):	29 Aug 2008		
Age (years):	≥ 65 years[a]		
Treatment Arm:	Rd	Rd18	MPT
Number of Subjects:	535	541	547
Demographic and Baseline Characteristics			
ECOG PS ≥ 2 (%)	22.6	21.3	20.7
Age > 75 years (%)	34.8	35.7	34.4
ISS Stage III in IVRS (%)	42.1	41.1	42.8
Creatinine clearance < 60 mL/min in IVRS (%)	49.9	47.0	47.2
β2-microglobulin > 5.5 mg/L (%)	41.9	41.4	42.8
Albumin ≤ 35 g/L (%)	35.9	38.6	40.8

β2= beta2; ECOG = Eastern Cooperative Oncology Group; ISS = International Staging System; ITT = intent to treat; IVRS = Interactive Voice Response System; R = lenalidomide; Rd = Rd given until documentation of PD; Rd18 = Rd given for 18 four-week cycles; T = thalidomide.

a. Subjects < 65 years could be included if they either refused to undergo SCT or were otherwise not eligible for SCT.

Table 13. Disease Characteristics at Baseline; ITT Population (Study MM-020)

Characteristic	Rd (N = 535) n (%)	Rd18 (N = 541) n (%)	MPT (N = 547) n (%)	Total (N = 1623) n (%)
BMA/BMB from Screening				
BMA/BMB Sample Adequate[b]	534 (99.8)	540 (99.8)	543 (99.3)	1617 (99.6)
BMA Adequate	514 (96.1)	516 (95.4)	521 (95.2)	1551 (95.6)
BMB Adequate	167 (31.2)	180 (33.3)	175 (32.0)	522 (32.2)
BMA/BMB Sample Not Adequate[c]	1 (0.2)	1 (0.2)	4 (0.7)	6 (0.4)
Prior EMP				
Yes	24 (4.5)	38 (7.0)	28 (5.1)	90 (5.5)
No	511 (95.5)	503 (93.0)	519 (94.9)	1533 (94.5)
History of Bone Lesion				
Yes	380 (71.0)	382 (70.6)	394 (72.0)	1156 (71.2)
No	154 (28.8)	158 (29.2)	153 (28.0)	465 (28.7)
Unknown	1 (0.2)	1 (0.2)	0 (0.0)	2 (0.1)
Prior Radiation for MM[d]				
Yes	71 (13.3)	73 (13.5)	75 (13.7)	219 (13.5)
No	464 (86.7)	467 (86.3)	472 (86.3)	1403 (86.4)
Unknown	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.1)
ECOG Performance Status				
Grade 0	155 (29.0)	163 (30.1)	156 (28.5)	474 (29.2)
Grade 1	257 (48.0)	263 (48.6)	275 (50.3)	795 (49.0)
Grade 2	119 (22.2)	113 (20.9)	111 (20.3)	343 (21.1)
Grade ≥ 3	2 (0.4)	2 (0.4)	2 (0.4)	6 (0.4)
Missing	2 (0.4)	0 (0.0)	3 (0.5)	5 (0.3)
Cytogenetic Risk[e]				
Adverse risk	170 (31.8)	185 (34.2)	189 (34.6)	544 (33.5)
Non-Adverse Risk	298 (55.7)	290 (53.6)	283 (51.7)	871 (53.7)
Favorable Hyperdiploidy	112 (20.9)	103 (19.0)	102 (18.6)	317 (19.5)
Normal	148 (27.7)	131 (24.2)	141 (25.8)	420 (25.9)
Uncertain Risk	38 (7.1)	56 (10.4)	40 (7.3)	134 (8.3)
Not Evaluable	34 (6.4)	35 (6.5)	44 (8.0)	113 (7.0)
Missing	33 (6.2)	31 (5.7)	31 (5.7)	95 (5.9)
Characteristic	**Rd (N = 535) n (%)**	**Rd18 (N = 541) n (%)**	**MPT (N = 547) n (%)**	**Total (N = 1623) n (%)**
β2-microglobulin				
> 5.5 mg/L	224 (41.9)	224 (41.4)	234 (42.8)	682 (42.0)
≤ 5.5 mg/L	309 (57.8)	316 (58.4)	312 (57.0)	937 (57.7)
Missing	2 (0.4)	1 (0.2)	1 (0.2)	4 (0.2)
Albumin				
≤ 35 g/L	192 (35.9)	209 (38.6)	223 (40.8)	624 (38.4)
> 35 g/L	343 (64.1)	331 (61.2)	324 (59.2)	998 (61.5)

Characteristic	Rd (N = 535) n (%)	Rd18 (N = 541) n (%)	MPT (N = 547) n (%)	Total (N = 1623) n (%)
Missing	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.1)
Lactic Dehydrogenase				
< 200 U/L	448 (83.7)	442 (81.7)	434 (79.3)	1324 (81.6)
≥ 200 U/L	86 (16.1)	99 (18.3)	112 (20.5)	297 (18.3)
Missing	1 (0.2)	0 (0.0)	1 (0.2)	2 (0.1)
MM Subtype				
IgA	138 (25.8)	142 (26.2)	123 (22.5)	403 (24.8)
IgA and IgG	7 (1.3)	6 (1.1)	8 (1.5)	21 (1.3)
IgA and IgM	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.1)
IgD	4 (0.7)	7 (1.3)	4 (0.7)	15 (0.9)
IgG	334 (62.4)	331 (61.2)	350 (64.0)	1015 (62.5)
IgM	3 (0.6)	1 (0.2)	1 (0.2)	5 (0.3)
Not available (includes light-chain disease)	49 (9.2)	54 (10.0)	60 (11.0)	163 (10.0)

BMA = bone marrow aspirate; BMB = bone marrow biopsy; d = low-dose dexamethasone; ECOG = Eastern Cooperative Oncology Group; EMP = extramedullary plasmacytoma; Ig = immunoglobulin; ISS = International Staging System; ITT = Intent-to-treat; IVRS = interactive voice response system; M = melphalan; MM = multiple myeloma; P = prednisone; R = lenalidomide; T = thalidomide.

[a] ISS Stage and Renal Inefficiency categories are from IVRS. Subjects were stratified at randomization by stage (Stage I or II versus Stage III).

[b] Subjects with BMA adequate sample and/or BMB adequate sample.

[c] Four subjects with inadequate BMA/BMB samples had EMP tests. .

[d] Prior radiation for MM is from PRIORTX page.

[e] Cytogenetic risk categories are mutually exclusive. Definitions: **Adverse risk** category: t(4;14), t(14;16), del(13q) or monosomy 13, del(17p), 1q gain; **Non-adverse risk** categories include favorable hyperdiploidy: t(11;14), gains of 5/9/15; normal: a normal result, gains other than 5/9/15, IgH deletion; and uncertain risk: probes used for analysis cannot place subject in any of the other risk categories. Not evaluable: no specimen received, test failure, or insufficient number of cells available for analysis.

Note: BMA, BMB, EMP, and bone lesion before or on randomization date.

Data cutoff date = 24 May 2013.

Numbers analysed

The intent-to-treat (ITT) population is defined as all subjects who are randomised, independent of whether they received study treatment or not.

The safety population is defined as all randomised subjects who receive at least one dose of the study treatment (either lenalidomide or dexamethasone or melphalan or prednisone or thalidomide).

The efficacy-evaluable (EE) population is defined as ITT subjects who meet protocol requirements (meets eligibility criteria and/or have measurable disease at baseline) and are evaluated after receiving at least one dose of study treatment.

The number of patients included in the ITT, EE and safety populations is summarised in Table 14.

Table 14. Analysis Set (Study MM-020)

Analysis Set	Rd n (%)	Rd18 n (%)	MPT n (%)	Total n (%)
Intent-to-treat Population[a]	535 (100.0)	541 (100.0)	547 (100.0)	1623 (100.0)
Safety Population[b]	532 (99.4)	540 (99.8)	541 (98.9)	1613 (99.4)
Efficacy-evaluable Population[c]	508 (95.0)	521 (96.3)	506 (92.5)	1535 (94.6)

d = low-dose dexamethasone; M = melphalan; P = prednisone; R = lenalidomide; T = thalidomide.

Outcomes and estimation

Primary objective: Progression free survival

The efficacy results in terms of the primary endpoint of Progression free survival are summarised in Table 15 and Figure 6.

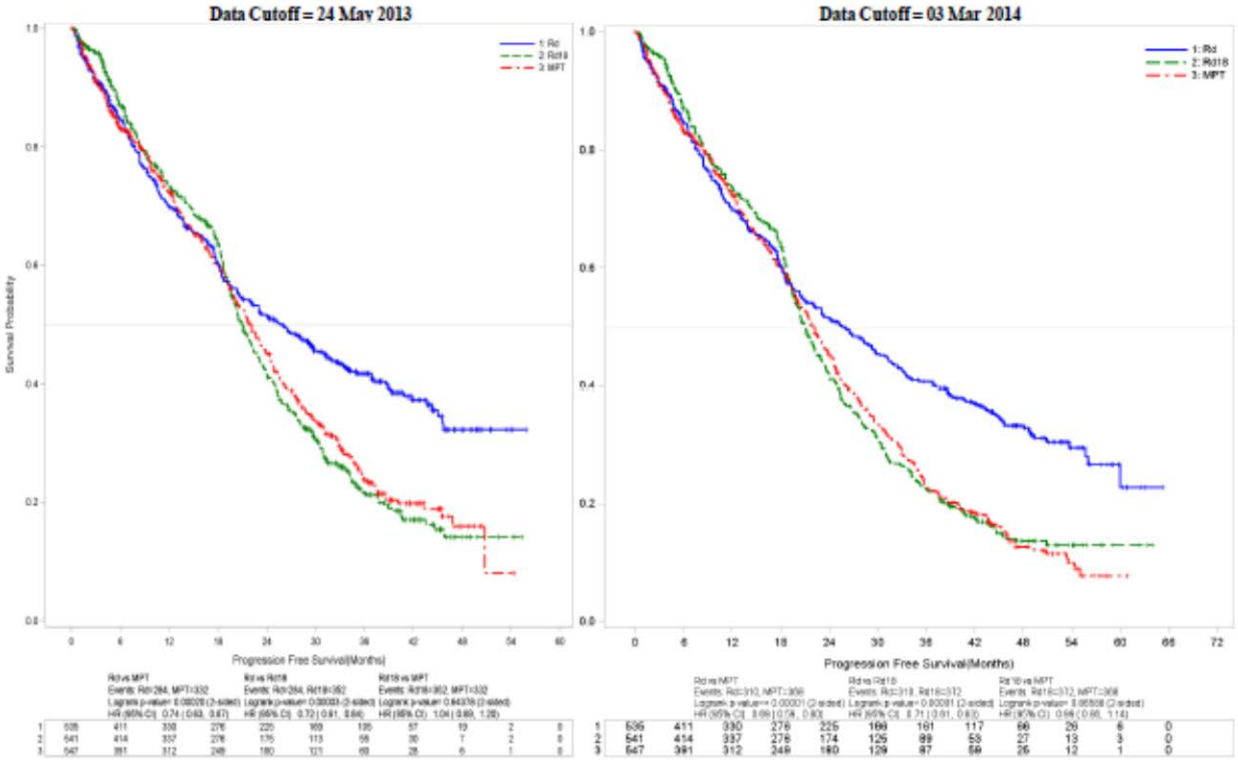
Table 15. Progression-free Survival (Investigator Assessment) Using Protocol-defined Censoring Rules as of the 24 May 2013 and 03 Mar 2014 Data Cutoff Dates –Study MM-020 (ITT Population)

	Data Cutoff of 24 May 2013			Data Cutoff of 03 Mar 2014		
	Rd (N = 535)	Rd18 (N = 541)	MPT (N = 547)	Rd (N = 535)	Rd18 (N = 541)	MPT (N = 547)
PFS Events, n (%)						
Censored	251 (46.9)	189 (34.9)	215 (39.3)	225 (42.1)	169 (31.2)	179 (32.7)
Progressed	231 (43.2)	312 (57.7)	282 (51.6)	251 (46.9)	332 (61.4)	317 (58.0)
Died[a]	53 (9.9)	40 (7.4)	50 (9.1)	59 (11.0)	40 (7.4)	51 (9.3)
PFS Time (months)						
Median[b]	26.0	21.0	21.9	26.0	21.0	21.9
(95% CI)[c]	(20.7, 30.1)	(19.7, 22.4)	(19.8, 23.9)	(20.7, 29.7)	(19.7, 22.4)	(19.8, 23.9)
Event-free						
24 months (SE) %	51.41 (2.30)	41.43 (2.34)	45.16 (2.40)	51.41 (2.30)	41.41 (2.35)	45.16 (2.40)
36 months (SE) %	41.65 (2.38)	21.57 (2.13)	23.62 (2.25)	40.80 (2.32)	22.55 (2.04)	23.10 (2.11)
48 months (SE) %	32.24 (3.05)	14.08 (2.37)	15.98 (2.74)	33.26 (2.37)	13.62 (1.85)	12.66 (1.84)
Comparison	**Rd vs MPT**	**Rd vs Rd18**	**Rd18 vs MPT**	**Rd vs MPT**	**Rd vs Rd18**	**Rd18 vs MPT**
HR (95% CI)[d]	0.74 (0.63, 0.87)	0.72 (0.61, 0.84)	1.04 (0.89, 1.20)	0.69 (0.59, 0.80)	0.71 (0.61, 0.83)	0.99 (0.86, 1.14)
Log-rank Test, p-value[e]	< 0.001	< 0.001	0.644	< 0.001	< 0.001	0.866

CI = confidence interval; d = low-dose dexamethasone; HR = hazard ratio; ITT = intent to treat; M = melphalan; NE = not estimable; P = prednisone; PFS = progression-free survival; R = lenalidomide; Rd = Rd given until documentation of progressive disease; Rd18 = Rd given for ≤ 18 four-week cycles; SE = standard error; T = thalidomide; vs = versus.

[a] Includes subjects who died on study (ie, during active treatment and PFS follow-up phases).
[b] The median is based on the Kaplan-Meier estimate.
[c] 95% confidence interval about the median PFS time.
[d] Based on Cox proportional hazards model comparing the hazard functions associated with the indicated treatment groups.
[e] The p-value is based on the unstratified log-rank test.

Figure 6. Progression-free Survival (Investigator Assessment) Using Protocol-defined Censoring Rules as of the 24 May 2013 and 03 Mar 2014 Data Cut-off Dates – Study MM-020 (ITT Population)



Key secondary endpoints

Results of OS are reported in Table 16 and Figure 7.

Table 16. Overall Survival as of the 24 May 2013 and 03 Mar 2014 Data Cut-off Dates - Study MM-020 (ITT Population)

	Data Cutoff of 24 May 2013			Data Cutoff of 03 Mar 2014		
	Rd (N = 535)	Rd18 (N = 541)	MPT (N = 547)	Rd (N = 535)	Rd18 (N = 541)	MPT (N = 547)
OS Events, n (%)						
Censored	362 (67.7)	349 (64.5)	338 (61.8)	327 (61.1)	313 (57.9)	286 (52.3)
Died	173 (32.3)	192 (35.5)	209 (38.2)	208 (38.9)	228 (42.1)	261 (47.7)
OS Time (months)						
Median[a]	55.1	53.6	48.2	58.9	56.7	48.5
(95% CI)[b]	(55.1, NE)	(47.0, NE)	(44.3, NE)	(56.0, NE)	(50.1, NE)	(44.2, 52.0)
Event-free						
24 months (SE) %	79.62 (1.77)	76.12 (1.86)	72.99 (1.94)	79.62 (1.77)	76.12 (1.86)	72.99 (1.94)
36 months (SE) %	69.94 (2.09)	65.62 (2.17)	62.44 (2.20)	70.09 (2.03)	66.30 (2.07)	62.15 (2.13)
48 months (SE) %	59.39 (2.81)	55.74 (3.00)	51.40 (3.13)	60.05 (2.28)	56.78 (2.33)	50.93 (2.35)
Comparison	**Rd vs MPT**	**Rd vs Rd18**	**Rd18 vs MPT**	**Rd vs MPT**	**Rd vs Rd18**	**Rd18 vs MPT**
HR (95% CI)[c]	0.78 (0.64, 0.96)	0.90 (0.73, 1.10)	0.88 (0.72, 1.07)	0.75 (0.62, 0.90)	0.91 (0.75, 1.09)	0.83 (0.69, 0.99)
Log-rank Test, p-value[d]	0.017	0.307	0.184	0.002	0.305	0.034

CI = confidence interval; d = low-dose dexamethasone; HR = hazard ratio; ITT = intent to treat; M = melphalan; NE = not estimable; P = prednisone; OS = overall survival; R = lenalidomide; Rd = Rd given until documentation of PD; Rd18 = Rd given for ≤ 18 four-week cycles; SE = standard error; T = thalidomide; vs = versus.

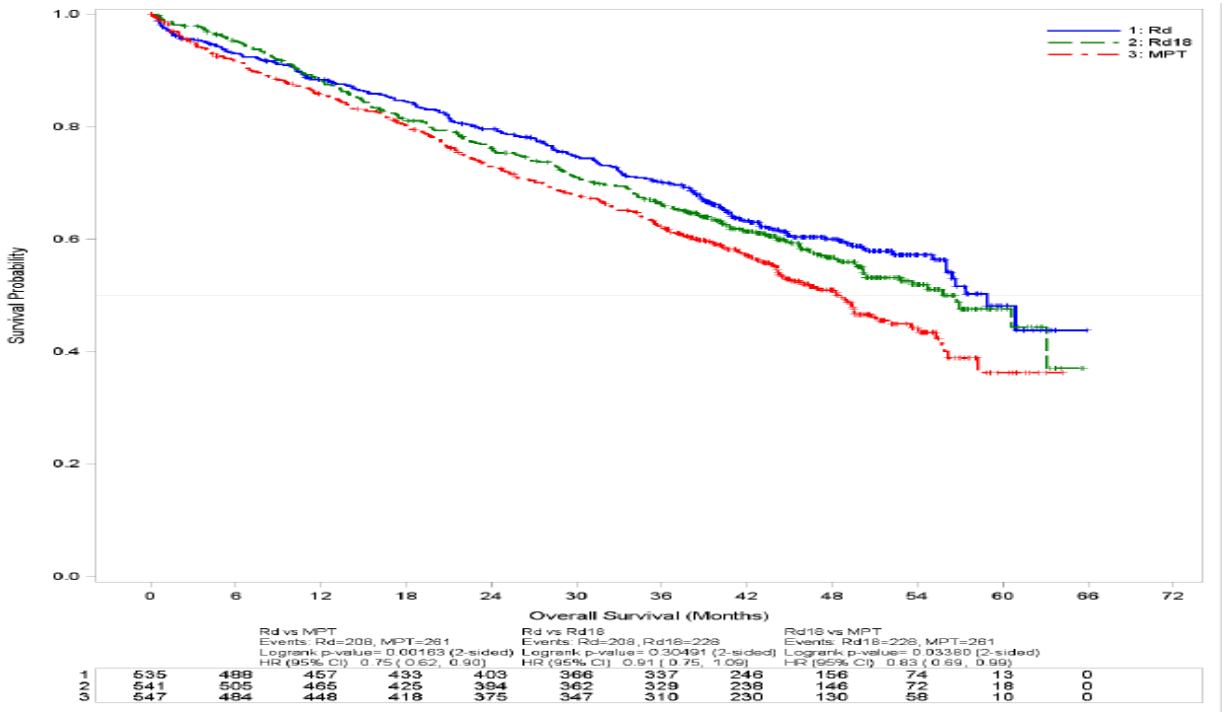
[a] The median is based on the Kaplan-Meier estimate (based on follow-up and censoring, medians are only nominal at this point).

[b] 95% confidence interval about the median OS time.

[c] Based on Cox proportional hazards model comparing the hazard functions associated with the indicated treatment groups.

[d] The p-value is based on the unstratified log-rank test.

Figure 7. Kaplan-Meier Plots of Overall Survival Between arm Rd, Rd18 and MTP; ITT Population; Cut-off date 03 Mar 2014 (Study MM-020)



Results of PFS2 are reported in Table 17.

Table 17. Progression-free Survival After Next-line Therapy (PFS2) as of the 24 May 2013 and 03 Mar 2014 Data Cut-off Dates – Study MM-020 (ITT Population)

	Data Cutoff of 24 May 2013			Data Cutoff of 03 Mar 2014		
	Rd (N = 535)	Rd18 (N = 541)	MPT (N = 547)	Rd (N = 535)	Rd18 (N = 541)	MPT (N = 547)
PFS2 Events, n (%)						
Censored	292 (54.6)	279 (51.6)	261 (47.7)	250 (46.7)	234 (43.3)	197 (36.0)
Progressed after second-line AMT[a]	72 (13.5)	74 (13.7)	82 (15.0)	106 (19.8)	120 (22.2)	133 (24.3)
Took third-line therapy[a]	45 (8.4)	60 (11.1)	63 (11.5)	37 (6.9)	52 (9.6)	62 (11.3)
Died	126 (23.6)	128 (23.7)	141 (25.8)	142 (26.5)	135 (25.0)	155 (28.3)
PFS2 Time (months)						
Median[b]	42.9	39.4	36.3	42.9	40.0	35.0
(95% CI)[c]	(38.3, 47.9)	(35.8, 44.8)	(30.4, 40.1)	(38.1, 47.4)	(36.2, 44.2)	(30.4, 37.8)
Event-free						
24 months (SE) %	73.00 (1.95)	69.86 (2.00)	64.19 (2.10)	73.58 (1.94)	70.25 (1.99)	64.57 (2.09)
36 months (SE) %	56.13 (2.28)	53.98 (2.29)	50.16 (2.26)	56.78 (2.21)	54.78 (2.19)	48.35 (2.20)
48 months (SE) %	43.67 (3.06)	39.84 (3.07)	33.13 (3.17)	45.31 (2.35)	41.91 (2.33)	33.78 (2.24)
Comparison	**Rd vs MPT**	**Rd vs Rd18**	**Rd18 vs MPT**	**Rd vs MPT**	**Rd vs Rd18**	**Rd18 vs MPT**
HR (95% CI)[d]	0.78 (0.66, 0.93)	0.92 (0.78, 1.10)	0.85 (0.72, 1.00)	0.74 (0.63, 0.86)	0.92 (0.78, 1.08)	0.80 (0.69, 0.93)
Log-rank Test, p-value[e]	0.005	0.372	0.055	< 0.001	0.316	0.004

CI = confidence interval; d = low-dose dexamethasone; HR = hazard ratio; ITT = intent to treat; M = melphalan; P = prednisone; PD = progressive disease; PFS2 = progression-free survival after next-line therapy; R = lenalidomide; Rd = Rd given until documentation of PD; Rd18 = Rd given for ≤ 18 four-week cycles; SE = standard error; T = thalidomide; vs = versus.

[a] The start of third-line therapy was used as a surrogate for second PD for subjects where second PD data were not available and/or at sites where Protocol Amendment 3 (adding systematic, prospective collection of date of PD after second-line therapy) had not been implemented until the respective data cutoff date.

[b] The median is based on the Kaplan-Meier estimate.

[c] 95% confidence interval about the median PFS2 time.

[d] Based on Cox proportional hazards model comparing the hazard functions associated with the indicated treatment groups.

[e] The p-value is based on the unstratified log-rank test.

The myeloma response results are presented in Table 18.

Table 18. Myeloma Response Rates Based on IRAC Review (ITT Population) (cut-off date 24 May 2013)

	Rd (N = 535) n (%)	Rd18 (N = 541) n (%)	MPT (N = 547) n (%)
Response[a]			
Complete Response (CR)	81 (15.1)	77 (14.2)	51 (9.3)
Very Good Partial Response (VGPR)	152 (28.4)	154 (28.5)	103 (18.8)
Partial Response (PR)	169 (31.6)	166 (30.7)	187 (34.2)
Stable Disease (SD)	101 (18.9)	111 (20.5)	145 (26.5)
Progressive Disease (PD)	7 (1.3)	12 (2.2)	19 (3.5)
Response Not Evaluable (NE)[b]	25 (4.7)	21 (3.9)	42 (7.7)
Dichotomized response			
CR or VGPR or PR	402 (75.1)	397 (73.4)	341 (62.3)
SD, PD, or NE[b]	133 (24.9)	144 (26.6)	206 (37.7)
Two consecutive negative M-protein and negative immunofixation with missing bone marrow[c]	30 (5.6)	35 (6.5)	20 (3.7)
	Dichotomized Response		
Comparison between treatment arms:	**p-value[d]**		**Odds Ratio (95% CI)**
Rd versus MPT	< 0.00001		1.83 (1.41, 2.37)
Rd versus Rd18	0.53065		1.10 (0.83, 1.44)
Rd18 versus MPT	0.00010		1.67 (1.29, 2.15)

CI = confidence interval; d = low-dose dexamethasone; IRAC = Independent Response Adjudication Committee; ITT = intent-to-treat; M = melphalan; P = prednisone; R = lenalidomide; T = thalidomide.

[a] The best response of a subject.

[b] Including subjects who did not have any response assessment data, or not evaluable.

[c] Subjects with potential CR responses; missing only bone marrow for confirmation.

[d] Probability from Fisher Exact test with normal approximation.

Median duration of Response for ITT Populations (cut-off date 24 May 2013) was 35.0 months (95% CI: 27.9, 43.4) for Rd, 22.1 (95% CI: 20.3, 24.0) for Rd18 and 22.3 (95% CI: 20.2, 24.9) for MTP (data not shown).

Summary of main studies

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 19. Summary of Efficacy for trial MM-015

Title: A Phase III, multicentre, randomised, double-blind, placebo-controlled, 3-arm parallel-group study to determine the efficacy and safety of lenalidomide (Revlimid) in combination with melphalan and prednisone *versus* placebo plus melphalan and prednisone in patients with newly diagnosed multiple myeloma who are 65 years of age or older			
Study identifier	MM-015		
Design	Phase III, multicentre, randomised, double-blind, placebo-controlled, 3-arm parallel-group		
	Duration of main phase: Duration of Extension phase:		28-day cycles (until PD) (induction+maintenance) Median follow-up 62.5 months
Hypothesis	Superiority		
Treatments groups	MPR + R		M 0.18 mg/kg and P 2 mg/kg on Days 1- 4 and R 10 mg on Days 1-21 for up to 9 28-day cycles (induction) + R 10 mg on Days 1 to 21 from cycle 10 until PD (28-day cycles); 152 patients randomised
	MPR + p		M 0.18 mg/kg and P 2 mg/kg on Days 1- 4 and R 10mg on Days 1 to 21 for up to 9 28-day cycles (induction) + Pbo on Days 1- 21 from cycle 10 until PD (28-day cycles); 153 patients randomised
	MPT		M 0.18 mg/kg and P 2 mg/kg on Days 1- 4 and Pbo on Days 1- 21 for up to 9 28-day cycles+ Pbo on Days 1- 21 from cycle 10 until PD (28-day cycles); 154 patients randomised
Endpoints and definitions	Primary endpoint	Progression Free Survival (PFS)	time between randomisation and disease progression per investigator assessment based on the [EBMT/IBMTR/ABMTR] response criteria, or death on study, whichever occurred earlier (Investigator Assessment)
	Secondary endpoint	Overall Survival (OS)	time from randomisation to death due to any cause
	Secondary endpoint	Response Rate	CR, PR, Stable Disease and Response Not Evaluable (based on EBMT criteria)
	Secondary endpoint	Duration of Response	time when the response criteria are first met for CR or VGPR or PR until the first date the response criteria are met for PD or until the subject dies from any cause, whichever occurs first
Database lock	30 April 2013		
Results and Analysis			
Analysis description	**Primary Analysis**		

Analysis population and time point description	ITT (cut-off date at 30 April 2013); all randomised patients: 459					
Descriptive statistics and estimate variability	Treatment group	MPR + R	MPR + p	MPp+p		
	Number of subject	152	153	154		
	Median PFS (months)	27.4	14.3	13.1		
	95% CI	(21.3, 35.0)	(13.2,15.7)	(12.0, 14.8)		
	Median OS (months)	55.9	51.9	53.9		
	95% CI	(49.1 – 67.5)	(43.1 – 60.6)	(47.3 – 64.2)		
	CR n (%)	30 (19.7)	17 (11.1)	9 (5.8)		
	-	-	-	-		
	PR n (%)	90 (59.2)	99 (64.7)	75 (48.7)		
	-	-	-	-		
	Stable Disease n (%)	24 (15.8)	31 (20.3)	63 (40.9)		
	-	-	-	-		
	Response Not Evaluable n (%)	8 (5.3)	4 (2.6)	7 (4.5)		
	-	-	-	-		
	Median Duration of Response (months)	26.5	12.4	12.0		
	(95% CI)	(19.41, 35.76)	(11.18, 13.85)	(9.47, 14.54)		
Effect estimate per comparison	Primary endpoint (PFS)	Comparison groups		MPR+R vs MPp+p	MPR+R vs MPR+p	MPR+p vs MPp+p
		Hazard Ratio		0.371	0.474	0.776
		95% CI		(0.274, 0.503)	(0.347, 0.647)	(0.595, 1.012)
		P-value		<0.001	<0.001	0.059
	Secondary endpoint (OS)	Comparison groups		MPR+R vs MPp+p	MPR+R vs MPR+p	MPR+p vs MPp+p
		Hazard Ratio		0.948	0.882	1.069
		95% CI		(0.696, 1.292)	(0.647, 1.203)	(0.790, 1.445)
		P-value (Long-rank)		0.736	0.428	0.667
	Secondary endpoint (Response Rate)	Comparison groups		MPR+R vs MPp+p	MPR+R vs MPR+p	MPR+p vs MPp+p
		Odds Ratio		3.13	1.20	2.61
		95% CI		(1.89, 5.17)	(0.70, 2.05)	(1.60, 4.25)
		P-value		<0.001	0.584	<0.001

	Secondary endpoint (Duration of response)	Comparison groups	MPR+R vs MPp+p	MPR+R vs MPR+p	MPR+p vs MPp+p
		Hazard Ratio	0.370	0.433	0.857
		95% CI	(0.259, 0.529)	(0.307, 0.612)	(0.622, 1.181)
		P-value	<0.001	<0.001	0.344
Notes	Stratification factors: age (≤ 75 vs > 75years); ISS (stages 1 or 2 vs stage 3)				

Table 20. Summary of Efficacy for trial MM-020

Title: A Phase III, randomised, open-label, 3-arm study to determine the efficacy and safety of Lenalidomide (Revlimid) plus low-dose dexamethasone when given until progressive disease or for 18 four-week cycles *versus* the combination of melphalan, prednisone, and thalidomide given for 12 six-week cycles in patients with previously untreated multiple myeloma who are either 65 years of age or older or not candidates for stem cell transplantation			
Study identifier	MM-020, IFM 07-01		
Design	Phase III, randomised, open-Label, 3-arm		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		Until PD (Rd); 18 four-week cycles (Rd18); 12 six-week cycles (MPT) not applicable 45.5 months (median time of follow-up)
Hypothesis	Superiority		
Treatments groups	Rd		Revlimid 25 mg PO QD Days 1- 21 + low-dose dexamethasone 40 mg PO QD on Days 1, 8, 15, and 22 of each 4-week cycle; until PD or intolerable toxicity; 535 patients randomised
	Rd18		Revlimid 25 mg PO QD Days 1- 21 + low-dose dexamethasone 40 mg PO QD on Days 1, 8, 15, and 22 of each 4-week cycle; for 18 four-week cycles; 541 patients randomised
	MPT		Melphalan 0.25 mg/kg + prednisone 2 mg/kg PO QD on Days 1- 4 + thalidomide 200 mg PO QD on Days 1- 42 of each 6-week cycle; up to 12 cycles (or until PD or intolerable toxicity); 547 patients randomised
Endpoints and definitions	Primary endpoint	Progression Free Survival (PFS)	time from randomisation to the first documentation of disease progression based on the IMWG criteria or death, due to any cause, during the study up to the end of the PFS follow-up phase
	Secondary endpoint	Overall Survival (OS)	time from randomisation to death due to any cause
	Secondary endpoint	Myeloma Response	Overall response rate (CR, VGPR, or PR), CR, VGPR and PR according to IMWG criteria
	Secondary endpoint	Duration of Response	from time of initial response to confirmed disease progression using the IMWG criteria
Database lock	03 March 2014		

Results and Analysis

Analysis description	Primary Analysis					
Analysis population and time point description	ITT (cut-off date at 03 March 2014); all randomised patients: 1623					
Descriptive statistics and estimate variability	Treatment group	Rd	Rd18	MPT		
	Number of subject	535	541	547		
	Median PFS (months)	26.4	21.1	22.7		
	95% CI	(22.2 – 29.6)	(19.8 – 23.1)	(21.0 – 24.7)		
	Median OS (months)	58.9	56.7	48.5		
	95% CI	(56 – NE)	(50.1 – NE)	(44.2 – 52.0)		
	Overall response n (%) (cut-off 24 May 2013)	402 (75.1)	397 (73.4)	341 (62.3)		
	-	-	-	-		
	CR n (%)	81 (15.1)	77 (14.2)	51 (9.3)		
	-	-	-	-		
	VGPR n (%)	152 (28.4)	154 (28.5)	103 (18.8)		
	-	-	-	-		
	PR n (%)	169 (31.6)	166 (30.7)	187 (34.2)		
	-	-	-	-		
	Median Duration of Response (months)	35.0	22.1	22.3		
	(95% CI)	(27.9, 43.4)	(20.3, 24.0)	(20.2, 24.9)		
Effect estimate per comparison	Primary endpoint (PFS)	Comparison groups		Rd vs MPT	Rd vs Rd18	Rd18 vs MPT
		Hazard Ratio		0.71	0.73	1.01
		95% CI		(0.62, 0.82)	(0.63, 0.84)	(0.88, 1.15)
		P-value		<0.001	<0.001	0.925
	Secondary endpoint (OS)	Comparison groups		Rd vs MPT	Rd vs Rd18	Rd18 vs MPT
		Hazard Ratio		0.75	0.91	0.83
		95% CI		(0.62, 0.90)	(0.75, 1.09)	(0.69, 0.99)
		P-value		0.002	0.305	0.034
	Secondary endpoint (Myeloma Response)	Comparison groups		Rd vs MPT	Rd vs Rd18	Rd18 vs MPT
		Odds Ratio		1.83	1.10	1.67
		95% CI		(1.41, 2.37)	(0.83, 1.44)	(1.29, 2.15)
		P-value		<.00001	0.53065	0.00010

	Secondary endpoint (Duration of Response)	Comparison groups	Rd vs MPT	Rd vs Rd18	Rd18 vs MPT
		Hazard Ratio	0.63	0.60	1.03
		95% CI	(0.51, 0.76)	(0.50, 0.72)	(0.86, 1.23)
		P-value	<0.00001	<0.00001	0.76740
Notes	Stratification factors: age (≤ 75 vs > 75 years); International Staging System ISS (Stages I or II vs III); country				

Analysis performed across trials (pooled analyses and meta-analysis)

An analysis performed across trials MM-020 and MM-015 has been performed. Given the differences in patient characteristics, study design and dose/regimens including drug combinations, as well as treatment durations, any inter trial comparison is hazardous (see discussion on clinical safety).

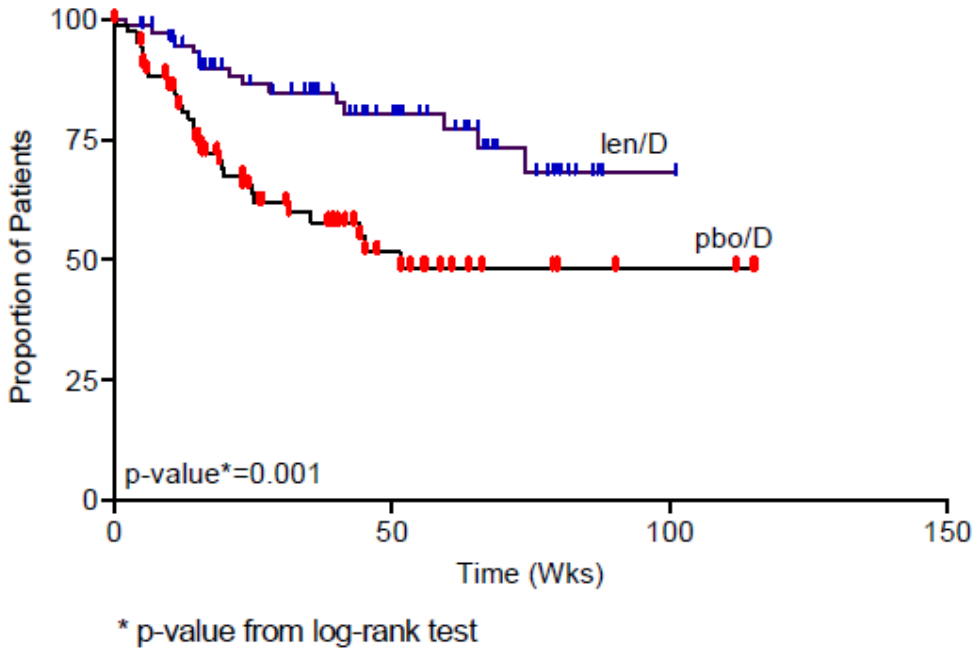
Supportive study

SWOG S0232

Study SWOG S0232 was sponsored by the Southwest Oncology Group (SWOG) with 198 patients enrolled in US centers. It was a double-blind, placebo-controlled, Phase 3 trial comparing the combination of standard-dose dexamethasone plus lenalidomide (RD) (n = 97) to placebo plus standard-dose dexamethasone (n = 95) in patients with new diagnosed Multiple Myeloma (NDMM) who were not immediately undergoing to autologous stem cell transplant (ASCT). Dosage regimen for induction was 3 cycles x 35-days Revlimid (R) 25 mg or placebo PO QD on Days 1-28, plus dexamethasone (D) 40 mg PO QD on Days 1-4, 9-12, and 17-20. Dosage regimen for maintenance was 28-day cycles R 25 mg or placebo PO QD on Days 1-21, plus D 40 mg PO QD on Days 1-4 and 15-18.
Patients were treated until PD occurred or withdrawal for any reason.

The primary endpoint was the Progression-free Survival (PFS), calculated as the weeks between study registration/randomisation and documented disease progression, as determined by IRAC review of myeloma response, or death, whichever occurred first. Results are shown in Figure 8.

Figure 8. Kaplan-Meier Estimate of Progression-free Survival up to Study Unblinding on 11 May 2007; Based on IRAC Review of Myeloma Response; ITT Population (Study SWOG S0232)



IRAC = Independent Response Assessment Committee; ITT = intent to treat

One-year PFS rate was 78% in lenalidomide plus dexamethasone treatment arm *versus* 52% of the control arm (p = 0.002). After Study E4A03 showed a survival advantage and a reduction of early mortality for the Rd regimen, the SWOG Data Safety Monitoring Committee (DSMC) concluded that it was no longer feasible to conduct the SWOG 0232 study. After closure of ECOG E4A03, SWOG 0232 study was terminated.

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The safety and efficacy of lenalidomide was assessed in a Phase III multicenter, randomised double blind 3 arm study (MM-015) of patients who were 65 years or older and had a serum creatinine < 2.5 mg/dL. The study compared lenalidomide in combination with melphalan and prednisone (MPR) with or without lenalidomide maintenance monotherapy until disease progression, to that of melphalan and prednisone for a maximum of 9 cycles. Patients were randomised in a 1:1:1 ratio to one of 3 treatment arms. Patients were stratified at randomisation by age (≤ 75 vs. > 75 years) and stage (ISS; Stages I and II vs. stage III). The primary efficacy endpoint in the study was PFS. In total 459 patients were enrolled into the study, with 152 patients randomised to MPR+R, 153 patients randomised to MPR+p and 154 patients randomised to MPp+p. The demographics and disease-related baseline characteristics of the patients were well balanced in all 3 arms; notably, approximately 50% of the patients enrolled in each arm had the following characteristics; ISS Stage III, and creatinine clearance < 60 mL/min. The median age was 71 in the MPR+R and MPR+p arms and 72 in the MPp+p arm (see SmPC section 5.1).

The safety and efficacy of lenalidomide was assessed in a Phase III, multicenter, randomised, open-label, 3-arm study (MM-020) of patients who were at least 65 years of age or older or, if younger than 65 years of age, were not candidates for stem cell transplantation because they declined to undergo stem cell transplantation or stem cell transplantation is not available to the patient due to cost or other reason. The study (MM-020) compared lenalidomide and dexamethasone (Rd) given for 2 different durations of time (i.e., until progressive disease

[Arm Rd] or for up to eighteen 28-day cycles [72 weeks, Arm Rd18]) to that of melphalan, prednisone and thalidomide (MPT) for a maximum of twelve 42-day cycles (72 weeks). Patients were randomised (1:1:1) to 1 of 3 treatment arms. Patients were stratified at randomisation by age (≤75 versus >75 years), stage (ISS Stages I and II versus Stage III), and country. The primary efficacy endpoint in the study was PFS. In total 1623 patients were enrolled into the study, with 535 patients randomised to Rd, 541 patients randomised to Rd18 and 547 patients randomised to MPT. The demographics and disease-related baseline characteristics of the patients were well balanced in all 3 arms. In general, study subjects had advanced-stage disease: of the total study population, 41% had ISS stage III, 9% had severe renal insufficiency (creatinine clearance [CrCl] < 30 mL/min). The median age was 73 years in the 3 arms (see SmPC section 5.1).

Both MPT and lenalidomide/low-dose dexamethasone are considered appropriate regimens for the treatment of TNE patients with NDMM (NCCN Category 1) and in Europe, MPT is considered standard of care.

The primary endpoint was PFS based on blinded review by an independent review committee. In this setting, PFS is an acceptable primary endpoint.

Efficacy data and additional analyses

The PFS analysis of the study MM-015 based on investigator assessment (cut-off date 30 April 2013) has provided convincing evidence of efficacy of lenalidomide with a clinically meaningful and statistically significant improvement in adult patients with previously untreated multiple myeloma who are not eligible for transplant. The risk of disease progression or death was reduced by 63% in Arm MPR+R compared to Arm MPp+p (HR=0.37, 95% CI = 0.27-0.50, p < 0.001). The improvement in median PFS time between Arms MPR+R (27.4 months) and MPp+p (13.1 months) was 14.3 months. At 3 years after randomisation, an estimated 39% of subjects have not progressed or died in Arm MPR+R compared with 6% of subjects in Arm MPp+p. At 4 years after randomisation, 29% of subjects in Arm MPR+R remained event free compared with 5% of the subjects in Arm MPp+p.

The PFS2 results are consistent with PFS results: the observed HR of 0.701 (95% CI = 0.536-0.916) with log-rank test p-value = 0.009 indicates a 30% reduction in the risk of death or having second objective disease progression to the start third-line AMT for Arm MPR+R compared to Arm MPp+p and translates into a 10.9 month improvement in median PFS2 from 28.8 months to 39.7 months.

Results from secondary efficacy endpoint myeloma response rate in MM-015 were consistent with those of the primary endpoint (PFS) analysis showing superiority of MPR+R over MPp+p.: the addition of lenalidomide to MP induction therapy was associated with notably higher response rates (78.9% and 75.8%, respectively) compared to 54.5% for MP alone (Arm MPp+p) (p<0.001).

The median duration of response was longest in Arm MPR+R (26.5 months) compared to Arms MPR+p (12.4 months) and MPp+p (12.0 months).

During the assessment the CHMP raised a major objection about the absence of a demonstrated trend in OS in favour of MPR+p or MPR+R. The observed HR was 0.95(95% CI: 0.70–1.29), favoring Arm MPR+R. The median OS was 55.9 months for Arm MPR+R and 53.9 months for Arm MPp+p and the estimated 5-year OS rate was 47% for Arm MPR+R and 44% for Arm MPp+p. The OS hazard ratio (HR) between arms MPR+R versus MPp+p would be expected to be about 0.8 (not 0.95) based on the improvement in PFS, if not confounded. Potential factors impacting OS are considered and discussed. The high cross-over rate (60% of all patients) to lenalidomide containing regimens in the MPp+p arm appears to be an explanation. If cross-over to lenalidomide was the main reason for the absence of an OS difference, this would have been expected to be reflected also in PFS2 data. The median PFS difference, however, has only decreased from about 14 months (median 27 vs. 13

months) in the PFS1 analyses to 11 months (median 40 vs. 29 months). Of note PFS curves followed a non-exponential distribution meaning that focus on medians only might be misleading and the HR increased from 0.37 (PFS1) to 0.70 (PFS2).] In addition, an imbalance in risk factors contributed to the higher event rate of deaths prior to progression during induction therapy comparing MPR+R with MPR+p. This had also contributed to absence of an overall survival benefit for the MPR+R arm.

The results of the updated PFS analysis (cut-off date 3 March 2014) of the study MM-020 showed a statistically significant improvement in PFS for Arm Rd arm compared with Arm MPT (HR 0.69, 95% CI 0.59 - 0.80, p < 0.001) indicating a 31% reduction in the risk of PD or death for subjects in Arm Rd compared with those in Arm MPT. As of the 3 March 2014 data cut-off date, the median follow-up time for all surviving subjects was 45.5 months with 697 events having occurred, representing 43% (697/1623) of the ITT.

Consistent with the PFS improvement, fewer deaths have occurred so far in Arm Rd (208/535 or 38.9%) compared with Arm Rd18 (228/541 or 42.1%) or Arm MPT (261/547 or 47.7%). The results indicated a 25% reduction in risk of death in favour of Arm Rd versus Arm MPT (HR = 0.75, 95% CI 0.62-0.90, p=0.002) with a 10.4-month improvement in median OS. A worse-case scenario simulation of assigning an equal number of 36 additional deaths (to reach 50% of OS events in the ITT population) to each of Arms Rd and MPT still shows an estimated HR of 0.79 (95% CI 0.64-0.91) with a log-rank p-value of 0.002.

The significant improvement in PFS is further supported by patient-assessed QoL for MM-020 study. This has not been evidenced in MM-015 study.

ECOG E4A03 study was a randomised Phase 3 trial of lenalidomide plus standard-dose dexamethasone (RD) versus lenalidomide plus low-dose dexamethasone (Rd) conducted in NDMM patients in the TNE or TE setting. Its results have shown that low dose dexamethasone provides benefit in terms of efficacy (longer overall survival, reduction of early mortality) and safety (lower toxicity of dexamethasone) than RD. However, first-line therapy in MM differs whether patients are candidates to transplant or not, so the ECOG E4A03 results are supportive only for the selection of the Rd dose regimen for Study MM-020.

SWOG S0232 study was a phase 3 trial comparing the combination of standard-dose dexamethasone plus lenalidomide (RD) to placebo plus standard-dose dexamethasone in patients with NDMM who were not immediately undergoing ASCT. The contribution of this supportive trial to the extension of indication pertains to the choice of dexamethasone dose.

2.5.4. Conclusions on the clinical efficacy

The results of the two pivotal studies MM-015 and MM-020 are considered of clinical relevance. The statistically significant and clinically relevant improvement in PFS together with the OS results/analyses support a clinical benefit associated with lenalidomide treatment in the target population.

2.6. Clinical safety

Patient exposure

Table 21. Summary of the safety database in transplant not eligible patients with NDMM.

	Cut-off date	Patients exposed	Patients exposed to the proposed dose range	Discontinued for any reason

Placebo-controlled				
SWOG S0232	Data release date: 11 May 2007 Extended follow-up date: 23 Oct 2008	194	1. len/D, n = 97 2. placebo/D, n = 95	
Active –controlled				
MM-020	24 May 2013	1613	1.Rd until PD, n = 532 2. Rd x 18 cycles, n = 540 3. MPT, n = 541	411 in Arm Rd 259 in Arm Rd18 301 in Arm MPT
MM-015	30 Apr 2013	455	1. MPR+R, n = 150 2. MPR+p, n = 152 3. MPp+p, n = 153	175 during induction therapy 263 from maintenance phase 74 in Arm MPR+R 89 in Arm MPR+p 100 in Arm MPp+p
ECOG E4A03	Data release date: 26 Mar 2007 Extended follow-up date: 01 Jul 2008	442	1. len/D, n = 222 2. len /d, n = 220	*355 followed up* 31 in len/D 51 in len/d
Supportive analysis				
SPM meta-analysis	24 May 2013 (MM-020) 30 Apr 2013 (MM-015) 07 May 2013 (IFM 2005-02) 02 May 2013 (CALGB 100104)	NA > 3000 patients and included 1900 patients randomised to lenalidomide containing treatment arms.	NA	NA
Post marketing + Compassionate use	Since June 06	92,968 in US 147,270 in EU and other territories outside the US	NA	NA

Table 22. Summary of exposure in the two main Phase III studies: MM-020 and MM-015 (cut-off date 24 May 2013 for Study MM-020 and 30 Apr 2013 for Study MM-005)

	Study MM-020			Study MM-015[a]		
	Rd (N = 532)	Rd18 (N = 540)	MPT (N = 541)	MPR+R (N = 150)	MPR+p (N = 152)	MPp+p (N = 153)
Treatment Duration (weeks)[b]						
Median	80.2	72.0	67.1	62.6	53.0	53.0
Min, max	0.7, 246.7	0.9, 102.6	0.1, 110.0	3.4, 297.0	2.0, 162.7	1.0, 160.3
Treatment Duration (weeks)[b] for Subjects Who Entered Maintenance[c]						
N	–	–	–	88	94	102
Median	–	–	–	123.5	71.2	69.5
Min, max	–	–	–	40.3, 297.0	37.6, 162.7	39.7, 160.3
Cumulative Exposure						
Total person-years on study treatment	921	587	549	259	170	169

d = low-dose dexamethasone; M = melphalan, max = maximum; min = minimum; p = placebo; P = prednisone; R = lenalidomide; Rd = Rd given until documentation of progressive disease; Rd18 = Rd given for ≤ 18 four-week cycles; T =thalidomide.

[a] Combined induction and maintenance therapy periods.

[b] In Study MM-020, treatment duration was defined as [treatment end date - treatment start date + 1]/7. In Study MM-015, treatment duration was calculated from the first of the dosing start dates to the last of the last cycle end dates of the 3 study drugs.

[c] Treatment duration during the combined induction and maintenance therapy periods for subjects who entered the maintenance therapy period.

Adverse events

MM-020

On a system organ class (SOC) basis, AEs most frequently reported (> 50% of the patients overall) during the active treatment period included general disorders and administration site conditions, gastrointestinal disorders, nervous system disorders, blood and lymphatic system disorders, musculoskeletal disorders, infections and infestations, and respiratory, thoracic and mediastinal disorders.

On a preferred term (PT) basis, the most frequently reported AEs included constipation, anaemia, and neutropenia (> 40% patients overall), followed by peripheral oedema, fatigue, diarrhoea (> 30% patients overall), asthenia, nausea, back pain, peripheral sensory neuropathy, thrombocytopenia, rash, and insomnia (> 20% patients overall). Diarrhoea, back pain, and insomnia were reported more frequently (with a difference of at least 5%) in Arm Rd18 compared with Arm MPT. Constipation, peripheral sensory neuropathy, neutropenia and thrombocytopenia, on the other hand, were reported more frequently in Arm MPT than in Arms Rd or Rd18. While less frequent, muscle spasm, pneumonia, decreased appetite, hyperglycaemia, and cataract were reported more frequently (a difference of at least 5%) in Arm Rd18 compared with Arm MPT, and paraesthesia, dizziness, peripheral neuropathy, leucopenia, and lymphopenia were reported more frequently in Arm MPT than in Arm Rd18. The reporting of other AEs was otherwise comparable across the Rd18 and MPT arms. As expected, common AEs were generally reported at a higher frequency in Arm Rd than in Arm Rd18, with reasonable differences that reflect the difference in treatment duration per study protocol. Cataract, however, was reported in more than twice as many patients in Arm Rd than in Arm Rd18.

Table 23. Overview of treatment-emergent AEs by treatment arm (MM-020).

Subjects with at least 1:	Rd (N = 532) n (%)	Rd18 (N = 540) n (%)	MPT (N = 541) n (%)
AE	529 (99.4)	536 (99.3)	539 (99.6)
Grade 3/4 (NCI CTCAE) AE	453 (85.2)	433 (80.2)	480 (88.7)
Grade 5 AEs	50 (9.4)	36 (6.7)	38 (7.0)
SAE	359 (67.5)	308 (57.0)	270 (49.9)
Treatment-related AE (any drug)	506 (95.1)	501 (92.8)	527 (97.4)
Grade 3/4 (NCI CTCAE) treatment-related AE (any drug)	373 (70.1)	326 (60.4)	423 (78.2)
Treatment-related SAE (any drug)	195 (36.7)	158 (29.3)	142 (26.2)
AE leading to treatment discontinuation of lenalidomide or thalidomide	109 (20.5)	93 (17.2)	146 (27.0)
AE leading to treatment discontinuation of entire regimen	96 (18.0)	84 (15.6)	71 (13.1)

AE = adverse event; d = low-dose dexamethasone; M = melphalan; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Event; p = placebo; P = prednisone; R = lenalidomide; SAE = serious adverse event; T = thalidomide.
Note: Severity of the toxicities was graded according to the NCI CTCAE Version 3.0.
Data cutoff: 24 May 2013
Source: CSR MM-020, Table 14.3.1.2.1.1, Table 14.3.1.2.8.1, Table 14.3.1.2.8.2, and Table 14.3.1.2.8.4

Table 24. Treatment emergent adverse event (TEAE) reported by at least 10% of the patients in any treatment arm (MM-020)

System Organ Class Preferred Term[a]	Study MM-020 Rd (N = 532) n (%)	Rd18 (N = 540) n (%)	MPT (N = 541) n (%)
Subjects with ≥ 1 AE	**529 (99.4)**	**536 (99.3)**	**539 (99.6)**
General Disorders and Administration Site Conditions	**437 (82.1)**	**430 (79.6)**	**422 (78.0)**
Oedema peripheral	211 (39.7)	169 (31.3)	215 (39.7)
Fatigue	173 (32.5)	177 (32.8)	154 (28.5)
Asthenia	150 (28.2)	123 (22.8)	124 (22.9)
Pyrexia	114 (21.4)	102 (18.9)	76 (14.0)
Gastrointestinal Disorders	**434 (81.6)**	**411 (76.1)**	**412 (76.2)**
Diarrhoea	242 (45.5)	208 (38.5)	89 (16.5)
Constipation	229 (43.0)	212 (39.3)	285 (52.7)
Nausea	152 (28.6)	128 (23.7)	165 (30.5)
Vomiting	93 (17.5)	68 (12.6)	109 (20.1)
Abdominal pain	69 (13.0)	41 (7.6)	30 (5.5)
Dyspepsia	57 (10.7)	28 (5.2)	36 (6.7)
Dry mouth	37 (7.0)	38 (7.0)	62 (11.5)
Musculoskeletal and Connective Tissue Disorders	**408 (76.7)**	**367 (68.0)**	**311 (57.5)**
Back pain	170 (32.0)	145 (26.9)	116 (21.4)
Muscle spasms	109 (20.5)	102 (18.9)	61 (11.3)
Arthralgia	101 (19.0)	71 (13.1)	66 (12.2)
Bone pain	87 (16.4)	77 (14.3)	62 (11.5)
Pain in extremity	79 (14.8)	66 (12.2)	61 (11.3)
Musculoskeletal pain	67 (12.6)	59 (10.9)	36 (6.7)
Musculoskeletal chest pain	60 (11.3)	51 (9.4)	39 (7.2)
Infections and Infestations	**398 (74.8)**	**377 (69.8)**	**305 (56.4)**
Bronchitis	90 (16.9)	59 (10.9)	43 (7.9)
Nasopharyngitis	80 (15.0)	54 (10.0)	33 (6.1)
Urinary tract infection	76 (14.3)	63 (11.7)	41 (7.6)
Upper respiratory tract infection	69 (13.0)	53 (9.8)	31 (5.7)
Pneumonia	66 (12.4)	68 (12.6)	40 (7.4)
Nervous System Disorders	**371 (69.7)**	**333 (61.7)**	**429 (79.3)**
Peripheral sensory neuropathy	109 (20.5)	92 (17.0)	191 (35.3)
Paraesthesia	85 (16.0)	74 (13.7)	103 (19.0)
Dizziness	84 (15.8)	70 (13.0)	114 (21.1)
Headache	75 (14.1)	52 (9.6)	56 (10.4)
Tremor	75 (14.1)	73 (13.5)	100 (18.5)
Neuropathy peripheral	34 (6.4)	22 (4.1)	62 (11.5)
Blood and Lymphatic System Disorders	**346 (65.0)**	**325 (60.2)**	**423 (78.2)**
Anaemia	233 (43.8)	193 (35.7)	229 (42.3)
Neutropenia	186 (35.0)	178 (33.0)	328 (60.6)
Thrombocytopenia	104 (19.5)	100 (18.5)	135 (25.0)
Leukopenia	63 (11.8)	60 (11.1)	94 (17.4)

System Organ Class Preferred Term[a]	Study MM-020 Rd (N = 532) n (%)	Rd18 (N = 540) n (%)	MPT (N = 541) n (%)
Lymphopenia	59 (11.1)	43 (8.0)	71 (13.1)
Respiratory, Thoracic and Mediastinal Disorders	**306 (57.5)**	**259 (48.0)**	**246 (45.5)**
Cough	121 (22.7)	94 (17.4)	68 (12.6)
Dyspnoea	117 (22.0)	89 (16.5)	113 (20.9)
Metabolism and Nutrition Disorders	**298 (56.0)**	**274 (50.7)**	**192 (35.5)**
Decreased appetite	123 (23.1)	115 (21.3)	72 (13.3)
Hypokalaemia	91 (17.1)	62 (11.5)	38 (7.0)
Hyperglycaemia	62 (11.7)	52 (9.6)	19 (3.5)
Hypocalcaemia	57 (10.7)	56 (10.4)	31 (5.7)
Skin and Subcutaneous Tissue Disorders	**285 (53.6)**	**276 (51.1)**	**217 (40.1)**
Rash	114 (21.4)	131 (24.3)	93 (17.2)
Psychiatric Disorders	**255 (47.9)**	**234 (43.3)**	**167 (30.9)**
Insomnia	147 (27.6)	127 (23.5)	53 (9.8)
Depression	58 (10.9)	46 (8.5)	30 (5.5)
Vascular Disorders	**189 (35.5)**	**148 (27.4)**	**138 (25.5)**
Deep vein thrombosis	54 (10.2)	36 (6.7)	20 (3.7)
Eye Disorders	**171 (32.1)**	**126 (23.3)**	**86 (15.9)**
Cataract	73 (13.7)	31 (5.7)	5 (0.9)
Investigations	**169 (31.8)**	**173 (32.0)**	**141 (26.1)**
Weight decreased	72 (13.5)	78 (14.4)	48 (8.9)

AE = adverse event; d = low-dose dexamethasone; M = melphalan; p = placebo; P = prednisone; R = lenalidomide; T = thalidomide.

[a] System organ classes and preferred terms are coded using MedDRA version 15.1. If the same AE was reported multiple times within a given preferred term, only one event with the worst severity was counted per subject. Note: System organ classes and preferred terms are listed in descending order of frequency for the Arm Rd.

Data cutoff: 24 May 2013

Table 25. Summary of Grade 3 or 4 Adverse Events by Onset Period for Subjects with Treatment Duration > 24 Months in Arm Rd – Events Reported in at Least 2% of Subjects During the Overall Study (Study MM-020 – Safety Population).

System Organ Class Preferred Term[a]	Time of Onset From Treatment Start (Arm Rd) (N=201)			
	0-6 Months n (%)	6-12 Months n (%)	12-18 Months n (%)	18-24 Months n (%)
Subjects With ≥ 1 Grade 3 or 4 AE	**105 (52.2)**	**75 (37.3)**	**74 (36.8)**	**86 (42.8)**
Blood and Lymphatic System Disorders	**44 (21.9)**	**27 (13.4)**	**29 (14.4)**	**18 (9.0)**
Neutropenia	30 (14.9)	22 (10.9)	20 (10.0)	13 (6.5)
Anaemia	12 (6.0)	4 (2.0)	5 (2.5)	4 (2.0)
Lymphopenia	11 (5.5)	3 (1.5)	1 (0.5)	1 (0.5)
Leukopenia	6 (3.0)	2 (1.0)	4 (2.0)	2 (1.0)
Thrombocytopenia	4 (2.0)	6 (3.0)	5 (2.5)	1 (0.5)
Infections and Infestations	**15 (7.5)**	**17 (8.5)**	**7 (3.5)**	**18 (9.0)**
Pneumonia	3 (1.5)	5 (2.5)	2 (1.0)	3 (1.5)
Urinary tract infection	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.0)
Cellulitis	0 (0.0)	2 (1.0)	1 (0.5)	0 (0.0)
Lower respiratory tract infection	2 (1.0)	1 (0.5)	1 (0.5)	0 (0.0)
Sepsis	0 (0.0)	1 (0.5)	1 (0.5)	1 (0.5)
General Disorders and Administration Site Conditions	**19 (9.5)**	**10 (5.0)**	**11 (5.5)**	**15 (7.5)**
Fatigue	4 (2.0)	3 (1.5)	5 (2.5)	6 (3.0)
Asthenia	10 (5.0)	4 (2.0)	4 (2.0)	4 (2.0)
Oedema peripheral	1 (0.5)	1 (0.5)	1 (0.5)	2 (1.0)
Metabolism and Nutrition Disorders	**16 (8.0)**	**6 (3.0)**	**9 (4.5)**	**13 (6.5)**
Hyperglycaemia	8 (4.0)	4 (2.0)	1 (0.5)	3 (1.5)
Hypokalaemia	4 (2.0)	0 (0.0)	1 (0.5)	3 (1.5)
Decreased appetite	1 (0.5)	0 (0.0)	0 (0.0)	3 (1.5)
Hypocalcaemia	1 (0.5)	1 (0.5)	2 (1.0)	0 (0.0)
Gout	2 (1.0)	0 (0.0)	1 (0.5)	0 (0.0)
Musculoskeletal and Connective Tissue Disorders	**10 (5.0)**	**8 (4.0)**	**7 (3.5)**	**12 (6.0)**
Back pain	7 (3.5)	1 (0.5)	1 (0.5)	6 (3.0)
Pain in extremity	1 (0.5)	3 (1.5)	0 (0.0)	0 (0.0)
Gastrointestinal Disorders	**11 (5.5)**	**10 (5.0)**	**8 (4.0)**	**8 (4.0)**
Diarrhoea	2 (1.0)	3 (1.5)	4 (2.0)	4 (2.0)
Constipation	3 (1.5)	1 (0.5)	0 (0.0)	1 (0.5)
Eye Disorders	**1 (0.5)**	**5 (2.5)**	**6 (3.0)**	**10 (5.0)**
Cataract	1 (0.5)	3 (1.5)	4 (2.0)	7 (3.5)
Cataract subcapsular	0 (0.0)	1 (0.5)	0 (0.0)	3 (1.5)
Nervous System Disorders	**5 (2.5)**	**8 (4.0)**	**7 (3.5)**	**10 (5.0)**
Neuropathy peripheral	0 (0.0)	1 (0.5)	4 (2.0)	4 (2.0)
Vascular Disorders	**15 (7.5)**	**3 (1.5)**	**3 (1.5)**	**3 (1.5)**
Deep vein thrombosis	11 (5.5)	2 (1.0)	2 (1.0)	2 (1.0)
Hypertension	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)
Hypotension	1 (0.5)	1 (0.5)	0 (0.0)	1 (0.5)
Respiratory, Thoracic and Mediastinal Disorders	**7 (3.5)**	**5 (2.5)**	**4 (2.0)**	**6 (3.0)**
Pulmonary embolism	3 (1.5)	1 (0.5)	1 (0.5)	3 (1.5)

System Organ Class Preferred Term[a]	Time of Onset From Treatment Start (Arm Rd) (N=201)			
	0-6 Months n (%)	6-12 Months n (%)	12-18 Months n (%)	18-24 Months n (%)
Chronic obstructive pulmonary disease	0 (0.0)	0 (0.0)	0 (0.0)	3 (1.5)
Dyspnoea	0 (0.0)	0 (0.0)	1 (0.5)	2 (1.0)
Dyspnoea exertional	1 (0.5)	0 (0.0)	0 (0.0)	1 (0.5)
Skin and Subcutaneous Tissue Disorders	**15 (7.5)**	**0 (0.0)**	**2 (1.0)**	**0 (0.0)**
Rash	13 (6.5)	0 (0.0)	0 (0.0)	0 (0.0)
Investigations	**7 (3.5)**	**4 (2.0)**	**4 (2.0)**	**2 (1.0)**
Weight decreased	2 (1.0)	0 (0.0)	2 (1.0)	1 (0.5)
Injury, Poisoning and Procedural Complications	**2 (1.0)**	**1 (0.5)**	**5 (2.5)**	**6 (3.0)**
Fall	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.0)
Neoplasms Benign, Malignant and Unspecified (Incl Cysts And Polyps)	**1 (0.5)**	**1 (0.5)**	**3 (1.5)**	**2 (1.0)**
Squamous cell carcinoma of skin	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.5)
Basal cell carcinoma	1 (0.5)	1 (0.5)	2 (1.0)	2 (1.0)
Psychiatric Disorders	**2 (1.0)**	**2 (1.0)**	**3 (1.5)**	**2 (1.0)**
Confusional state	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)
Depression	1 (0.5)	1 (0.5)	2 (1.0)	0 (0.0)

AE = adverse event; d = low-dose dexamethasone; R = lenalidomide.

a System organ classes and preferred terms are coded using MedDRA version 15.1. If the same AE was reported multiple times within a given preferred term, only 1 event with the worst severity was counted per onset period per subject. System organ classes and preferred terms are listed in descending order of frequency of Grade 3 or 4 AEs for the overall treatment column.

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For the combined induction and maintenance therapy periods, the most frequently reported AEs were the haematologic adverse events of neutropenia, thrombocytopenia, anaemia, and leucopenia. The frequency of these events was higher in patients receiving MPR-containing regimens.

The most frequently reported (at least 10% of the patients overall) non-haematologic AEs pertained to the general disorders and administration site conditions and gastrointestinal SOCs. On a PT basis, the most frequently reported non-haematologic AEs were fatigue, pyrexia, peripheral oedema, asthenia, constipation, nausea, diarrhoea, vomiting, bone pain, back pain, musculoskeletal pain, arthralgia, nasopharyngitis, upper respiratory tract infection, bronchitis, anorexia, dizziness, headache, cough, dyspnoea, rash, and insomnia.

Constipation, diarrhoea, and cough were reported more frequently (with a difference of at least 5%) in patients receiving lenalidomide during both the induction and maintenance therapy period (MPR+R) than in patients receiving lenalidomide followed by placebo (MPR+p) or placebo (MPp+p), while nausea, back pain, and headache were reported more frequently in the MPp+p arm of the study than in either of the MPR+p or MPR+R arm of the study. Rash was reported more frequently in the lenalidomide-containing arms of the study (MPR+R and MPR+p) than in the placebo arm (MPp+p).

Table 26. Overview of treatment-emergent AEs by treatment arm (MM-015)

Subjects with at least 1:	Combined Induction and Maintenance Therapy Periods			Induction Therapy Period		Maintenance Therapy Period[a]		
	MPR+R (N = 150) n (%)	MPR+p (N = 152) n (%)	MPp+p (N = 153) n (%)	MPR+R/MPR+p (N = 302) n (%)	MPp+p (N = 153) n (%)	MPR+R (N = 88) n (%)	MPR+p (N = 94) n (%)	MPp+p (N = 102) n (%)
AE	150 (100.0)	151 (99.3)	153 (100.0)	298 (98.7)	152 (99.3)	79 (89.8)	73 (77.7)	85 (83.3)
Grade 3/4 (NCI CTCAE) AE	139 (92.7)	130 (85.5)	107 (69.9)	256 (84.8)	90 (58.8)	55 (62.5)	25 (26.6)	34 (33.3)
Grade 5 AEs	10 (6.7)	8 (5.3)	7 (4.6)	12 (4.0)	5 (3.3)	3 (3.4)	3 (3.2)	2 (2.0)
SAE	76 (50.7)	64 (42.1)	57 (37.3)	110 (36.4)	42 (27.5)	33 (37.5)	15 (16.0)	24 (23.5)
Treatment-related AE (any drug)[b]	148 (98.7)	147 (96.7)	141 (92.2)	290 (96.0)	139 (90.8)	58 (65.9)	39 (41.5)	36 (35.3)
Grade 3/4 (NCI CTCAE) treatment-related AE (any drug)	133 (88.7)	118 (77.6)	73 (47.7)	238 (78.8)	69 (45.1)	31 (35.2)	9 (9.6)	6 (5.9)
Treatment-related SAE (any drug)	40 (26.7)	35 (23.0)	14 (9.2)	72 (23.8)	12 (7.8)	4 (4.5)	5 (5.3)	3 (2.9)
AE leading to treatment discontinuation of lenalidomide or placebo	39 (26.0)	26 (17.1)	14 (9.2)	41 (13.6)	10 (6.5)	20 (22.7)	4 (4.3)	4 (3.9)
AE leading to treatment discontinuation of entire regimen	37 (24.7)	23 (15.1)	14 (9.2)	36 (11.9%)	10 (6.5%)	20 (22.7)[c]	4 (4.3)[c]	4 (3.9)[c]

AE = adverse event; d = low-dose dexamethasone; M = melphalan; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Event; p = placebo; P = prednisone; R = lenalidomide; SAE = serious adverse event; T = thalidomide.

[a] AEs described during the maintenance period are those AEs that were newly occurring or worsening during the maintenance period.

[b] Related to lenalidomide or placebo only during maintenance therapy period of Study MM-015.

[c] By study design, discontinuation of the entire regimen during the maintenance therapy period of Study MM-015 reflects discontinuation of lenalidomide or placebo.

Note: Severity of the toxicities was graded according to the NCI CTCAE Version 3.0 for Study MM-015.

Data cutoff: 30 Apr 2013

Source: CSR MM-015 Table 14.3.2.1.1, Table 14.3.2.1.2, Table 14.3.2.1.3.1, Table 14.3.2.5.1, Table 14.3.2.5.2, Table 14.3.2.8.19, Table 14.3.2.10.3, Table 14.3.2.12.2.3, and Table 14.3.2.12.5;
SCS MM-015 Table 14.3.2.8.20.3, Table 14.3.2.10.6.2, Table 14.3.2.10.6.3, and Table 14.3.2.12.14

Table 27. Treatment-emergent, Grade 3/4, and Serious Adverse Events, Induction Phase (MM-015)

System Organ Class Preferred Term	Summary of Treatment-emergent Adverse Events Reported in at Least 10% of Subjects		Summary of Grade 3/4 Treatment-emergent Adverse Events Reported in at Least 5% of Subjects		Serious Treatment-emergent Adverse Events Reported in at Least 2% of Subjects	
	MPR+R and MPR+p (N = 302) n (%)	MPp+p (N = 153) n (%))	MPR+R and MPR+p (N = 302) n (%)	MPp+p (N = 153) n (%)	MPR+R and MPR+p (N = 302) n (%)	MPp+p (N = 153) n (%))
BLOOD AND LYMPHATIC SYSTEM DISORDERS						
Anaemia [a, b, c]	194 (64.2)	77 (50.3)	**77 (25.5)**	**21 (13.7)**	12 (4.0)	2 (1.3)
Febrile neutropenia [c]	-	-	-	-	11 (3.6)	0 (0.0)
Neutropenia [a, b, c]	239 (79.1)	77 (50.3)	**205 (67.9)**	**46 (30.1)**	10 (3.3)	1 (0.7)
Thrombocytopenia [a, b]	203 (67.2)	64 (41.8)	**116 (38.4)**	**19 (12.4)**	-	-
Leukopenia [b]	108 (35.8)	48 (31.4)	77 (25.5)	21 (13.7)	-	-
CARDIAC DISORDERS						
Atrial fibrillation	-	-	-	-	4 (1.3)	3 (2.0)
GASTROINTESTINAL DISORDERS						
Constipation	88 (29.1)	37 (24.2)	-	-	-	-
Nausea [a]	75 (24.8)	51 (33.3)	-	-	-	-
Vomiting	37 (12.3)	19 (12.4)	-	-	5 (1.7)	3 (2.0)
Diarrhea	70 (23.2)	33 (21.6)	-	-	-	-
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS						
Pyrexia [a]	69 (22.8)	27 (17.6)	-	-	8 (2.6)	4 (2.6)
Fatigue	94 (31.1)	53 (34.6)	-	-	-	-
Oedema peripheral [a]	**62 (20.5)**	**22 (14.4)**	-	-	-	-
Asthenia	51 (16.9)	20 (13.1)	-	-	-	-
INFECTIONS AND INFESTATIONS						
Pneumonia	-	-	-	-	12(4.0)	8 (5.2)
Nasopharyngitis	36 (11.9)	21 (13.7)	-	-	-	-
METABOLISM AND NUTRITION DISORDERS						
Anorexia	55 (18.2)	22 (14.4)	-	-	-	-
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS						
Bone pain	74 (24.5)	35 (22.9)	-	-	4 (1.3)	3 (2.0)
Muscle spasms [a]	33 (10.9)	7 (4.6)	-	-	-	-
Back pain [a]	27 (8.9)	26 (17.0)	-	-	-	-
Musculoskeletal pain	31 (10.3)	19 (12.4)	-	-	-	-
NERVOUS SYSTEM DISORDERS						
Dizziness	33 (10.9)	14 (9.2)	-	-	-	-
PSYCHIATRIC DISORDERS						
Insomnia	31 (10.3)	20 (13.1)	-	-	-	-
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS						
Dyspnea	36 (11.9)	17 (11.1)	-	-	-	-
Cough	47 (15.6)	17 (11.1)	-	-	-	-
SKIN AND SUBCUTANEOUS TISSUE DISORDERS						
Rash [a]	**69 (22.**	**11 (7.2**	-	-	-	-

M = melphalan; MedDRA = Medical Dictionary for Drug Regulatory Activities; p = placebo; P = prednisone; R = lenalidomide; TEAE = treatment-emergent adverse event.

[a] Denotes a ≥ 5% difference in adverse events between Arms MPR+R plus MPR+p and Arm MPp+p.

[b] Denotes a ≥ 5% difference in grade 3/4 adverse events between Arms MPR+R plus MPR+p and Arm MPp+p.

[c] Denotes a ≥ 2% difference in serious adverse events between Arms MPR+R plus MPR+p and Arm MPp+p.
Note: System organ classes and preferred terms are coded using the MedDRA dictionary (version 10). If multiple adverse events were reported within a given preferred term, only 1 event was counted per subject.
Note: Dash (-) indicates that data does not match cutoff criteria (ie, TEAE in at least 10%, grade 3/4 TEAE in at least 5%, and serious adverse events in at least 2% of subjects).

Table 28. Treatment emergent AEs in at least 5%, Maintenance Phase (MM-015)

System Organ Class Preferred Term	MPR+R (N = 88) n (%)	MPR+p (N = 94) n (%)	MPp+p (N = 102) n (%)
Subject with at least 1 adverse event during the maintenance therapy period	84 (95.5)	77 (81.9)	92 (90.2)
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
Neutropenia [a, b, c]	56 (63.6)	27 (28.7)	23 (22.5)
Anemia [a, b, c]	35 (39.8)	20 (21.3)	33 (32.4)
Thrombocytopenia [a, b, c]	30 (34.1)	23 (24.5)	18 (17.6)
Leukopenia [a, b]	27 (30.7)	20 (21.3)	23 (22.5)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
Bone pain [a, b]	24 (27.3)	17 (18.1)	21 (20.6)
Back pain	6 (6.8)	8 (8.5)	7 (6.9)
Musculoskeletal pain [b]	10 (11.4)	2 (2.1)	7 (6.9)
Arthralgia	4 (4.5)	8 (8.5)	5 (4.9)
Muscle spasms [a, b]	7 (8.0)	2 (2.1)	2 (2.0)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
Fatigue [a, b, c]	18 (20.5)	8 (8.5)	14 (13.7)
Pyrexia	8 (9.1)	8 (8.5)	10 (9.8)
Asthenia	5 (5.7)	5 (5.3)	8 (7.8)
Edema peripheral	3 (3.4)	6 (6.4)	7 (6.9)
INFECTIONS AND INFESTATIONS			
Nasopharyngitis [a, b]	11 (12.5)	7 (7.4)	5 (4.9)
Bronchitis [a]	7 (8.0)	4 (4.3)	2 (2.0)
Upper respiratory tract infection [b]	7 (8.0)	2 (2.1)	4 (3.9)
GASTROINTESTINAL DISORDERS			
Diarrhea [a, b]	21 (23.9)	7 (7.4)	6 (5.9)
Constipation	8 (9.1)	5 (5.3)	5 (4.9)
Nausea	7 (8.0)	4 (4.3)	5 (4.9)
Abdominal pain [b]	6 (6.8)	1 (1.1)	3 (2.9)
Dyspepsia [b]	5 (5.7)	0	1 (1.0)
NERVOUS SYSTEM DISORDERS			
Headache [a]	4 (4.5)	7 (7.4)	10 (9.8)
Paresthesia	5 (5.7)	4 (4.3)	2 (2.0)
METABOLISM AND NUTRITION DISORDERS			
Hyperglycemia [c]	6 (6.8)	4 (4.3)	10 (9.8)
Anorexia [a, c]	6 (6.8)	6 (6.4)	1 (1.0)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
Cough [a, b]	11 (12.5)	5 (5.3)	7 (6.9)
Dyspnea	5 (5.7)	2 (2.1)	3 (2.9)
INVESTIGATIONS			
Blood creatinine increased [c]	6 (6.8)	2 (2.1)	8 (7.8)
Carbon dioxide decreased	1 (1.1)	5 (5.3)	3 (2.9)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
Rash [a]	7 (8.0)	3 (3.2)	2 (2.0)
Pruritus	5 (5.7)	1 (1.1)	2 (2.0)

Table 29. Summary of Grade 3/4 Treatment-emergent Adverse Events Reported in at Least 2% of Subjects in Any Treatment Arm During the Maintenance Phase (MM-015).

System Organ Class Preferred Term	Study CC-5013-MM-015		
	MPR+R (N = 88) n (%)	MPR+p (N = 94) n (%)	MPp+p (N = 102) n (%)
Neutropenia [a,]	33 (37.5)	5 (5.3)	7 (6.9)
Anaemia [a]	3 (3.4)	6 (6.4)	6 (5.9)
Leukopenia [a,]	7 (8.0)	3 (3.2)	5 (4.9)
Thrombocytopenia [a,]	5 (5.7)	3 (3.2)	4 (3.9)
Granulocytopenia [a]	3 (3.4)	0 (0.0)	0 (0.0)
Diarrhea [a]	**4 (4.5)**	0 (0.0)	0 (0.0)
Pyrexia [a]	0 (0.0)	0 (0.0)	3 (2.9)
Fatigue [a]	**2 (2.3)**	0 (0.0)	0 (0.0)
Asthenia	-	-	-
Herpes zoster	-	-	-
Blood creatinine increased [a]	0 (0.0)	2 (2.1)	2 (2.0)
Hyperglycaemia [a]	0 (0.0)	1 (1.1)	2 (2.0)
Hyperuricaemia [a]	1 (1.1)	2 (2.1)	0 (0.0)
Diabetes mellitus [a]	2 (2.3)	0 (0.0)	0 (0.0)
Bone pain [a]	**3 (3.4)**	0 (0.0)	6 (5.9)
Musculoskeletal pain [a]	0 (0.0)	0 (0.0)	2 (2.0)
Renal failure acute [a]	0 (0.0)	0 (0.0)	2 (2.0)
Lung disorder	-	-	-
Deep vein thrombosis [a]	**2 (2.3)**	1 (1.1)	0 (0.0)

M = melphalan; MedDRA = Medical Dictionary for Drug Regulatory Activities; p = placebo; P = prednisone;
R = lenalidomide; TEAE = treatment-emergent adverse events.
[a] Denotes a ≥ 2% difference between any arms in Study CC-5013-MM-015.
Note: This table includes all grade 3 or 4 adverse events that had a start date on or after the maintenance therapy dosing date.

Serious adverse event / deaths / other significant events

For MM-020, a total of 571 (35.4%) deaths were reported during the study, most (445/571; 77.9%) of which occurred during the follow-up phase. The overall percentage of deaths was lower in the Rd arm of the study than in the Rd18 or MPT arm (171/532 [32.1%] versus 192/540 [35.6%] and 208/541 [38.4%].

Table 30. Summary of deaths including 126 deaths on treatment (within 28 days of the last dose) and 445 deaths during the follow-up period (occurring > 28 days after the last dose) (MM-020).

Death from:	Rd (N = 532) n (%)	Rd18 (N = 540) n (%)	MPT (N = 541) n (%)
Total Deaths	171 (32.1)	192 (35.6)	208 (38.4)
Active Treatment Phase[a]	51 (9.6)	37 (6.9)	38 (7.0)
During Follow-up[b]	120 (22.6)	155 (28.7)	170 (31.4)

d = low-dose dexamethasone; M = melphalan; P = prednisone; R = lenalidomide; T = thalidomide.
[a] Death between first dose date and last dose date + 28 days.
[b] Death after last dose date + 28 days.
Cutoff date: 24 May 2013
Source: CSR MM-020, Table 14.3.2.1.1

Deaths occurring within the first 4 months after the first dose of study drug (either during treatment or the follow-up period) are referred to as “early deaths”. Although patients in the Rd and Rd18 arms received the same study treatment during this timeframe, early deaths were reported more frequently in the Rd arm (24/532 [4.5%]) compared with the Rd18 arm (17/540 [3.1%]). The frequency in the MPT arm was even higher (33/541 [6.1%]). The most common cause of early deaths was attributed to infections and infestations (27/1613; 1.7%), reported with similar frequencies in the Rd18 and MPT arms of the study (Rd18: 8/540 [1.5%], MPT: 8/541 [1.5%]), and with a somewhat higher frequency in the Rd arm (11/532 [2.1%]).

Early deaths from neoplasms benign, malignant and unspecified, including cysts and polyps (mostly MM/disease progression) were reported in 12 (0.7%) patients, and occurred more frequently in the MPT arm of the study than in the Rd or Rd18 arm (8/541 [1.5%] versus 1/532 [0.2%] and 3/540 [0.6%]). Deaths from PD remained higher in the MPT arm of the study over the entire observation period.

Early deaths from cardiac disorders were reported in 9 patients overall (Rd: 5/532 [0.9%]; Rd18: 3/540 [0.6%], MPT: 1/541 [0.2%]). The higher number of early deaths due to cardiac reasons in the Rd arm somewhat reflected the frequency of Grade 5 cardiac arrhythmias.

Other causes of early deaths included acute pulmonary oedema, pulmonary embolism, acute respiratory failure, acute renal failure, general physical health deterioration, death, and suicide in the Rd arm of the study; general physical health deterioration and shock in the Rd18 arm; and pulmonary embolism, acute respiratory failure, pneumonia aspiration, peptic ulcer haemorrhage, oesophageal haemorrhage, cerebral haemorrhage, general physical health deterioration, acute renal failure, renal failure, cerebrovascular accident (CVA), death, and suicide in the MPT arm of the study.

A total of 126 (7.8%) patients died during the active treatment period or within 28 days after the last dose of study drug. Deaths on treatment were reported with a similar frequency in the Rd18 and MPT arms of the study (37 [6.9%] and 38 [7.0%] patients, respectively), and more frequently in the Rd arm of the study (51 [9.6%] patients). This is to be expected in light of the longer treatment duration in the Rd arm (921 person-years) compared to the Rd18 and MPT arms (587 and 549 person-years, respectively.

The most common causes of deaths on treatment (reported in at least 1% of the patients overall) included AEs pertaining to the infections and infestations (41/1613; 2.5%), cardiac disorders (23/1613; 1.4%), general disorders and administration site conditions (21/1613; 1.3%), and neoplasm benign, malignant and unspecified, including cysts and polyps (16/1613; 1.0%) SOCs.

Of the 445 patients who died during the follow-up period, the most common cause of death was MM (218 [49.0%]).

When analysing cumulative deaths over time (6 months and over), the most frequent causes were PD, infections, cardiac event and renal failure.

For MM-015, a total of 244 (53.6%) deaths were reported during the study, most (223/244; 91.4%) of which occurred during the follow-up phase. The overall percentage of deaths was lower in the MPR+R arm of the study than in the MPR+p or MPp+p arm, particularly during the post-treatment phase of the study.

A total of 21 (4.6%) patients died on treatment (up to 30 days after the last dose of study drug): 9 in Arm MPR+R, 5 in Arm MPR+p, and 7 in Arm MPp+p. On-treatment deaths mostly occurred during the induction therapy period. Fourteen deaths overall (i.e., whether they occurred on treatment or during the follow-up period) occurred within 4 months after the first dose of study drug, with no consistent pattern across treatment arms (MPR+R: 7/150 [4.7%], MPR+p: 2/152 [1.3%], MPp+p: 5/153 [3.3%].

Table 31. Summary of deaths including deaths during the induction period, the maintenance period, and the post-treatment period is provided by treatment arm (MM-015).

Death from:	MPR+R (N = 150) n (%)	MPR+p (N = 152) n (%)	MPp+p (N = 153) n (%)
Total Deaths	76 (50.7)	84 (55.3)	84 (54.9)
Induction Therapy Period	7 (4.7)	4 (2.6)	6 (3.9)
Maintenance Therapy Period	2 (1.3)	1 (0.7)	1 (0.7)
Post treatment (OLEP or Follow-up)	67 (44.7)	79 (52.0)	77 (50.3)

M = melphalan; p = placebo; OLEP = open-label extension phase; P = prednisone; R = lenalidomide.
Data cutoff: 30 Apr 2013
Source: CSR MM-015, Table 14.3.2.9.7, Table 14.3.2.9.10.11, Table 14.2.9.10.17, and Table 14.3.2.9.10.18

The most common cause of early death was cardiac disorders (5/455; 1.1%) followed by infections and infestations (4/455; 0.9%). More patients in the MPR+R died from cardiac disorders or infections than in the MPR+p arm (cardiac disorders: 4 versus none; infections: 3 versus 1).

Early deaths from cardiac disorders were reported more frequently in patients receiving MPR+R than in patients receiving Rd (MPR+R: 2.7%; Rd: 0.9%).

Four patients died during the maintenance therapy period: 2 in the MPR+R arm, and 1 in each of MPR+p and MPp+p treatment arm. Cause of death included subarachnoid haemorrhage and cardiovascular insufficiency in the MPR+R arm of the study, and multiple myeloma in 1 patient in each of the MPR+p and MPp+p arms of the study.

Of the 382 patients who were in post-treatment as of the 30 Apr 2013 data cut-off date, a total of 209 (54.7%) patients died. The cause of death was MM in approximately half (110/209; 52.6%) of the patients.

For both studies, when 4 baseline disease characteristics were used to estimate the extent of patients' frailty ECOG performance status, age, ISS disease stage, and baseline renal function, it was observed consistently that patients in the worse stratum died at a higher rate compared to those in the better stratum of each baseline characteristic variable.

On-treatment deaths from infections and infestations were reported in 20/532 (3.8%) patients receiving Rd and in 4/302 (1.3%) patients receiving MPR+R/MPR+p.

On-treatment deaths from cardiac disorders were reported in 10/532 (1.9%) patients in the Rd arm, and in 4/302 (1.3%) patients in the MPR+R/MPR+p arms, including 4 deaths from cardiac arrest in the Rd arm and 1 in the MPR+R/MPR+p arms, 2 deaths from cardiac failure in the Rd arm, and 2 deaths from MI/IHD in the Rd arm. In both studies, most of the patients who died from cardiac causes had baseline risk factors such as older age, hypertension, and relevant prior history and majority of these patients had comorbidities.

In both studies, the most frequently reported SAEs in the lenalidomide-containing arms were in the infections and infestations SOC, with pneumonia the most frequently reported event.

Table 32. TEAE SAEs reported by at least 1% of patients in any treatment arm (MM-020)

System Organ Class Preferred Term[a]	Study MM-020 Rd (N = 532) n (%)	Rd18 (N = 540) n (%)	MPT (N = 541) n (%)
Subjects with ≥ 1 SAE	**359 (67.5)**	**308 (57.0)**	**270 (49.9)**
Infections and Infestations	**163 (30.6)**	**128 (23.7)**	**89 (16.5)**
Pneumonia	52 (9.8)	48 (8.9)	35 (6.5)
Sepsis	15 (2.8)	10 (1.9)	8 (1.5)
Bronchitis	12 (2.3)	6 (1.1)	2 (0.4)
Cellulitis	8 (1.5)	3 (0.6)	2 (0.4)
Lower respiratory tract infection	8 (1.5)	3 (0.6)	4 (0.7)
Respiratory tract infection	8 (1.5)	5 (0.9)	4 (0.7)
Urinary tract infection	8 (1.5)	5 (0.9)	3 (0.6)
Lobar pneumonia	7 (1.3)	7 (1.3)	3 (0.6)
Influenza	6 (1.1)	3 (0.6)	1 (0.2)
Upper respiratory tract infection	6 (1.1)	9 (1.7)	2 (0.4)
Respiratory, Thoracic and Mediastinal Disorders	**71 (13.3)**	**42 (7.8)**	**47 (8.7)**
Pulmonary embolism	20 (3.8)	15 (2.8)	20 (3.7)
Dyspnoea	14 (2.6)	7 (1.3)	8 (1.5)
Chronic obstructive pulmonary disease	9 (1.7)	5 (0.9)	2 (0.4)
Respiratory failure	7 (1.3)	5 (0.9)	4 (0.7)
Pulmonary oedema	6 (1.1)	1 (0.2)	2 (0.4)
Cardiac Disorders	**70 (13.2)**	**51 (9.4)**	**44 (8.1)**
Atrial fibrillation	18 (3.4)	12 (2.2)	9 (1.7)
Cardiac failure	10 (1.9)	11 (2.0)	8 (1.5)
Cardiac failure congestive	7 (1.3)	5 (0.9)	5 (0.9)
Myocardial infarction	7 (1.3)	2 (0.4)	2 (0.4)
Acute myocardial infarction	6 (1.1)	1 (0.2)	4 (0.7)
Angina pectoris	6 (1.1)	2 (0.4)	0 (0.0)
General Disorders and Administration Site Conditions	**62 (11.7)**	**47 (8.7)**	**41 (7.6)**
Pyrexia	18 (3.4)	11 (2.0)	8 (1.5)
General physical health deterioration	13 (2.4)	13 (2.4)	12 (2.2)
Asthenia	10 (1.9)	2 (0.4)	5 (0.9)
Gastrointestinal Disorders	**54 (10.2)**	**39 (7.2)**	**37 (6.8)**
Diarrhoea	7 (1.3)	8 (1.5)	4 (0.7)
Vomiting	7 (1.3)	4 (0.7)	8 (1.5)
Nausea	6 (1.1)	2 (0.4)	7 (1.3)
Musculoskeletal and Connective Tissue Disorders	**52 (9.8)**	**41 (7.6)**	**28 (5.2)**
Back pain	19 (3.6)	19 (3.5)	10 (1.8)
Bone pain	10 (1.9)	6 (1.1)	6 (1.1)
Nervous System Disorders	**49 (9.2)**	**25 (4.6)**	**37 (6.8)**
Syncope	8 (1.5)	3 (0.6)	8 (1.5)
Presyncope	6 (1.1)	1 (0.2)	2 (0.4)

System Organ Class Preferred Term[a]	Study MM-020 Rd (N = 532) n (%)	Rd18 (N = 540) n (%)	MPT (N = 541) n (%)
Metabolism and Nutrition Disorders	**43 (8.1)**	**42 (7.8)**	**24 (4.4)**
Dehydration	6 (1.1)	9 (1.7)	7 (1.3)
Hyponatraemia	6 (1.1)	6 (1.1)	1 (0.2)
Hypercalcaemia	5 (0.9)	10 (1.9)	7 (1.3)
Renal and Urinary Disorders	**43 (8.1)**	**43 (8.0)**	**31 (5.7)**
Renal failure acute	20 (3.8)	16 (3.0)	10 (1.8)
Renal failure	8 (1.5)	18 (3.3)	14 (2.6)
Injury, Poisoning and Procedural Complications	**41 (7.7)**	**29 (5.4)**	**32 (5.9)**
Femur fracture	6 (1.1)	1 (0.2)	0 (0.0)
Humerus fracture	6 (1.1)	1 (0.2)	1 (0.2)
Blood and Lymphatic System Disorders	**40 (7.5)**	**30 (5.6)**	**45 (8.3)**
Anaemia	24 (4.5)	15 (2.8)	23 (4.3)
Neutropenia	9 (1.7)	5 (0.9)	7 (1.3)
Febrile neutropenia	5 (0.9)	7 (1.3)	13 (2.4)
Thrombocytopenia	5 (0.9)	6 (1.1)	10 (1.8)
Neoplasms Benign, Malignant and Unspecified (Incl Cysts and Polyps)	**40 (7.5)**	**28 (5.2)**	**16 (3.0)**
Squamous cell carcinoma of skin	14 (2.6)	5 (0.9)	1 (0.2)
Basal cell carcinoma	10 (1.9)	4 (0.7)	1 (0.2)
Vascular Disorders	**35 (6.6)**	**19 (3.5)**	**21 (3.9)**
Deep vein thrombosis	19 (3.6)	11 (2.0)	8 (1.5)
Hypotension	7 (1.3)	7 (1.3)	1 (0.2)
Psychiatric Disorders	**18 (3.4)**	**13 (2.4)**	**8 (1.5)**
Confusional state	7 (1.3)	6 (1.1)	2 (0.4)

d = low-dose dexamethasone; M = melphalan; P = prednisone; R = lenalidomide; SAE = serious adverse event; T = thalidomide.

[a] System organ classes and preferred terms are coded using MedDRA version 15.1 for Study MM-020. If the same AE was reported multiple times within a given preferred term, only one event with the worst severity was counted per subject.

Note: System organ classes and preferred terms are listed in descending order of frequency for the Arm Rd.
Data cutoff: 24 May 2013
Source: CSR MM-020, Table 14.3.1.4.2.1

For the lenalidomide and dexamethasone arms (Study MM-020), infections and infestations was followed by the respiratory, thoracic and mediastinal disorders and the cardiac disorders SOCs, with pulmonary embolism and atrial fibrillation the most frequently reported events in these SOCs, respectively.

Table 33. TEAE of cardiac arrhythmia reported in at least 2% of the subjects in any treatment arm (MM-020)

Category Preferred Term*	Rd (N = 532) n (%)	Rd18 (N = 540) n (%)	MPT (N = 541) n (%)
Subjects with at least 1 TEAE of cardiac arrhythmia	**133 (25.0)**	**94 (17.4)**	**123 (22.7)**
Atrial fibrillation	37 (7.0)	25 (4.6)	25 (4.6)
Syncope	22 (4.1)	17 (3.1)	27 (5.0)
Bradycardia	20 (3.8)	11 (2.0)	25 (4.6)
Palpitations	16 (3.0)	8 (1.5)	9 (1.7)
Arrhythmia	12 (2.3)	6 (1.1)	10 (1.8)
Sinus bradycardia	12 (2.3)	7 (1.3)	17 (3.1)
Tachycardia	10 (1.9)	11 (2.0)	9 (1.7)

d = low-dose dexamethasone; M = melphalan; MedDRA = Medical Dictionary for Regulatory Activities; P = prednisone; R = lenalidomide; T = thalidomide; TEAE = treatment-emergent adverse event.
* Categories and preferred terms are coded using MedDRA version 15.1 for Study MM-020. If multiple AEs were reported within a given preferred term, only 1 event with the worst grade was counted per subject. Preferred terms are listed in descending order of frequency for the Arm Rd.
Data cutoff: 24 May 2013
Source: CSR MM-020, Table 14.3.2.3.4.2.1

In contrast, in Study MM-015, the blood and lymphatic system disorders and general disorders and administration site conditions SOCs followed the infections and infestations, with neutropenia/febrile neutropenia and pyrexia the most frequently reported events.

Serious AEs of pneumonia (9.8% versus 3.3%), sepsis (2.8% versus 0.7%), pulmonary embolism (3.8% versus 1.3%), atrial fibrillation (3.4% versus 1.7%), acute renal failure (3.8% versus 0.7%), and deep vein thrombosis (3.6% versus 0.7%) were reported more frequently in patients receiving Rd than in patients receiving MPR+R. Serious AEs of neutropenia (4.0% versus 0.7%), febrile neutropenia (6.0% versus 0.9%), and acute myeloid leukaemia (2.7% versus none), on the other hand, were more frequently reported in patients receiving MPR+R, than in patients receiving Rd. The intra-study comparison of these continuous treatment arms with their respective comparators (Rd18 and MPR+p) revealed comparable frequencies that showed limited impact of longer treatment duration with lenalidomide on the safety profile.

The frequency of SAEs of DVT was higher in the lenalidomide-containing regimens compared to the controls in both studies. Apart from the differences in study design, regimens and dosage of lenalidomide, there seemed to be added serious haematologic toxicities when combining lenalidomide with melphalan, and more serious infectious events when combining lenalidomide with dexamethasone.

Second primary malignancies (see SmPC section 4.4)

An increase of second primary malignancies (SPM) has been observed in clinical trials in previously treated myeloma patients receiving lenalidomide/dexamethasone (3.98 per 100 person -years) compared to controls (1.38 per 100 person-years). Non-invasive SPM comprise basal cell or squamous cell skin cancers. Most of the invasive SPMs were solid tumour malignancies.

In clinical trials of newly diagnosed multiple myeloma patients not eligible for transplant, a 4.9-fold increase in incidence rate of haematologic SPM (cases of AML, MDS) has been observed in patients receiving lenalidomide in combination with melphalan and prednisone until progression (1.75 per 100 person-years) compared with melphalan in combination with prednisone (0.36 per 100 person-years).

A 2.12-fold increase in incidence rate of solid tumour SPM has been observed in patients receiving lenalidomide (9 cycles) in combination with melphalan and prednisone (1.57 per 100 person-years) compared with melphalan in combination with prednisone (0.74 per 100 person-years).

In patients receiving lenalidomide in combination with dexamethasone until progression or for 18 months, the haematologic SPM incidence rate (0.16 per 100 person-years) was not increased as compared to thalidomide in combination with melphalan and prednisone (0.79 per 100 person-years).

A 1.3-fold increase in incidence rate of solid tumour SPM has been observed in patients receiving lenalidomide in combination with dexamethasone until progression or for 18 months (1.58 per 100 person-years) compared to thalidomide in combination with melphalan and prednisone (1.19 per 100 person-years).

In clinical trials of newly diagnosed multiple myeloma patients eligible for transplant, an increased incidence rate of haematologic SPM has been observed in patients receiving lenalidomide immediately following high-dose melphalan and Autologous Stem Cell Transplant (ASCT) compared with patients who received placebo (1.27 to 1.56 versus 0.46 to 0.53 per 100 person-years, respectively). Cases of B-cell malignancies (including Hodgkin's lymphoma) observed in the clinical trials were in patients who received lenalidomide in the post-ASCT setting.

The risk of occurrence of haematologic SPM must be taken into account before initiating treatment with Revlimid either in combination with melphalan or immediately following high-dose melphalan and ASCT. Physicians should carefully evaluate patients before and during treatment using standard cancer screening for occurrence of SPM and institute treatment as indicated.

Progression to acute myeloid leukaemia in low- and intermediate-1-risk MDS

- Karyotype

Baseline variables including complex cytogenetics are associated with progression to AML in subjects who are transfusion dependent and have a Del (5q) abnormality. In a combined analysis of two clinical trials of Revlimid in low- or intermediate-1-risk myelodysplastic syndromes, subjects who had a complex cytogenetics had the highest estimated 2-year cumulative risk of progression to AML (38.6%). The estimated 2-year rate of progression to AML in patients with an isolated Del (5q) abnormality was 13.8%, compared to 17.3% for patients with Del (5q) and one additional cytogenetic abnormality.

As a consequence, the benefit/risk ratio of Revlimid when MDS is associated with Del (5q) and complex cytogenetics is unknown.

- TP53 status

A TP53 mutation is present in 20 to 25% of lower-risk MDS Del 5q patients and is associated with a higher risk of progression to acute myeloid leukaemia (AML). In a post-hoc analysis of a clinical trial of Revlimid in low- or intermediate-1-risk myelodysplastic syndromes (MDS-004), the estimated 2-year rate of progression to AML was 27.5 % in patients with IHC-p53 positivity (1% cut-off level of strong nuclear staining, using immunohistochemical assessment of p53 protein as a surrogate for TP53 mutation status) and 3.6% in patients with IHC-p53 negativity (p=0.0038) (see SmPC section 4.8)

Figure 9. Cumulative Incidence Rates Over Time From Randomisation for Invasive Second Primary Malignancies – MM-015 (Safety Population)

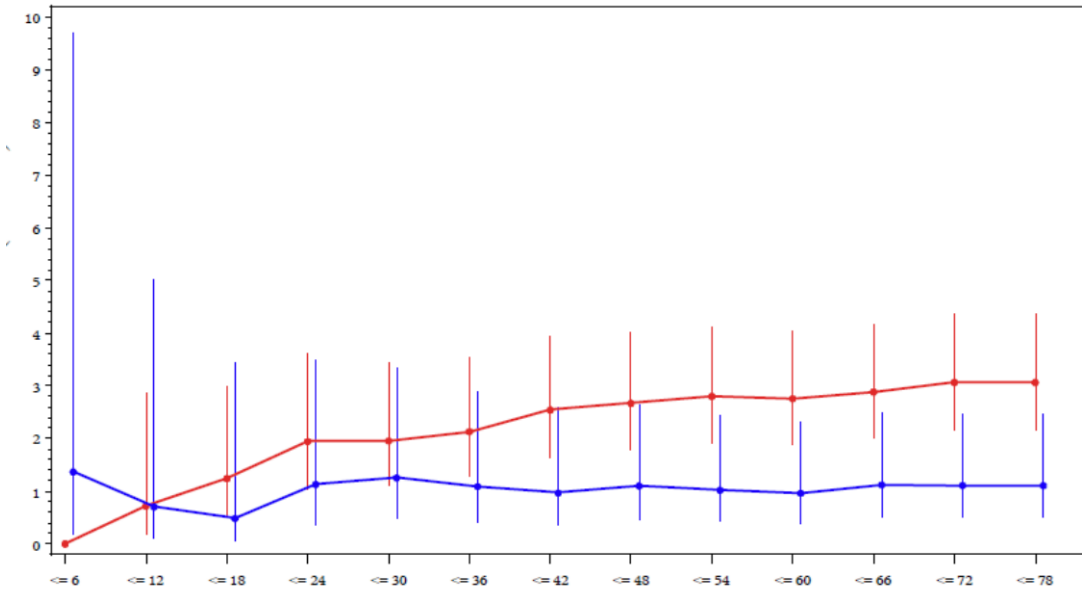

Figure 10. Cumulative Incidence Rates Over Time From Randomisation for Invasive Second Primary Malignancies – IFM 2005-02 (Post transplant, Safety Population)

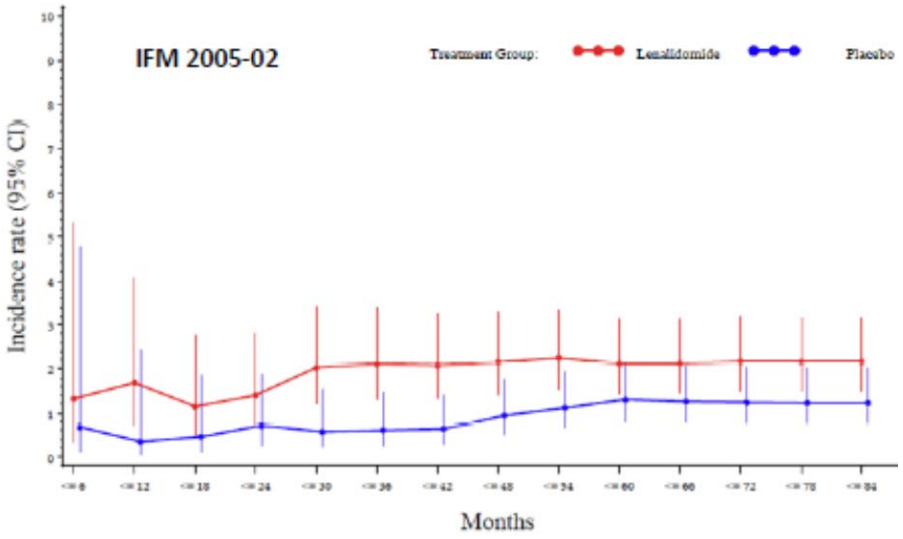

Figure 11. Cumulative Incidence Rates Over Time From Randomisation for Invasive Second Primary Malignancies – MM-020 (Safety Population)

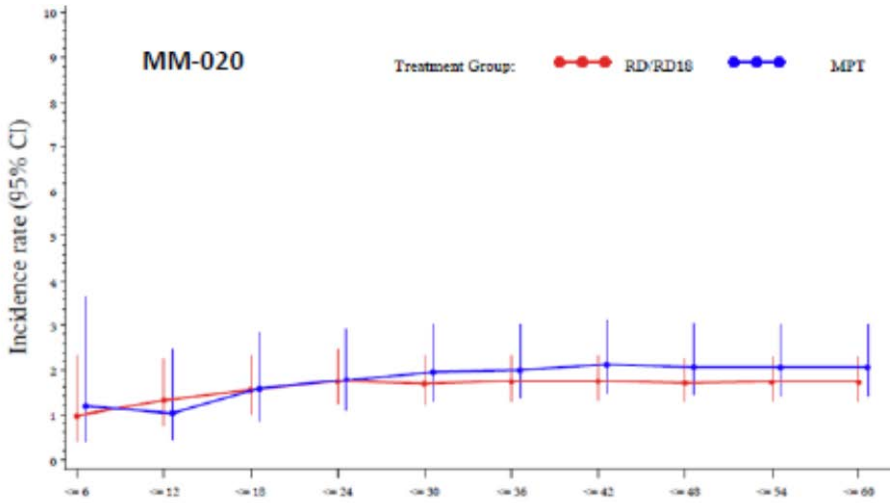

Table 34. Frequencies and Incidence Rates of Subjects With Second Primary Malignancies in Study MM-015 (Safety Population)

	Arm MPR+R (N = 150)			Arm MPR+p (N = 152)			Lenalidomide-containing Arms (MPR+R plus MPR+p) (N = 302)			Arm MPp+ (N = 153)		
SPM Category	**n (%)**	**IR/ 100 PY[a]**	**95% CI**	**n (%)**	**IR/ 100 PY[a]**	**95% CI**	**n (%)**	**IR/ 100 PY[a]**	**95% CI**	**n (%)**	**IR/ 100 PY[a]**	
Haematologic Malignancies	9 (6.0)	1.75	(0.91 – 3.36)	7 (4.6)	1.38	(0.66 – 2.90)	16 (5.3)	1.57	(0.96 – 2.56)	2 (1.3)	0.36	
AML	4 (2.7)	–	–	4 (2.6)	–	–	8 (2.6)	–	–	1 (0.7)	–	
MDS to AML	1 (0.7)	–	–	1 (0.7)	–	–	2 (0.7)	–	–	0	–	
MDS	3 (2.0)[b]	–	–	2 (1.3)	–	–	5 (1.7)[b]	–	–	1 (0.7)	–	
Other[c]	1 (0.7)	–	–	0	–	–	1 (0.3)	–	–	0	–	
Solid Tumors	5 (3.3)	0.97	(0.41 – 2.34)	11 (7.2)	2.16	(1.20 – 3.91)	16 (5.3)	1.57	(0.96 – 2.56)	4 (2.6)	0.74	
Invasive SPMs	**14 (9.3)**	**2.76**	**(1.64 – 4.66)**	**17 (11.2)[d]**	**3.37**	**(2.10 – 5.42)**	**31 (10.3)[d]**	**3.07**	**(2.16 – 4.36)**	**6 (3.9)**	**1.11**	
Non-invasive SPMs (Non-melanoma Skin Cancer)	4 (2.7)	0.77	(0.29 – 2.06)	6 (3.9)	1.19	(0.54 – 2.65)	10 (3.3)	0.98	(0.53 – 1.82)	8 (5.2)	1.51	
TOTAL SPMs	**18 (12.0)**	**3.58**	**(2.26 – 5.69)**	**22 (14.5)[d,e]**	**4.43**	**(2.92 – 6.73)**	**40 (13.2)[d,e]**	**4.01**	**(2.94 – 5.46)**	**14 (9.2)**	**2.69**	

AML = acute myeloid leukaemia; CI = confidence interval; IR = incidence rate; M = melphalan; MDS = myelodysplastic syndromes; p = placebo; P = prednisone; PY = person-year; R = lenalidomide; SPM = second primary malignancy.

[a] Person-year is defined as the time from the date of first dose of study drug to the onset date of the first SPM for subjects with SPMs and to the date of last follow-up for subjects without SPMs.

[b] Includes 1 case of chronic myelomonocytic leukaemia.

[c] Other haematologic malignancy includes 1 subject (Arm MPR+R) with T-cell type acute leukaemia.

Notes: 1) There have been no reports of B-cell malignancies during Study MM-015.

2) Total includes the number of subjects with ≥ 1 SPM. Subjects who had > 1 SPM (eg, 2 types of SPMs) or > 1 episode of an SPM are counted once in each SPM category and once in the total.

Data cutoff date = 30 Apr 2013.

Laboratory findings

Haematology

Laboratory shifts to Grade 3 or Grade 4 post-baseline values for ANC, platelets, and haemoglobin were observed more frequently in the melphalan/prednisone arms of Study MM-020 and of Study MM-015 during its induction therapy period, whether combined with thalidomide (MPT), lenalidomide (MPR+R/MPR+p), or placebo (MPp+p), than in the lenalidomide/dexamethasone arms of Study MM-020 (Rd and Rd18) or than in the lenalidomide arm (MPR+R) or placebo arms (MPR+p and MPp+p) of Study MM-015 during its maintenance therapy period.

Comparing the continuous lenalidomide treatment regimens (i.e., Arm Rd in Study MM-020 and Arm MPR+R in Study MM-015), laboratory shifts to Grade 3 or Grade 4 ANC occurred more frequently in Arm MPR+R than Arm Rd, while shifts to Grade 3 or Grade 4 haemoglobin occurred slightly more frequently in Arm Rd than Arm MPR+R. Shifts to Grade 3 platelets occurred slightly more frequently in Arm Rd, while shifts to Grade 4 platelets occurred more frequently in Arm MPR+R.

Serum Chemistry

Shifts to Grade 3 values for glucose were observed in higher proportions of subjects in the lenalidomide/dexamethasone arms of Study MM-020 (Arm Rd slightly more than Arm Rd18) compared with the melphalan/prednisone arms of Study MM-020 (Arm MPT) or of Study MM-015 (with or without lenalidomide) during its induction and maintenance therapy periods.

These findings are consistent with the known impact that continued dexamethasone therapy has on glucose metabolism. Shifts to Grade 3 values for inorganic phosphorus occurred in higher proportions of subjects in the continuous lenalidomide treatment regimens (i.e., Arm Rd of StudyMM-020 and Arm MPR+R of Study MM-015 during its induction and maintenance therapy periods). Shifts to Grade 4 values for glucose or inorganic phosphorus were rarely noted in either study. Shifts to Grade 4 uric acid values occurred in low and similar proportions in both studies. Shifts to Grade 3 serum creatinine values were infrequently observed in both studies, with similar frequencies across all arms in Study MM-020, and a slightly higher frequency in Arm MPp+p than the lenalidomide-containing arms of Study MM-015. Shifts to Grade 4 serum creatinine values were noted in only 2 subjects in Arm Rd in Study MM-020, and in no subjects in Study MM-015.

Vital Sign Abnormalities

The majority (>82%) of subjects in both studies had normal values for vital sign parameters during treatment. In both studies, shifts from normal baseline values to abnormal postbaseline values for DBP, SBP, pulse, and temperature were noted in < 15% of subjects in any treatment arm, except for pulse (17.4% in Arm MPT) in Study MM-020, with differences of < 5% between treatment arms within each study. In general, slightly higher percentages of subjects in the continuous lenalidomide treatment regimens (ie, Arm Rd in Study MM-020 and Arm MPR+R in Study MM-015) experienced shifts in DBP and/or SBP compared with the other respective arms in each study. Grade 3 or Grade 4 hypotension or hypertension was infrequently reported (≤ 2%) in any treatment arm in both studies

Electrocardiograms

Across both studies, approximately 5% of subjects overall with baseline and post-baseline ECG evaluations had worsening shifts to abnormal CS post-baseline values. No clinically meaningful differences between treatment arms of each study, or between the two studies, were noted in ECG evaluations.

It should be noted that a single dose of lenalidomide up to 50 mg is not associated with prolongation of the QT interval in healthy male subjects. This indicates that lenalidomide is not expected to result in clinically significant prolongation of the QT interval in patients at the approved therapeutic doses.

Safety in special populations

Revlimid should not be used in children and adolescents from birth to less than 18 years because of safety concerns (see SmPC section 4.4).

There was a higher rate of intolerance (grade 3 or 4 adverse events, serious adverse events, discontinuation) in patients with age > 75 years, ISS stage III, ECOG PS≥2 or CrCl<60 mL/min when lenalidomide is given in combination (see SmPC section 4.4).

In both studies, deaths and SAEs were reported more frequently in subjects with a baseline CrCl < 60 mL/min than in subjects with a baseline CrCl ≥ 60 mL/min. In both subgroups, deaths and SAEs were reported more frequently in subjects receiving Rd than in subjects receiving MPR+R. Adverse events leading to discontinuation of lenalidomide were reported more frequently in subjects receiving MPR+R than in subjects receiving Rd, but only in subjects with a baseline CrCl ≥ 60 mL/min.

Table 35. Overview of adverse events is presented by baseline renal function (CrCl ≥ 60 mL/min versus CrCl < 60mL/min), by treatment arms

	Study MM-020			Study MM-015		
				Combined Induction and Maintenance Therapy Periods		
	Rd (N = 532)	Rd18 (N = 540)	MPT (N = 541)	MPR + R (N = 150)	MPR + p (N = 152)	MPp + p (N = 153)
CrCl ≥ 60 mL/min						
Subjects with at least 1:	N = 267 n (%)	N = 287 n (%)	N = 289 n (%)	N = 71 n (%)	N = 82 n (%)	N = 77 n (%)
Grade 3/4 AE	221 (82.8)	224 (78.0)	258 (89.3)	65 (91.5)	63 (76.8)	48 (62.3)
Deaths	11 (4.1)	13 (4.5)	20 (6.9)	1 (1.4)	0 (0.0)	1 (1.3)
SAE	162 (60.7)	147 (51.2)	142 (49.1)	30 (42.3)	29 (35.4)	22 (28.6)
AE leading to treatment discontinuation of lenalidomide or thalidomide or placebo	44 (16.5)	36 (12.5)	76 (26.3)	19 (26.8)	9 (11.0)	4 (5.2)
CrCl < 60 mL/min						
Subjects with at least 1:	N = 265 n (%)	N = 253 n (%)	N = 252 n (%)	N = 77 n (%)	N = 69 n (%)	N = 75 n (%)
Grade 3/4 AE	232 (87.5)	209 (82.6)	222 (88.1)	72 (93.5)	66 (95.7)	58 (77.3)
Deaths	40 (15.1)	24 (9.5)	18 (7.1)	8 (10.4)	5 (7.2)	6 (8.0)
SAE	197 (74.3)	161 (63.6)	128 (50.8)	44 (57.1)	35 (50.7)	34 (45.3)
AE leading to treatment discontinuation of lenalidomide or thalidomide or placebo	65 (24.5)	57 (22.5)	70 (27.8)	20 (26.0)	17 (24.6)	10 (13.3)

AE = adverse event; d = low-dose dexamethasone; M = melphalan; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Event; p = placebo; P = prednisone; R = lenalidomide; SAE = serious adverse event; T = thalidomide.
Severity of the toxicities was graded according to the NCI CTCAE Version 3.0 in both Study MM-020 and Study MM-015.
Data cutoff: 24 May 2013 for MM-020; 30 Apr 2013 for MM-015
Source: SCS MM-020 Table 14.3.1.2.1.1.23, Table 14.3.1.2.1.1.24, Table 14.3.2.2.5.23, and Table 14.3.2.2.5.24
CSR MM-015 Table 14.3.2.8.7, Table 14.3.2.8.8, Table 14.3.2.9.10.7, Table 14.3.2.9.10.8, Table 14.3.2.11.15, and Table 14.3.2.11.16,
SCS MM-015 Table 14.3.2.92.1 and Table 14.3.2.92.2

Table 36. Overview of adverse events for each age stratum (≤ 75 years, > 75 years) by treatment arms.

	Study MM-020			Study MM-015		
				Combined Induction and Maintenance Therapy Periods		
	Rd (N = 532)	Rd18 (N = 540)	MPT (N = 541)	MPR + R (N = 150)	MPR + p (N = 152)	MPp + p (N = 153)
≤ 75 years						
Subjects with at least 1:	**N = 347n (%)**	**N = 348 n (%)**	**N = 357 n (%)**	**N = 114 n (%)**	**N = 116 n (%)**	**N = 116 n (%)**
AE	344 (99.1)	344 (98.9)	356 (99.7)	114 (100.0)	115 (99.1)	116 (100.0)
Grade 3/4 AE	290 (83.6)	269 (77.3)	319 (89.4)	105 (92.1)	95 (81.9)	80 (69.0)
Deaths	22 (6.3)	18 (5.2)	19 (5.3)	4 (3.5)	2 (1.7)	4 (3.4)
SAE	217 (62.5)	184 (52.9)	166 (46.5)	53 (46.5)	44 (37.9)	40 (34.5)
AE leading to treatment discontinuation of lenalidomide, thalidomide or placebo	64 (18.4)	49 (14.1)	92 (25.8)	30 (26.3)	18 (15.5)	11 (9.5)
> 75 years						
Subjects with at least 1:	**N = 185 n (%)**	**N = 192 n (%)**	**N = 184 n (%)**	**N = 36 n (%)**	**N = 36 n (%)**	**N = 37 n (%)**
AE	185 (100.0)	192 (100.0)	183 (99.5)	36 (100.0)	36 (100.0)	37 (100.0)
Grade 3/4 AE	163 (88.1)	164 (85.4)	161 (87.5)	34 (94.4)	35 (97.2)	27 (73.0)
Deaths	29 (15.7)	19 (9.9)	19 (10.3)	5 (13.9)	3 (8.3)	3 (8.1)
SAE	142 (76.8)	124 (64.6)	104 (56.5)	23 (63.9)	20 (55.6)	17 (45.9)
AE leading to treatment discontinuation of lenalidomide, thalidomide or placebo	45 (24.3)	44 (22.9)	54 (29.3)	9 (25.0)	8 (22.2)	3 (8.1)

AE = adverse event; d = low-dose dexamethasone; M = melphalan; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Event; p = placebo; P = prednisone; R = lenalidomide; SAE = serious adverse event; T = thalidomide.
Severity of the toxicities was graded according to the NCI CTCAE Version 3.0 in both Study MM-020 and Study MM-015.
Data cutoff: 24 May 2013 for MM-020; 30 Apr 2013 for MM-015
Source: CSR MM-020, Table 14.3.1.2.1.1.1 and Table 14.3.1.2.1.1.2; SCS MM-020 Table 14.3.2.2.5.1 and Table 14.3.2.2.5.2; CSR MM-015 Table 14.3.2.9.10.1 and Table 13.3.2.9.10.2; SCS MM-015, Table 14.3.2.1.1.1 and Table 14.3.2.1.1.2,

Safety related to drug-drug interactions and other interactions

Several recently completed *in vitro* studies using human biomaterials and clinical studies provide new clinical pharmacology information to support the use of lenalidomide for the treatment of MM. In October 2013, these were submitted to EMA to support a Type II to update the product information, specifically Sections 4.5 and 5.2 of the SmPC (data not shown).

Discontinuation due to adverse events

In MM-020 study, as of 24 May 2013, more subjects experienced at least 1 AE that led to discontinuation of thalidomide (MPT: 13.1%) than to discontinuation of lenalidomide in arms Rd (18.0%) and Rd18 (15.6%).

As of the 03 March 2014 data cut-off date, the rate of AEs leading to the discontinuation of lenalidomide or thalidomide is 22.6% for Arm Rd and 27.0% for Arm MPT, corresponding to a cumulative treatment exposure of 1002 and 549 person-years, respectively.

In MM-015 study, more subjects experienced at least 1 AE that led to discontinuation of lenalidomide in MPR+R arm than to discontinuation of control arm MPp+p whatever the period (induction, maintenance or combined induction+ maintenance).

Table 37. TEAEs leading to discontinuation of the entire regimen in at least 2% of the patients

System Organ Class Preferred Term[a]	Study MM-020			Study MM-015				
				Induction Therapy Period		Maintenance Therapy Period		
	Rd (N = 532) n (%)	Rd18 (N = 540) n (%)	MPT (N = 541) n (%)	MPR+R/MPR+p (N = 302) n (%)	MPp+p (N = 153) n (%)	MPR+R (N = 88) n (%)	MPR+p (N = 94) n (%)	MPp+p (N = 102) n (%)
Subjects with ≥ 1 AE leading to discontinuation of entire regimen	**96 (18.0)**	**84 (15.6)**	**71 (13.1)**	**36 (11.9)**	**10 (6.5)**	**20 (22.7)**	**4 (4.3)**	**4 (3.9)**
General Disorders and Administration Site Conditions	**12 (2.3)**	**16 (3.0)**	**3 (0.6)**	**0 (0.0)**	**1 (0.7)**	**1 (1.1)**	**0 (0.0)**	**0 (0.0)**
General physical health deterioration	4 (0.8)	11 (2.0)	1 (0.2)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)
Gastrointestinal Disorders	**7 (1.3)**	**3 (0.6)**	**2 (0.4)**	**1 (0.3)**	**0 (0.0)**	**3 (3.4)**	**1 (1.1)**	**0 (0.0)**
Diarrhoea	5 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (3.4)	0 (0.0)	0 (0.0)
Neoplasms Benign, Malignant and Unspecified (Incl Cysts and Polyps)	**6 (1.1)**	**4 (0.7)**	**5 (0.9)**	**2 (0.7)**	**1 (0.7)**	**10 (11.4)**	**1 (1.1)**	**0 (0.0)**
Acute myeloid leukaemia	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	4 (4.5)	0 (0.0)	0 (0.0)
Blood and Lymphatic System Disorders	**5 (0.9)**	**6 (1.1)**	**10 (1.9)**	**19 (6.3)**	**3 (2.0)**	**4 (4.5)**	**0 (0.0)**	**0 (0.0)**
Neutropenia	1 (0.2)	2 (0.4)	5 (0.9)	7 (2.3)	2 (1.3)	2 (2.3)	0 (0.0)	0 (0.0)
Thrombocytopenia	1 (0.2)	2 (0.4)	4 (0.7)	9 (3.0)	0 (0.0)	1 (1.1)	0 (0.0)	0 (0.0)

AE = adverse event; d = low-dose dexamethasone; M = melphalan; NR= Not reported; p = placebo; P = prednisone; R = lenalidomide; T = thalidomide.

[a] System organ classes and preferred terms are coded using MedDRA version 15.1 for Study MM-020, and MedDRA version 10.0 for Study MM-015. If the same AE was reported multiple times within a given preferred term, only one event with the worst severity was counted per subject.

Note: System organ classes and preferred terms are listed in descending order of frequency for the Arm Rd of Study MM-020.

Data cutoff: 24 May 2013 for MM-020; 30 Apr 2013 for MM-015

Source: CSR MM-020, Table 14.3.1.2.8.1, Table 14.3.1.2.8.2, Table 14.3.1.2.8.4; CSR MM-015, Table 14.3.2.12.2.3, and SCS MM-015 Table 14.3.2.12.14

Post marketing experience

Since the time of marketing authorisation, important identified and potential risks have been added to the Revlimid RMP for MM. These include: hypersensitivity and angioedema; serious cutaneous reactions such as Stevens-Johnson syndrome, toxic epidermal necrolysis and urticarial, diarrhea and constipation, tumour lysis syndrome (TLS) and second primary malignancy. In addition, during this reporting period hepatic disorders were added to the list of potential risks with Revlimid. More detailed descriptions with regard to cardiovascular events including atrial fibrillation, cardiac failure, cardiac arrhythmias, and myocardial infarction are listed as important potential risks. Another important potential risk identified as part risk for interstitial lung disease was interstitial pneumonitis. Potential risks such as QTc prolongation and hypothyroidism were removed due to downgrading of these events to routine pharmacovigilance monitoring following re-assessment of these risks.

A protocol design for a separate investigation of risk factors for ATE among MM patients treated with thalidomide or lenalidomide will also be submitted (see risk management plan).

The post-marketing safety profile of lenalidomide in the MM settings continues to be consistent with the clinical development programs. Expected AEs are easily monitored and generally manageable. The identified and potential safety concerns and missing information can be monitored by the relevant product information provided to health care professionals and patients in the labelling and provided patient information, as reflected in the RMP. All of these safety concerns are addressed in the planned pharmacovigilance actions. Risks are mitigated through the measures outlined in the risk minimisation plan. The safety profile of lenalidomide continues to be closely monitored with particular attention to important identified and potential risks.

2.6.1. Discussion on clinical safety

Any comparison of two treatment arms with continuous lenalidomide therapy from the pivotal studies is hazardous because of the differences in cohort size, study design, treatment duration and treatment/observation time: In the Rd cohort, 532 patients were treated for a total of 921 person-years; in the MPR+R cohort, 150 patients were treated for a total of 258.6 person-years. However, as lenalidomide is part of a doublet or a triplet, the contribution to toxicity of either alkylator or glucocorticoid cannot be ignored.

Haematologic AE were reported more frequently in patients receiving lenalidomide in combination with melphalan than in combination with dexamethasone. Neutropenia and anaemia were the most frequently reported haematologic AEs in patients receiving continuous treatment with lenalidomide. Neutropenia, anaemia and thrombocytopenia were reported more frequently in patients receiving lenalidomide in combination with melphalan than in combination with dexamethasone. These differences may be related to an additive effect of haematologic toxicity when combining lenalidomide with melphalan.

The major dose limiting toxicities of lenalidomide include neutropenia and thrombocytopenia. In newly diagnosed multiple myeloma patients treated with lenalidomide in combination with low dose dexamethasone, Grade 4 neutropenia was observed in the lenalidomide arms in combination with low dose dexamethasone to a lesser extent than in the comparator arm (8.5% in the Rd ([continuous treatment]) and Rd18 (treatment for 18 four-week cycles) lenalidomide/dexamethasone-treated patients compared with 15% in the melphalan/prednisone/thalidomide arm. Grade 4 febrile neutropenia episodes were consistent with the comparator arm (0.6 % in the Rd and Rd18 lenalidomide/dexamethasone-treated patients compared with 0.7% in the melphalan/prednisone/thalidomide arm (see SmPC sections 4.4 and 4.8). Patients should be advised to promptly report febrile episodes and dose reductions may be required (see SmPC section 4.2).

Grade 3 or 4 thrombocytopenia was observed to a lesser extent in the lenalidomide Rd and Rd18 arms than in the comparator arm (8.1% vs 11.1%, respectively). Patients and physicians are advised to be observant for signs and symptoms of bleeding, including petechiae and epistaxis, especially in patients receiving concomitant medicinal products susceptible to induce bleeding (see SmPC sections 4.4 and 4.8).

The combination of lenalidomide with melphalan and prednisone in newly diagnosed multiple myeloma patients is associated with a higher incidence of grade 4 neutropenia (34.1% in melphalan, prednisone and lenalidomide arm followed by lenalidomide (MPR+R) and melphalan, prednisone and lenalidomide followed by placebo (MPR+p) treated patients compared with 7.8% in MPp+p-treated patients;). Grade 4 febrile neutropenia episodes were observed infrequently (1.7% in MPR+R/MPR+p treated patients compared to 0.0 % in MPp+p treated patients (see SmPC sections 4.4 and 4.8).

The combination of lenalidomide with melphalan and prednisone in clinical trials of multiple myeloma patients is associated with a higher incidence of grade 3 and grade 4 thrombocytopenia (40.4% in MPR+R/MPR+p treated patients, compared with 13.7% in MPp+p treated patients). Patients and physicians are advised to be observant for signs and symptoms of bleeding, including petechiae and epistaxes, especially in patients receiving concomitant medicinal products medications that increase susceptibility to bleeding (see SmPC sections 4.4 and 4.8).

Among non-haematologic events, fatigue, asthenia and pyrexia were the 3 most common AEs across both studies, with an almost identical frequency across studies. Except for pyrexia, these events were reported more frequently in patients receiving Rd than in patients receiving MPR+R. Within each study, however, the frequency of these events in the continuous treatment arm was comparable to that of the comparator arm.

Diarrhea and insomnia were reported more frequently in patients receiving Rd than in patients receiving MPR+R. The frequency of these events was similar in all 3 arms of Study MM-015, and comparable to that observed in the MPT arm of Study MM-020.

Peripheral oedema, back pain and peripheral sensory neuropathy were also reported more frequently in patients receiving Rd than in patients receiving MPR+R. Intra study comparison however revealed that peripheral oedema was reported with a similar frequency in the Rd and MPT (comparator) arm of the study, and that the frequency of peripheral sensory neuropathy was lower in both the Rd and Rd18 arms compared with the MPT arm. There was no increase in peripheral neuropathy observed with long term use of lenalidomide for the treatment of newly diagnosed multiple myeloma (see SmPC section 4.8).

Back pain on the other hand, was reported in a higher proportion of patients receiving Rd regimens compared with patients receiving MP-containing regimens, either combined with lenalidomide or thalidomide, and there was a trend of increased risk with longer treatment duration.

Cataract was reported more frequently in the Rd arms in study MM-020. Given the long term administration of lenalidomide and the likeliness of elderly to develop visual disorders, the Revlimid SmPC should mention in section 4.4 that cataract has been reported with higher frequency in patients receiving lenalidomide in combination with dexamethasone particularly when used for a prolonged time. Regular monitoring of visual ability should be recommended in those patients.

Other common AEs were otherwise reported without meaningful differences between the Rd and MPR+R arms.

A safety topic review provided a cumulative review of encephalopathy from first administration in man through 26 June 2013. Six patients experienced encephalopathy in Study MM-020 (4 in the Rd arm and 2 in the Rd18 arm), and 2 patients in Study MM-015 (1 in each of the MPR+R and MPp+p arms). Overall, the reporting rate of encephalopathy was low, and a direct causal relationship between encephalopathy and lenalidomide could not be determined because most of the cases are confounded by alternative explanations and predisposing or risk factors for the development of encephalopathy.

SAEs of infections occurred with a higher frequency in Rd arm (30.6%) than Rd18 (23.7%) or MPT (16.5%) arms.The SAEs observed more frequently (≥5%) with lenalidomide in combination with Rd or Rd18 than with MPT were pneumonia (9.8%) and renal failure (including acute) (6.3%). These two SAEs are of particular concern since the target population is likely to have comorbidities such as renal or respiratory impairment. To allow early management of renal failure/acute renal failure or infections including pneumonia, the respective warnings in the SmPC have been amended (see SmPC, sections 4.2 and 4.4). The MAH will also conduct post-authorization safety study (PASS) that includes further assessment of the risk of renal failure/acute renal failure and infections in patients with NDMM (see risk management plan).

Treatment emergent adverse events grade 3 or 4 for cardiac, respiratory and renal system-organs show that lenalidomide-treated patients > 75 years have a worse safety profile than patients ≤ 75 years, combination Rd being less tolerated than MPR+R.

Early deaths were reported in MM-020 more frequently in the Rd arm (4.5%) compared with the Rd18 arm (3.1%). The frequency in the MPT arm was even higher (6.1%).

During the induction period of Study MM-015, early death without prior assessment of PD was observed at the same rate for the 2 induction regimens: 5.8% during MPR induction (7 subjects in Arm MPR+R and 4subjects in Arm MPR+p) and 3.9% (6 subjects) during MP induction.

Causes of early deaths were somewhat similar in both pivotal studies i.e. cardiac disorders, infections and infestations, neoplasms, progressive disease.

Myocardial infarction has been reported in patients receiving lenalidomide, particularly in those with known risk factors and within the first 12 months when used in combination with dexamethasone. Patients with known risk factors – including prior thrombosis – should be closely monitored, and action should be taken to try to minimise all modifiable risk factors (eg. smoking, hypertension, and hyperlipidaemia; see SmPC section 4.4).

There is an increased risk of venous thromboembolism (predominantly deep vein thrombosis and pulmonary embolism) and arterial thromboembolism (predominantly myocardial infarction and cerebrovascular event). Venous thromboembolism was seen to a lesser extent with lenalidomide in combination with melphalan and prednisone in newly diagnosed multiple myeloma and with monotherapy in myelodysplastic syndromes (See SmPC sections 4.5 and 4.8).

Second primary malignancies: Patients with MM have an increased risk for AML/MDS. The most consistently identified risk factor for invasive secondary malignancies in the MM studies was prior invasive malignancy. Cases of AML have been observed in clinical trials of newly diagnosed multiple myeloma in patients taking lenalidomide treatment in combination with melphalan or immediately following high dose melphalan and ASCT (see SmPC section 4.4). This increase was not observed, in clinical trials of newly diagnosed multiple myeloma in patients taking lenalidomide in combination with low dose dexamethasone compared to thalidomide in combination with melphalan and prednisone (see SmPC section 4.8).

The early documented difference in MM15 and the transplant studies is not compatible with lenalidomide being mutagenic or tumour inducing by other known mechanisms. A reasonable hypothesis is that the mutagenic insult of melphalan or high dose therapy as add-on to prior chromosomal aberrations leads to secondary tumours and that lenalidomide (and thalidomide) inhibits immunologic (or other) tumour control mechanisms resulting in early progression of the secondary malignancy. This reasonably means that long term lenalidomide therapy is a risk factor for “secondary tumours” also in patients not treated with mutagenic therapies, even though the risk is too small to be detected with certainty in clinical studies. As the licensed indications refer to severe conditions with expected short survival this constitutes no major concern.

The MAH will provide as an additional PV activity annual safety updates of the CONNECT MM registry within PSURs, in order to monitor and evaluate the frequencies of patients with SPMs and the incidence rates of AML, B-cell malignancies, and NMSCs. Additionally, a post authorisation safety study will further assess the safety profile of lenalidomide exploring SPMs risks in the TNE NDMM patients (see risk management plan).

There was a higher rate of intolerance (grade 3 or 4 adverse events, serious adverse events, discontinuation) in patients with age > 75 years, ISS stage III, ECOG PS$\geqslant$2 or CrCl<60 mL/min when lenalidomide is given in combination. Patients should be carefully assessed for their ability to tolerate lenalidomide in combination, with consideration to age, ISS stage III, ECOG PS$\leqslant$2 or CrCl<60 mL/min (see SmPC, sections 4.2, 4.4 and 4.8).

Recommended dose adjustments during treatment and restart of treatment to manage grade 3 or 4 thrombocytopenia, neutropenia, or other grade 3 or 4 toxicity judged to be related to lenalidomide are provided in section 4.2 of the SmPC. A summary of ADRs reported in clinical studies in patients with multiple myeloma treated with lenalidomide in combination with dexamethasone, or with melphalan and prednisone, or as monotherapy as well as from post-marketing use are reported in section 4.8 of the SmPC.

2.6.2. Conclusions on the clinical safety

As measured by study drug discontinuations, about 20%, the Rd regimen is moderately well tolerated taking duration of therapy into account, median about 20 months. From a tolerability perspective, dexamethasone 40

mg QD Days 1, 8, 15, and 22 of each 28-day cycle, seems to be the major problem even though typical lenalidomide adverse reactions were frequent.

The MPR regimen constitutes a rather intensive induction therapy and about 15% of the patients went off therapy during this phase, in patients > 75 years about 25%. Maintenance therapy with lenalidomide was overall well tolerated.

The CHMP considers the following measures necessary to address issues related to safety:

A post-authorisation non-interventional, safety study of transplant-ineligible patients with newly diagnosed multiple myeloma (NDMM) treated with lenalidomide to gather safety data on the use of lenalidomide in NDMM patients.

This PASS is intended to enhance understanding of the safety profile of lenalidomide among real-world, newly diagnosed transplant-ineligible MM patients, particularly for cardiovascular, cerebrovascular, and peripheral vascular events and in light of risk factors for these events.

2.7. Risk Management Plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

PRAC Advice

Based on the PRAC review of the Risk Management Plan version 24.0 the PRAC considers by consensus that the risk management system for lenalidomide (Revlimid) in the treatment of adult patients with previously untreated multiple myeloma who are not eligible for transplant is acceptable.

This advice is based on the following content of the Risk Management Plan.

Safety concerns

The applicant identified the following safety concerns in the RMP:

Table 38. Summary of the Safety Concerns

Summary of safety concerns	
Important identified risks	-Teratogenicity -Thrombocytopenia and bleeding -Neutropenia and infection -Thromboembolic events -Cutaneous reactions -Hypersensitivity and angioedema -Diarrhoea and constipation -TLS <u>Important Identified Risks Related to Indication/Target Population</u> -For NDMM: AML and B-cell malignancies[a] -For RRMM: NMSC[b]
Important potential risks	-Peripheral neuropathy -Cardiac failure -Cardiac arrhythmias -Renal failure -Ischaemic heart disease (including myocardial infarction)

	-Interstitial lung disease (interstitial pneumonitis) -Hepatic disorders -Off-label use <u>Important Potential Risks Related to Indication/Target Population</u> -For NDMM: NMSC[b] -For RRMM: AML and B-cell malignancies[a] -For MDS: AML and B-cell malignancies[a]; NMSC[b] -Other SPM (ie, those not detailed above for the NDMM, RRMM and MDS populations)
Missing information	-Paediatric use -Use in moderate and severe hepatic impairment -Use in breastfeeding

[a] The risk of AML and B-cell malignancies is an identified risk for the NDMM population, and a potential risk for the RRMM and MDS populations

[b] The risk of NMSC is an identified risk for the RRMM population, and a potential risk for the NDMM and MDS populations

The PRAC agreed.

Pharmacovigilance plans

Table 39. Ongoing and planned studies in the PhV development plan

Study / Activity **Type, Title and category (1-3)**	**Objectives**	**Safety concerns addressed**	**Status Planned, started**	**Date for submission of interim or final reports (planned or actual)**
Connect® MM Registry. *Category 3*	The primary objectives of the registry are to describe practice patterns of common first-line and subsequent treatment regimens (including lenalidomide based) in patients with previously untreated MM, whether or not eligible for transplant, as well as diagnostic patterns and second primary malignancy occurrence in a “real world” population.	SPM (AML and B-cell malignancies, NMSC and other SPM), cardiac events (cardiac failure, cardiac arrhythmias, ischaemic heart disease [including MI]), renal failure, neutropenia and infection.	Ongoing	Safety updates submitted with future PSURs.
Revlimid TNE	The primary objective	Cardiac events	Planned	The MAH

NDMM Registry *Noninterventional:* *Category 1*	is to further assess the safety profile of lenalidomide, including but not limited to cardio-vascular safety and the effect of potential risk factors on early cardiovascular events (including MI/ischaemic heart disease) in adult patients with previously untreated MM not eligible for transplant.	(cardiac failure, Cardiac arrhythmias, ischaemic heart disease [including MI]).	Protocol synopsis has been submitted.	commits to providing a full protocol for review within 1 month of EC approval. The final study report could be available in 2022. Safety updates submitted with future PSURs.
RRMM PASS *Noninterventional:* *Category 3*	To monitor safety in a "real world" situation.	Celgene PPP. Safety profile in a 'real world' setting.	Ongoing	Safety updates submitted with future PSURs.
MDS PASSes *Noninterventional:* *observational* *Category 1*	To gather safety data on the use of lenalidomide in MDS patients and monitor off-label use (prospective disease registry in transfusion-dependent low- and INT-1-risk MDS with an isolated del 5q and a retrospective drug utilisation study of Revlimid in MDS).	AML and survival. Safety profile in a 'real world' setting.	Planned Protocols Have been provided.	Safety updates submitted with future PSURs.
Pooled analysis of data from clinical trials of Revlimid. *Category 3*	To determine the incidence of VTEs and ATEs in patients with MM, with consideration of the thrombo-prophylactic agents used.	TEEs	Ongoing	To be submitted in the next PSUR update.
CONNECT® MDS/AML Disease Registry *Noninterventional:* *observational* *Category 3*	The primary objectives of the registry are to describe practice patterns of common first-line treatment regimens (including lenalidomide-based) in the community and academic settings. Additionally, the registry will provide insight into treatment regimens and therapy sequence in clinical practice as they	AML and B-cell malignancies NMSC Other SPM	Ongoing	Safety updates submitted with future PSURs.

	relate to clinical outcomes (response, OS, PFS) in patients with symptomatic MDS. Data regarding SPM are also being collected.			

The PRAC, having considered the data submitted, was of the opinion that the proposed post-authorisation PhV development plan is sufficient to identify and characterise the risks of the product.

Risk minimisation measures

Table 40. Summary table of Risk Minimisation Measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Important identified risk		
Teratogenicity	Routine risk minimisation activities (SmPC and PL). Section 4.3: Contraindicated in pregnant women and in women of childbearing potential unless all the conditions of the Celgene PPP are met. Section 4.4: Warnings and precautions for use -Criteria for women of non-childbearing potential -Counselling -Contraception -Pregnancy testing -Precautions for men -Additional precautions -Reference to educational materials. Section 4.6: Fertility, pregnancy and lactation Sections 4.8 and 5.3: The potential teratogenic effects of lenalidomide are highlighted. Specific pregnancy reporting form	-Celgene PPP -Educational Programme o Direct HCP communication prior to launch o Direct HCP communication with findings from CC-501-TOX-004 o HCP kit to include booklet o Treatment algorithm, pregnancy reporting form, patient card, patient brochure and checklists. -Therapy management o Criteria for determining women of childbearing potential, Contraceptive measures and pregnancy testing for women of childbearing potential o Advice in SmPC, Dear HCP letter and educational materials -System to ensure appropriate measures have been completed -Patient card to document childbearing status, counselling and pregnancy testing
Thrombocytopenia and Bleeding	-Section 4.2 of SmPC: dose reduction advice for thrombo- cytopenia. Section 4.4 of SmPC: warning of thrombocytopenia and bleeding, and advice for monitoring by blood testing. -Listed as ADRs in Section 4.8 of SmPC. -Advice to patients in PL	-'Dear HCP' letter prior to launch. -HCP Kit. -Patient Brochure.
Neutropenia and Infection	-Section 4.2 of SmPC: dose reduction advice for neutropenia.	-'Dear HCP' letter prior to launch. -HCP Kit.

	-Section 4.4 of SmPC: warning of neutropenia, and infection with or without neutropenia, and advice for monitoring by blood testing. Advice that patients should report febrile incidences promptly. -Listed as ADRs in Section 4.8 of SmPC. -Advice to patients in PL.	-Patient Brochure
Thromboembolic Events	-Section 4.4 of SmPC warning. -Listed as ADRs in Section 4.8 of SmPC. -Advice to patients in PL.	-'Dear HCP' letter prior to launch -HCP Kit -Patient Brochure
Cutaneous Reactions	-Stevens-Johnson syndrome and toxic epidermal necrolysis discussed in Sections 4.2, 4.4 and 4.8 of SmPC and in the PL.	-HCP Kit
Hypersensitivity and Angioedema	-SmPC Section 4.3: contraindicated in patients who are hypersensitive to the active substance or any of the excipients. -Allergic reactions discussed in Section 4.4. -Hypersensitivity listed as an ADR in Section 4.8 of SmPC and in PL. -Angioedema discussed in Sections 4.2 and 4.8 of SmPC and in the PL.	-HCP Kit
Diarrhoea and Constipation	-Listed as ADRs in Section 4.8 of SmPC and in the PL.	None
Tumour lysis Syndrome	-Section 4.4 of SmPC warning. -Listed as an ADR in Section 4.8 of SmPC.	-HCP Kit
Acute Myeloid Leukaemia and B-cell Malignancies	-Section 4.4 of SmPC warning. -Listed as ADRs in Section 4.8 of SmPC. -Advice to patients provided in PL. -Event specific questionnaire for the collection of the AE and follow-up.	-'Dear HCP' letter prior to launch. o 'Dear HCP' letter following EC Approval for MDS o 'Dear HCP' letter after CHMP opinion of Article 20 procedure EMEA/H/C/717/A20/048 received 22 Sep 2011. -HCP Kit.
Non-melanoma Skin Cancers	-Section 4.4 of SmPC warning. -SPM listed as ADRs in Section 4.8 of SmPC. -Advice to patients provided in PL. -Event specific questionnaire for the collection of the AE and follow-up.	-'Dear HCP' letter prior to launch. o 'Dear HCP' letter following EC Approval for MDS o 'Dear HCP' letter after CHMP opinion of Article 20 procedure EMEA/H/C/717/A20/048 received 22 Sep 2011. -HCP Kit.
Important potential risks		
Peripheral Neuropathy	-Section 4.4 of SmPC warning. -Listed as an ADR in Section 4.8 of SmPC.	-'Dear HCP' letter prior to launch -HCP Kit
Cardiac Failure and Cardiac Arrhythmias	-Listed as ADRs in Section 4.8 of SmPC. -Listed in PL.	None

Renal Failure	-Listed as an ADR in Section 4.8 of SmPC.	None
Ischaemic Heart Disease (including myocardial infarction)	The association between ischaemic heart disease and lenalidomide is unknown. Close monitoring will continue. Myocardial infarction is included in Sections 4.4 and 4.8 of the SmPC.	None
Interstitial Lung Disease (interstitial pneumonitis)	-Listed as an ADR in Section 4.8 of SmPC	None
Hepatic Disorders	-The possible occurrence of hepatic disorders is detailed in Section 4.4 and Section 4.8 of SmPC.	-Dear HCP letter after EC approval of variation EMEA/H/C/00717/058 received 19 Nov 2012.
Other SPM	-Section 4.4 of SmPC warning. -SPM listed as ADRs in Section 4.8 of SmPC. -Advice to patients provided in PL. -Event specific questionnaire for the collection of the AE and follow-up.	-'Dear HCP' letter prior to launch. o 'Dear HCP' letter following EC Approval for MDS o 'Dear HCP' letter after CHMP opinion of Article 20 procedure EMEA/H/C/717/A20/048 received 22 Sep 2011. -HCP Kit.
Off-label Use	-Collection of off-label use data detailed in Section 4.4 of SmPC	-'Dear HCP' letter prior to launch. o Dear HCP letter following EC Approval for MDS -HCP Kit.
Missing information		
Paediatric Use	-Section 4.2: advice to not use in the paediatric age group. -Advice to patients in PL.	None
Use in Moderate and Severe Hepatic Impairment	- Section 4.2: no specific dose recommendations.	None
Use in Breastfeeding	-Section 4.6: advice to discontinue breastfeeding during therapy with lenalidomide. -Advice to patients in PL.	None

The PRAC, having considered the data submitted, was of the opinion that the proposed risk minimisation measures are sufficient to minimise the risks of the product in the proposed indication.

The CHMP endorsed this advice without changes.

2.8. Product information

As a consequence of the new indication, sections 4.1, 4.2, 4.4, 4.8, and 5.1 of the SmPC have been updated. Particularly, new warnings regarding the higher rate of intolerance (in patients with age > 75 years) and cataract have been added to the product information. The Package Leaflet has been updated accordingly.

Furthermore, Annex II has been amended to reflect the additional PASS required:

A post-authorisation non-interventional, safety study of transplant-ineligible patients with newly diagnosed multiple myeloma (NDMM) treated with lenalidomide to gather safety data on the use of lenalidomide in NDMM patients.

2.8.1. User consultation

A full user consultation with target patient groups on the package leaflet has been submitted by the applicant and has been found acceptable.

3. Benefit-Risk Balance

Benefits

Beneficial effects

For both studies statistically significant difference in terms of PFS in TNE population in favour of treatment using lenalidomide in combination has been shown in pivotal and supportive studies in the different settings either as a doublet (Rd) or a triplet (MPR).

In the MM-015 study, continuous lenalidomide treatment (MPR+R) has a bigger impact on improvement of PFS than MP. Progression free survival was significantly longer in arm MPR+R than arm MPp+p (HR=0.37, CI 0.27-0.50, p < 0.001), corresponding to a median difference of about 14.3 months (27.4 months vs 13.1 months).

This effect was further substantiated by results in the secondary efficacy endpoints: PFS2 was significantly longer in arm MPR+R than arm MPp+p (HR=0.701, 95% CI = 0.536-0.916, p=0.009) corresponding to a median difference of 10.9 months (28.8 months to 39.7 months). The addition of lenalidomide to MP induction therapy was associated with notably higher response rates (78.9% and 75.8%, respectively) compared to 54.5% for MP alone (Arm MPp+p) (p<0.001). The median duration of response was longest in Arm MPR+R (26.5 months) compared to Arms MPR+p (12.4 months) and MPp+p (12.0 months).

In the MM-020 study, PFS was significantly longer in arm Rd than arm MPT (HR 0.69, 95% CI 0.59 - 0.80, p < 0.001) with a difference of 4.1 months in median PFS.

Overall survival (secondary endpoint) was also in favour of Arm Rd versus Arm MPT (HR= 0.75, 95% CI 0.62-0.90, p=0.002) with a 10.4-month difference in median OS. PFS2 was significantly longer in arm Rd than arm MPT (HR=0.75, 95% CI0.62-0.90, p=0.002) results corresponding to a median difference of 7.9 months (42.9 months to 35 months). The addition of lenalidomide to dexamethasone was associated with higher response rates (75.1% and 73.4%, respectively) compared to 62.3% for MPT alone. The median duration of response was longest in Arm Rd (35.0 months) compared to Arm MPT (22.3 months).

Uncertainty in the knowledge about the beneficial effects

One uncertainty that was identified during the assessment was the overall survival results in MM-015 study. However the absence of a survival benefit was attributed to long survival post-progression and the high rate of cross-over to lenalidomide containing regimens in the control arms therefore this uncertainty was satisfactorily addressed (see discussion on clinical efficacy). In any case, an important detriment in OS could be ruled out.

Risks

Unfavourable effects

The most frequent AEs were neutropenia and thrombocytopenia (more frequent in combination with melphalan), infections, and VTEs (more frequent in combination with dexamethasone). Among non-haematologic events, fatigue, asthenia, and pyrexia were the 3 most common AEs across both studies, with an almost identical frequency across studies. Except for pyrexia, these events were reported more frequently in patients receiving Rd than in patients receiving MPR+R. Within each study, however, the frequency of these events in the continuous treatment arm was comparable to that of the comparator arm.

The impact of lenalidomide on neutrophils and/or platelet is already been pointed out, in the SmPC, with a warning (threshold for ANC and/or platelet counts). However, SAEs of infections occurred with a higher frequency in Rd arm (30.6%) than Rd18 (23.7%) or MPT (16.5%) arms.

In both studies, continuous treatment with lenalidomide is associated with a higher frequency of myocardial infarction/ischaemic heart disease (MI/IHD) compared with fixed treatment duration and comparator arms, which is roughly proportionate with the longer duration of treatment (and observation for TEAEs) for subjects on the continuous treatment study arms. The small number of events and relatively large number of potential risk factors examined make it difficult to draw a definitive conclusion whether this imbalance is due to previous history of cardiac disorders or related to the drug.

SAEs and specifically treatment related SAE were reported more frequently in the Rd arm than the Rd18 or MPT.

Uncertainty in the knowledge about the unfavourable effects

The SAEs observed more frequently (⩾5%) with lenalidomide in combination with Rd or Rd18 than with MPT were pneumonia (9.8%) and renal failure (including acute) (6.3%). These two SAEs are of particular concern since the target population is likely to have comorbidities such as renal or respiratory impairment. To allow early management of renal failure/acute renal failure or infections including pneumonia, the respective warnings in the SmPC have been amended (see SmPC, sections 4.2 and 4.4). The MAH will also conduct post-authorisation safety study (PASS) that includes further assessment of the risk of renal failure/acute renal failure and infections in patients with NDMM (see risk management plan).

In the NDMM setting, there is a risk of occurrence of second primary malignancies (SPMs). A 4.9-fold increase in incidence rate of haematologic SPM (cases of AML, MDS) has been observed in patients receiving lenalidomide in combination with melphalan and prednisone until progression (1.75 per 100 person-years) compared with melphalan in combination with prednisone (0.36 per 100 person-years). In patients receiving lenalidomide in combination with dexamethasone until progression or for 18 months, the haematologic SPM incidence rate (0.16 per 100 person-years) was not increased as compared to thalidomide in combination with melphalan and prednisone (0.79 per 100 person-years). A 1.3-fold increase in incidence rate of solid tumour SPM has been observed in patients receiving lenalidomide in combination with dexamethasone until progression or for 18 months (1.58 per 100 person-years) compared to thalidomide in combination with melphalan and prednisone (1.19 per 100 person-years). The MAH will provide as an additional PV activity annual safety updates of the CONNECT MM registry within PSURs, in order to monitor and evaluate the frequencies of patients with SPMs and the incidence rates of AML, B-cell malignancies, and NMSCs. Additionally, a post authorisation safety study will further assess the safety profile of lenalidomide exploring SPMs risks in the TNE NDMM patients (see risk management plan and Annex II).

Early deaths were reported more frequently in the Rd arm (4.5%) compared with the Rd18 arm (3.1%). The frequency in the MPT arm was even higher (6.1%). Causes of early deaths were somewhat similar in both pivotal studies i.e. cardiac disorders, infections and infestations, neoplasms, progressive disease. It is not possible to exclude any association between early death from cardiac cause and lenalidomide in combination with dexamethasone. In order to monitor the occurrence of cardiac events and to further explore and understand the relationship between MI/IHD and lenalidomide, the MAH proposes 2 additional PV measures: a regular update on the Connect MM Registry data and a PASS/product registry for TNE NDMM in selected European countries following the approval. Furthermore the SmPC has been updated to reflect this issue.

Benefit-risk balance

Importance of favourable and unfavourable effects

Myeloma is highly symptomatic during active and progressive disease, therefore a delay in progression or death (PFS) of the magnitude observed, i.e., difference in median PFS of 4 months or 14 months, is considered clinically meaningful. Supportive data in terms of secondary endpoints, including OS in study MM-020 were adequate. During induction therapy pain was improved in the lenalidomide arms. This is as expected due to higher response rates, pain being a cardinal symptom in MM.

The major dose limiting toxicities of lenalidomide include neutropenia and thrombocytopenia. The most frequent AEs were neutropenia and thrombocytopenia (more frequent in combination with melphalan), infections, and VTEs (more frequent in combination with dexamethasone). The AR profiles of the MPR+R and Rd regimens are considered sufficiently well characterised from a risk perspective and are generally manageable and are considered acceptable. “Side effects” as captured by the PRO showed no difference between study arms.

Benefit-risk balance

The ADRs of lenalidomide are generally manageable and are considered acceptable. Therefore, in view of the clinically meaningful benefits in terms of PFS, the benefit-risk balance for lenalidomide in the target population is positive.

Discussion on the benefit-risk balance

The results of the two main studies MM-015 AND MM-020 are considered of clinical relevance. The statistically significant and clinically relevant improvement in PFS supports a clinical benefit associated with lenalidomide treatment in the target population.

The benefit of adding lenalidomide until progression to a 9-cycle MP induction regimen was large (acknowledging though that MP is no longer considered the most active regimen). The absence of a survival benefit is likely due to long survival post-progression and a high proportion of patients switching treatment to lenalidomide. Lenalidomide maintenance (vs. placebo) was reasonably well tolerated and apparently did not negatively affect the activity of next-line therapies in terms of PFS2; no detriment in terms of OS is expected.

When contextualised, the MPR+R regimen tested in MM-015 is still regarded as a clinically relevant regimen for the indication proposed, i.e. treatment naïve and transplant ineligible patients with multiple myeloma.

The Rd regimen administered until progression has clearly shown to provide a clinically meaningful improvement in PFS (primary endpoint) and OS (secondary endpoint) over a MPT regimen that is currently a first line treatment option for transplant non-eligible patients with MM. Thus a favourable B/R has been shown. Although there might be an increased risk for solid tumour development in patients treated with Rd regimens,

the signal was weak. In view of the magnitude of the signal and the favourable results of in terms of OS, the adverse consequences on the benefit-risk balance are not considered to be of concern.

4. Recommendations

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Revlimid is not similar to Thalidomide Celgene neither to Imnovid within the meaning of Article 3 of Commission Regulation (EC) No. 847/200. See appendix 1.

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus the addition of the 20 mg strength and considers by majority decision that the risk-benefit balance of Revlimid in the treatment of adult patients with previously untreated multiple myeloma who are not eligible for transplant is favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Conditions and requirements of the Marketing Authorisation

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

Additional risk minimisation measures

1. The MAH shall agree the details of a controlled distribution system with the National Competent Authorities and must implement such programme nationally to ensure that:

- Prior to launch, all doctors who intend to prescribe Revlimid and all pharmacists who may dispense Revlimid receive a Direct Healthcare Professional Communication as described below.
- Prior to prescribing (and where appropriate, and in agreement with the National Competent Authority, prior to dispensing) all healthcare professionals who intend to prescribe (and dispense) Revlimid are provided with a physician information pack containing the following:
  - Educational Health Care Professional's kit
  - Educational brochures for Patients
  - Patient cards
  - Summary of Product Characteristics (SmPC) and Package Leaflet and Labelling.

2. The MAH shall implement a pregnancy prevention programme (PPP) in each Member State. Details of the PPP should be agreed with the National Competent Authorities in each Member State and put in place prior to the marketing of the product.

3. The MAH should agree the final text of the Direct Healthcare Professional Communication and the physician information pack contents with the National Competent Authority in each Member State and ensure that the materials contain the key elements as described below.

4. The MAH should agree on the implementation of the patient card system in each Member State.

5. The MAH should also agree with each Member State:

- The details of the implementation of the MDS Post-Authorisation Safety Study (MDS PASS)
- The set-up of national measures to assess the effectiveness of and compliance with the PPP.

Key elements to be included

Direct Healthcare Professional Communications

The Direct Healthcare Professional Communication shall consist of two parts:

- A core text as agreed by the CHMP.
- National specific requirements agreed with the National Competent Authority regarding:
  - Distribution of the product
  - To ensure that all appropriate measures have been performed prior to Revlimid being dispensed

The Educational Healthcare Professional's Kit

The Educational Health Care Professional's Kit shall contain the following elements:

- Brief background on lenalidomide and its licensed indication
- Posology
- The need to avoid foetal exposure due to teratogenicity of lenalidomide in animals and the expected teratogenic effect of lenalidomide in humans including a summary of the results of study CC-5013-TOX-004
- Obligations of the health care professional in relation to the prescribing of Revlimid
  - Need to provide comprehensive advice and counselling to patients
  - That patients should be capable of complying with the requirements for the safe use of Revlimid
  - Need to provide patients with appropriate patient educational brochure and patient card
- Safety advice relevant to all patients
  - Description and management of neutropenia and thrombocytopenia including incidence rates from clinical trials
  - Description and management of thromboembolic risk including incidence rates from clinical trials and post-marketing experience
  - Use in patients with hepatic and/or renal impairment
  - Disposal of unwanted medicine
  - Local country specific arrangements for a prescription for Revlimid to be dispensed
  - Description of risk of hypothyroidism
  - Explanation of unknown risk of neuropathy with long term use

- Description of the risk of progression to AML in MDS patients including incidence rates from clinical trials
- Description of the PPP and categorisation of patients based on sex and childbearing potential
  - Algorithm for implementation of PPP
  - Definition of women of childbearing potential (WCBP) and actions the physician should take if unsure
- Safety advice for women of childbearing potential
  - The need to avoid foetal exposure
  - Description of the PPP
  - Need for adequate contraception (even if woman has amenorrhoea) and definition of adequate contraception
  - Pregnancy test regime
    - Advice on suitable tests
    - Before commencing treatment
    - During treatment based on method of contraception
    - After finishing treatment
  - Need to stop Revlimid immediately upon suspicion of pregnancy
  - Need to tell treating doctor immediately upon suspicion of pregnancy
- Safety advice for men
  - The need to avoid foetal exposure
  - The need to use condoms if sexual partner is pregnant or a WCBP not using effective contraceptions (even if man has had a vasectomy)
    - During Revlimid treatment
    - For one week following final dose.
  - That if his partner becomes pregnant whilst he is taking Revlimid or shortly after he has stopped taking Revlimid he should inform his treating doctor immediately
- Requirements in the event of pregnancy
  - Instructions to stop Revlimid immediately upon suspicion of pregnancy
  - Need to refer to physician specialised or experienced in dealing with teratology and its diagnosis for evaluation and advice
  - Local contact details for reporting of any suspected pregnancy
  - Pregnancy reporting form
- Check list for physicians ensuring that patients receive the appropriate counselling concerning the treatment, contraceptive methods and pregnancy prevention appropriate for their sex and childbearing status
- Details on the MDS PASS emphasising that prior to prescribing Revlimid, the healthcare professionals should enroll MDS patients into the PASS.
- Adverse event reporting forms

Educational Brochures for patients

The Educational brochures for patients should be of 3 types:
- Brochure for women patients of childbearing potential and their partners
- Brochure for women patients who are not of childbearing potential
- Brochure for male patients

All patient brochures should contain the following elements:
- That lenalidomide is teratogenic in animals and is expected to be teratogenic in humans
- That Revlimid may cause neutropenia and thrombocytopenia and the need for regular blood tests
- That Revlimid may cause venous and arterial thromboembolism
- Description of the patient card and its necessity
- Disposal of unwanted medicine
- National or other applicable specific arrangements for a prescription for Revlimid to be dispensed
- That the patient should not give Revlimid to any other person
- That the patient should not donate blood
- That the patient should tell their doctor about any adverse events
- That a study is being conducted to collect information regarding the safety of the drug and to monitor its appropriate use; and that MDS patients should be included in the study prior to the start of the treatment with Revlimid

The following information should also be provided in the appropriate brochure:

Brochure for women patients with childbearing potential

- The need to avoid foetal exposure
- Description of the PPP
- Need for adequate contraception and definition of adequate contraception
- Pregnancy test regime
  - Before commencing treatment
  - During treatment, every 4 weeks except in case of confirmed tubal sterilisation
  - After finishing treatment
- The need to stop Revlimid immediately upon suspicion of pregnancy
- The need to contact their doctor immediately upon suspicion of pregnancy

Brochure for male patients

- The need to avoid foetal exposure
- The need to use condoms if sexual partner is pregnant or a WCBP not using effective contraceptions (even if man has had vasectomy)
  - During Revlimid treatment
  - For one week following final dose
- That if his partner becomes pregnant he should inform his treating doctor immediately

Patient Card

The patient card shall contain the following elements:

- Verification that appropriate counselling has taken place
- Documentation of childbearing status potential
- Pregnancy test dates and results

- **Obligation to complete post-authorisation measures**
- The MAH shall complete, within the stated timeframe, the below measures:

Description	**Due date**
A post-authorisation non-interventional, safety study of patients with myelodysplastic syndromes (MDS) treated with lenalidomide to gather safety data on the use of lenalidomide in MDS patients and monitor off-label use.	Annual safety updates with PSURs
A post-authorisation non-interventional, safety study of transplant-ineligible patients with newly diagnosed multiple myeloma (NDMM) treated with lenalidomide to gather safety data on the use of lenalidomide in NDMM patients.	Annual safety updates with PSURs Final report of study results: 31 December 2022

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable.