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EMA/432817/2012
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Revlimid

lenalidomide

Procedure No.: EMEA/H/C/000717/X/0046/G

Note

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

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List of abbreviations

ASCT	Autologous stem cell transplantation
B/R	benefit-risk ratio
CAC	Central Adjudication Committee
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
DMC	Data Monitoring Committee
DSMC	Data and Safety Monitoring Committee
EU	European Union
HR	Hazard ratio
IA	Interim analysis
IFM	Intergroupe francophone du myélome
IMWG	International myeloma Working Group
IR	Incidence rate
IRC	Independent review committee
ITT	Intent to treat
IVRS	Interactive Voice Response System
Len	Lenalidomide
len/D	Lenalidomide +dexamethasone
MM	Multiple myeloma
MPB	Combination of [melphalan, prednisone, bortezomib]
MPT	Combination of [melphalan, prednisone, thalidomide]
MPR	Combination of [melphalan, prednisone, lenalidomide]
MPR+R	Combination of [melphalan, prednisone, lenalidomide] for induction followed by Lenalidomide for maintenance
MPR+p	Combination of [melphalan, prednisone, lenalidomide] followed by placebo for maintenance
MPp+p	Combination of [melphalan, prednisone] followed by placebo for maintenance
NDMM	Newly diagnosed multiple myeloma
Pbo	Placebo
Pbo/D	Placebo+dexamethasone
PD	Progressive disease
PFS	Progression-free survival
PR	Partial response
PY	Patient-year
RRMM	Relapsed or refractory multiple myeloma
QoL	Quality of life
SD	Stable disease
SPM	Second primary malignancies
TE	transplant-eligible, transplant candidate
TNE	transplant-non eligible
TTP	Time to progression
VAD	Vincristine, doxorubicin and dexamethasone
VD	bortezomib + dexamethasone
VGPR	Very good partial response

1. Scientific discussion

Multiple myeloma (MM) is a plasma cell malignancy of the bone marrow that accounts for approximately 10% of haematologic cancers. The number of new cases of MM per year in the European Union (EU) is approximately 29,000 and it causes nearly 19,000 deaths per year in Europe. Therefore, MM has an orphan disease classification. A single clone of plasma cells producing a monoclonal immunoglobulin (the monoclonal protein [M-protein]) is the characteristic finding associated with MM. The malignant proliferation of the plasma cell clone causes increasing levels of M-protein in the serum and urine and may result in bone marrow failure, suppression of uninvolved immunoglobulin levels, and skeletal destruction. Interactions between myeloma cells and the bone marrow microenvironment play a crucial role in the pathogenesis of MM.

The adhesion of marrow accessory cells and extracellular matrix proteins to myeloma cells and the secretion of cytokines, growth factors, and chemokines by both myeloma cells and marrow stromal cells activate signaling pathways that promote the proliferation and survival of the myeloma cell. Clinical complications of progressive MM include recurrent infections, cytopenias, renal failure, hyperviscosity syndrome, hypercalcaemia, bone pain, and pathologic fractures. Additionally, MM is typically a disease of older patients with a median age at diagnosis of 65 to 70 years. Despite advances in the treatment of MM that include high-dose chemotherapy supported by stem cell transplantation (SCT) and the discovery of active novel agents such as thalidomide, bortezomib and lenalidomide, which have improved the overall clinical condition and survival of patients, MM remains incurable. Treatment strategies are needed comprising new combinations of active agents to increase response rates and improve the quality of responses and so is the use of effective maintenance therapy to prolong duration of response.

Lenalidomide is an immunomodulating agent. Its 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.

Revlimid was granted a marketing authorisation in the EU on 14 June 2007 as 5, 10, 15 and 25 mg hard capsules, in combination with dexamethasone for the treatment of multiple myeloma patients who have received at least one prior therapy.

In this application, the MAH submitted a group of 2 new strengths (2.5 and 7.5 mg hard capsules), variation to add new pack sizes and a variation for a new indication of *Revlimid for the maintenance treatment of newly diagnosed multiple myeloma patients who have not progressed following initial treatment with melphalan, prednisone and Revlimid or following autologous stem cell transplantation*.

During the evaluation, the MAH proposed for Revlimid to be indicated *in newly diagnosed patients with multiple myeloma, in combination with melphalan and prednisone as induction therapy followed by maintenance Revlimid monotherapy in non-transplant eligible patients ≤ 75 years of age.*

Further to the assessment of the CHMP and their conclusions as detailed in this report, the MAH decided to withdraw the variations in the group for the new indication in newly diagnosed MM patients.

1.1. Quality aspects

1.1.1. Introduction

This application concerns a grouped submission of a line extension to add the following strengths: 2.5 mg and 7.5 mg as packs of 21 capsules.

1.1.2. Active Substance

No information is presented for the drug substance. This information can be found in the EPAR of Revlimid published on the EMA website.

1.1.3. Finished Medicinal Product

Compared to the currently authorised capsules, the MAH has applied with this line extension for additional strengths 2.5 mg and 7.5 mg.

The capsules contain the following standard Ph.Eur. excipients: lactose anhydrous (diluent), microcrystalline cellulose (diluent), croscarmellose sodium (disintegrant) and magnesium stearate (lubricant).

The components of the capsule shells (titanium dioxide, FD & C blue, yellow iron oxide, gelatine and ink) comply with their Ph. Eur. monographs or European Commission Directive 95/45/EC of July 25, 1995 and amendments thereafter. Information pertaining to the components and source of gelatine in the capsule shells was provided.

Revlimid Capsules are provided in a PVC/PCTFE blister with push through foil. The components of the packaging (PVC/ACLAR/alu blisters) are the same as those used for the previous strengths.

Pharmaceutical Development

The impact of particle size and polymorphism were studied during the pharmaceutical development. Lenalidomide was micronized to ensure a defined distribution of particle sizes that assures blend and content uniformity. Based on the interconversion studies, lenalidomide active substance was not expected to convert to any other polymorphic form during drug product manufacture or storage. The capsules (all strengths) were produced using a single polymorph form of lenalidomide although it was demonstrated that using a mixture of polymorph had no impact on the dissolution profile.

The same excipients were used as for the approved formulations.

The 2.5 mg capsules were developed using a size 4 capsule and are dose proportional to the approved 5 mg and 10 mg capsules. The 7.5 mg capsules were developed using a size 2 capsule and are dose proportional to the 15 mg capsules.

Bioequivalence study: Information was provided in the Clinical summary. Dissolution data was provided for batches 434727 (2.5 mg capsule), 0077A (5 mg capsule) and 000451 (7.5 mg capsule) as well as dissolution data for 10 mg, 15 mg and 25 mg capsules in 0.01N HCL where all capsules are dissolved within 15 minutes. The 7.5-mg lenalidomide capsule uses the same formulation as the currently approved 15-mg capsules and their *in vitro* dissolution profiles are similar. The 15-mg lenalidomide capsule has been demonstrated to be bioequivalent to the 5-mg lenalidomide capsules in humans. Therefore, a bioequivalence study is not required for the 7.5 mg capsule.

No overage was included in the formulation for lenalidomide capsules (all strengths).

The manufacturing process was based on typical manufacturing procedures for capsule formulations and the available equipment at the manufacturing sites. The manufacturing process was optimized as necessary for the specific equipment available at each site. Information regarding batch sizes and validation history for the approved dosage forms was presented. No information was provided regarding the actual manufacturing process development. This was however accepted since the new dosage forms only relates to the amount of powder mix filled in each capsule.

Adventitious agents

For gelatine, satisfactory certificate of suitability from the suppliers were presented. Magnesium stearate is vegetable derived. Lactose is sourced from healthy animals under the same conditions as milk collected for human consumption (EMEA 410/01 rev 2). In summary, no risk of TSE is anticipated.

Manufacture of the product

The manufacture of the 2.5 mg and 7.5 mg capsule strengths is a simple process: weighing of ingredients, blending and filling the capsules. The appropriate size capsule is filled to the specified weight for either a 2.5 mg or 7.5 mg dosage. The filled capsules are packed into PVC/ACLAR-blister with push through foil. It is stated that no reprocessing or reworking processes are applied in the manufacture of Lenalidomide Capsules.

Appropriate in-process controls were applied throughout the manufacturing process.

Process validation for the 2.5 mg is provided for both sites. A commitment to validate for the 7.5 mg prior to launch has also been provided. Validation protocols have been provided and the commitment has been accepted.

The excipients of the capsule fills are all tested in accordance with the specifications and test methods described in the Ph. Eur.

Regarding the capsule shells, adequate manufacturer's specification includes testing for appearance, colour, loss on drying, disintegration time, identity of gelatine, microbiological tests as per Ph Eur. and physical dimensions. The components of the printing inks are in compliance with Ph Eur. or USP/NF. In addition, the hard capsule colorants comply with the relevant EC Directives on colorants in foodstuffs.

Adequate information for the analytical methods has been presented.

Product specification

The specifications for Revlimid capsules of all strengths were provided. The specifications for the approved strengths have not been evaluated since no changes compared to the approved specification were introduced.

The proposed specifications at release/end of shelf life for the new strengths 2.5 mg and 7.5 mg capsules include appearance, identification (HPLC and UV), assay of the active substance (HPLC), related substances (HPLC), dissolution (HPLC), uniformity of dosage units (Ph Eur. 2.9.40) and microbial contamination (Ph Eur. 5.1.4 category 3A). The specifications were correctly justified.

Non-compendial analytical methods have been described and validated in accordance with ICH guidelines if necessary.

Batch analyses data for three production scale of the 2.5 mg strength and three pilot batches of the 7.5 mg strength confirm the consistency of the manufacturing process. All the results comply with the retained specifications.

Container closure system: Revlimid capsules 2.5 mg and 7.5 mg, are packaged in blisters (PVC/ACLAR) with push-through aluminium foil. The packaging materials have been adequately characterised and comply with Ph Eur. 3.1.11. The components of the packaging are the same as those used for the previous strengths. It has been demonstrated to be suitable as Revlimid has been shown to be stable over a period of 3 years.

The specifications proposed for Revlimid capsules are generally suitable. Analytical methods and their improvements during development were well described.

Stability of the product

Stability studies were conducted on 2 pilot batches and 1 commercial batch for the 2.5 mg strength, and 2 pilot batches for the 7.5 mg strength. These studies were carried out under the conditions described in the ICH guidelines: 25°C/60 RH % (24 months data), 30°C/65 RH % (3 months data), 40°C/75 RH % (6 months data).

The batches were tested for appearance, assay, related impurities and dissolution with the analytical procedures presented in section 3.2.P.5.

Photostability studies were performed for the originally approved 5 mg strengths with no significant change in degradation product level.

Minor cosmetic orange brown spots were observed at intermediate and accelerated conditions but no trends were seen at long term conditions. No other trends were observed except for an increase in impurities. All results are within the proposed specifications.

Stability data support the proposed shelf life and storage conditions as defined in the Summary of Product Characteristics (SPC).

1.1.4. Discussion on chemical, pharmaceutical and biological aspects

Quality Development

Overall, satisfactory quality documentation has been provided.

There was no new information provided for the active substance and this was accepted. The information can be found in the published EPAR.

Regarding the finished medicinal product, the manufacturing process is a standard process. It is adequately described and controlled. It should ensure a consistent quality for the medicinal product.

Appropriate specifications have been selected for these new strengths 2.5 mg and 7.5 mg hard-capsules. Stability studies under ICH conditions have demonstrated the good stability of the new strengths. Stability data support the proposed shelf life and storage conditions as defined in the Summary of Product Characteristics (SPC).

In summary, the results of tests carried out indicate satisfactory and uniformity of important product characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in the clinic.

At the time of the CHMP opinion, there were some outstanding quality issues with no impact on the benefit/risk. The applicant undertook to provide with the necessary information as a follow-up recommendation and to submit variations if required following the evaluation of this additional information.

1.1.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of those new strengths 2.5 mg and 7.5 mg Revlimid capsules is considered acceptable when used with the conditions defined in the SPC. Physicochemical and biological aspects relevant to the uniform clinical performance have been investigated and are controlled satisfactorily.

1.1.6. Recommendation for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

- It is noted that the process will be validated at this scale prior to launch (100 000 capsules, 7.5 mg).

1.2. Non-clinical aspects

The application did not include any new nonclinical data as the nonclinical information which was submitted in the initial marketing authorisation was considered applicable to the proposed new indication.

An updated environmental risk assessment is submitted to cover all multiple myeloma indications, i.e. NDMM and second-line MM.

Revlimid was proposed to be indicated in the treatment of newly diagnosed multiple myeloma (NDMM) patients, in addition to the currently approved indication in the treatment of multiple myeloma (MM) patients who have received as least one prior therapy. Consequently, the phase I $PEC_{SURFACEWATER}$ calculation was updated by the MAH.

Table 1. Summary of main study results

Substance (INN/Invented Name): Lenalidomide (REVLIMID)			
CAS-number (if available): 191732-72-6			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	Report no. APN 148	- 0.34	Potential PBT: no

Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surfacewater}$, default or refined (e.g. prevalence, literature)	0.0047	μg/L	< 0.01 threshold

1.2.1. Discussion on non-clinical aspects

At the time of initial MA, the Kow of lenalidomide was determined experimentally and was found to be low (0.46; log Kow = -0.34). Thus lenalidomide was considered to have negligible potential for bioaccumulation.

The phase I $PEC_{SURFACEWATER}$ calculation covering all MM indications, i.e. proposed and current indication remained below the action limit (0.01 µg/L).

1.2.2. Conclusion on the non-clinical aspects

The application did not contain any new non-clinical data as it is considered that the nonclinical information which was submitted in the initial MA application in refractory/relapsed MM is applicable to the new indication. This was considered acceptable notably because the dosing regimen proposed in the treatment of NDMM patients was the same as that used in the currently approved second-line indication (28-day cycles with recommended maximal starting dose of 25 mg/day given from day 1 to day 21 of each cycle). Thus, an increase in the systemic exposure to lenalidomide was not expected. An update of the SPC 5.3 was not deemed necessary.

The environmental risk assessment was updated. The predicted surface water concentration for lenalidomide indicated that its use in the proposed indication and in the currently approved indication should pose a negligible risk to the environment. Should any lenalidomide reach the environment through disposal of unused product, the environmental risk is likely to be minimal owing to the drug's low inherent toxicity and absence of bioaccumulation potential. Finally, with the withdrawal of the variation application for the new indication, the use of the product is not expected to change. As with all unused medications, appropriate disposal procedures should be employed.

1.3. Clinical aspects

1.3.1. 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

Study Identifier	Number of Study Centers Location	Study Start, Enrollment Status, Enrollment Total	Study Design, Type of Control	Test Product No Patients/arm Dosage Regimen Route of Administration	Study Objective	Duration of treatment	Gender M/F Median Age (Range)	Diagnosis Inclusion Criteria	Primary Endpoints
CC-5013-MM-015	82 sites EU (70) Australia (8) Israel (4)	01 Feb 2007 Enrollment Complete 459 patients	Phase 3 multicenter randomised double-blind 3-arm parallel-group, placebo-controlled study	MPR+R[a] N=152 MPR+p[a] N=153 MPp+p[a] N=154 Oral administration	To determine the efficacy of MPR compared with placebo plus MP in patients with NDMM who are ≥ 65years	Until PD occurred patient permanently discontinued R/p treatment, or up to the time that all patients have been followed for at least 5 years from randomisa-tion or have died	MPR+R 71/81 71 years (65-87) MPR+p 82/71 71 years (65-86) MPp+p 75/79 72 years (65-91)	Age≥65years Symptomatic NDMM as defined in protocol; Karnofsky performance status≥60 %	PFS Safety (AEs, clinical laboratory assessments vital signs, physical exams and ECGs)
IFM 2005-02	78 sites France (59) Belgium (10) Switzerland (9)	12 jun 2006 Enrollment Complete 614 patients	Phase 3 multicenter randomised double-blind 2-arm parallel-group, Placebo-controlled study	len[b] N=307 pbo[b] N=307 Oral administration	To determine the efficacy of lenalidomide maintenance following ASCT in extending post-transplanta-tion PFS	Until PD occurred death, or patient withdrew for another reason	len 169/138 57 years (22-67) Pbo 181/126 57 years (32-66)	Age 18 to 65 years ; symptomatic NDMM as defined in protocol; within 6 months post-ASCT	PFS Safety (AEs, clinical laboratory assessments vital signs, physical exams and ECGs)
CALGB 100104	Data not avaible	15 Apr 2005 Enrollment Complete 460 patients	Phase 3 multicenter randomised double-blind 2-arm parallel-group, placebo-controlled study	Len[c] N=231 pbo[c] N=229 Oral administration	To determine the efficacy of lenalidomide maintenance in prolonging TTP[d] following single ASCT	Until PD occurred, death, or patient withdrew for another reason	len 121/110 58 years (29-71) Pbo 129/100 58 years (39-71)	Age<70years 100-110 days After single ASCT; ≤1 year from diagnosis; Stage I-III disease	TTP[d] Safety (AEs, clinical laboratory assessments vital signs, physical exams and ECGs)

Study Identifier	Number of Study Centers, Location	Study Start, Enrollment Status, Enrollment Total	Study Design, Type of Control	Test Product, No. Subjects/Arm Dosage Regimen, Route of Administration	Study Objective	Duration of Treatment	Gender M/F, Median Age (Range)	Diagnosis Inclusion Criteria	Primary Endpoints
SWOG S0232	41 sites US (41)	15 Oct 2004 Enrollment complete 198 subjects	Phase 3, multicenter, randomized, double-blind, parallel-group, placebo-controlled study	len/D[e] N = 100 pbo/D[e] N = 98 Oral administration	To compare the effects of treatment with len/D vs. pbo/D on PFS in subjects with NDMM	Until PD occurred or subject withdrew for another reason	len/D 56/44 65.1 years (36.9-89.0) pbo/D 56/42 63.3 years (37.6-87.0)	Age ≥ 18 years with NDMM; no immediate plans to undergo ASCT, and measurable disease; Zubrod performance status of 0-3 and adequate bone marrow, liver, and renal function	PFS Safety (AEs and clinical laboratory assessments)
ECOG E4A03	138 sites US (138)	26 Oct 2004 Enrollment complete 445 subjects	Phase 3, multicenter, open-label, randomized study No control	len/D[f] N = 223 len/d[f] N = 222 Oral administration	To evaluate RR and toxicity of len/D vs. len/d during the first 4 cycles of treatment in subjects with NDMM	Until PD occurred or subject withdrew for another reason	len/D 132/91 66.1 years (36.3-87.7) len/d 121/101 65.2 years (35.0-85.9)	Age ≥ 18 years; symptomatic multiple myeloma ≤ 90 days of study start; measureable M-protein; ECOG performance status 0, 1, or 2.	Myeloma RR during the first 4 cycles of treatment Safety (AEs and clinical laboratory assessments)

AE = adverse event; ASCT = autologous stem cell transplantation; d = low-dose dexamethasone; D = standard-dose dexamethasone; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EU = Europe; F = female; len = lenalidomide; M = male; M = melphalan; NDMM = newly diagnosed multiple myeloma; No. = number; P = prednisone; p = placebo; pbo = placebo; PD = progressive disease; PFS = progression-free survival; R = lenalidomide; RR = response rate; TTP = time to progression; US = United States.

a MPR+R, MPR+p, and MPp+p regimens: Induction therapy period (first 9 cycles) = 0.18 mg/kg of melphalan (M) and 2 mg/kg of prednisone (P) daily on Days 1 to 4 of each 28-day cycle plus 10 mg of lenalidomide (R) or placebo (p) once daily on Days 1 to 21 of each 28-day cycle; maintenance therapy period (from Cycle 10 to disease progression) = 10 mg of lenalidomide (R) or placebo (p) once daily on Days 1 to 21 of each 28-day cycle.

b len and pbo regimens: Consolidation treatment period = 25 mg of lenalidomide (len) once daily on Days 1 to 21 of each 28-day cycle for 2 cycles; maintenance therapy period = starting dose of 10 mg of lenalidomide (len) or placebo (pbo) once daily continuous dosing until relapse. After 3 months, the lenalidomide dosage could be increased to 15 mg daily if the neutrophil and platelet counts were adequate.

c len and pbo regimens: The choice of the regimens for the preparatory induction treatment and stem cell harvest were up to the investigator. Following the induction treatment and stem cell harvest, all subjects received high-dose melphalan followed by ASCT. After ASCT, subjects with ≥ stable disease were randomized to receive maintenance therapy with 10 mg of lenalidomide or placebo daily continuous dosing until disease progression. After 3 months, the lenalidomide dosage could be increased to 15 mg daily if the neutrophil and platelet counts were adequate.

d In Study CALGB 100104, the primary endpoint was called TTP, however, by definition, the calculation used was for PFS, which was defined as disease progression or death due to any cause and calculated from Day 0 of ASCT.

1.3.2. Pharmacokinetics

Lenalidomide pharmacokinetics has already been assessed at the time of initial MA and subsequent PK follow up measures.

Results of study CC-5013-BE-002 have been submitted previously. They demonstrated the bioequivalence from one lenalidomide 15 mg capsule (test) relative to that from three lenalidomide 5 mg capsules (reference). Results of study CC-5013-BE-004 have demonstrated the bioequivalence from one lenalidomide 25 mg capsule (test) relative to that from five lenalidomide 5 mg capsules (reference).

In this application, results of study CC-5013-CP-010 were submitted to support the new dosage strengths of 2.5 mg and 7.5 mg.

The bioequivalence study CC-5013-CP-010 included 27 healthy volunteers, males of 18 to 55 years, non smokers. Twenty six completed the study. A unique dose of 10 mg of lenalidomide was administered at two periods (randomised cross-over study): 4 capsules of 2,5 mg (Test) vs. 2 capsules of 5 mg (Reference).

Plasma concentrations of lenalidomide were determined by liquid chromatography coupled with mass spectrometry (LC-MS-MS). AUC values were determined by non compartmental PK analysis.

The statistical analysis (ANOVA) was performed after log transformation for Cmax, AUCt (AUC from time 0 to last available concentration: i.e., 24 hrs after dosing) and AUC∞ (AUC extrapolated to infinity). The parameter tmax was compared by a non-parametric method.

For the Test/Reference ratio, the 90% confidence intervals of Cmax, AUCt, and AUC∞ were [92.70 – 111.87], [98.46 – 104.93] and [97.85 – 103.84] respectively. These IC fell within the generally accepted bioequivalence limits of 80% to 125%.

For median difference (Test – Reference), 90% confidence interval for tmax was 0 – 0.25 hours (median values for Test and Reference of 0.875 and 0.750 hours, respectively).

The bioequivalence between 2.5 mg capsule and 5 mg capsule has formally been demonstrated.

1.3.3. Pharmacodynamics

No new clinical pharmacology studies have been conducted specifically for the NDMM application.

1.3.4. Discussion on clinical pharmacology

Bioequivalence has already been demonstrated between different formulations at the time of the initial MA.

The 7.5 mg capsule uses the same formulation blend and is dose proportional in its active and inactive ingredients to the approved 15 mg capsule. The in vitro dissolution profile of the 7.5 mg capsule is similar to that of the 15 mg capsule. The 15 mg lenalidomide capsule has been demonstrated to be bioequivalent to the 5 mg lenalidomide capsules in humans. Therefore, a bioequivalence study is not required for the 7.5-mg capsule.

The 2.5 mg capsule uses the same formulation blend and is dose proportional in its active and inactive ingredients to the approved 5 and 10 mg capsules.

This justifies that bioequivalence has only been investigated between 2.5 mg capsule and 5 mg capsule. Results of study CC-5013-CP-010 submitted in this application demonstrated the bioequivalence between 2.5 mg capsule and 5 mg capsule.

Furthermore, the 7.5 mg strength could support dose adjustment (7.5 mg daily dose replacing the currently approved starting dose regimen of 15 mg every other day) for patients with severe renal impairment receiving lenalidomide in the current indication: this is subject to submission of supportive data through a variation further to the approval of the 2.5 and 7.5mg strengths.

1.3.5. Conclusions on clinical pharmacology

CC-5013-CP-010 results have demonstrated the bioequivalence between 2.5 mg capsule and 5 mg capsule. This supports the new dosage strengths of 2.5 mg and 7.5 mg.

1.4. Clinical efficacy

As indicated in the above table, this application was supported by 5 studies.

The results of the 2 main studies, Study CC-5013-MM-015 and Study IFM 2005-02, and the supportive study, CALGB 100104, provided data in support of lenalidomide maintenance treatment in 2 different NDMM populations (transplantation-ineligible [TNE] and eligible [TE]) that received 2 different first-line induction treatments (MPR and HDC supported by ASCT).

The main study CC-5013-MM-015, also provided data for the use of lenalidomide in induction combination with MP in the first-line treatment of TNE NDMM patients, while the 2 supportive studies, SWOG S0232 and ECOG E4A03, provide additional data for lenalidomide to reduce tumour mass in another combination, i.e., with dexamethasone in the first-line treatment of a mixed population of TNE and TE NDMM patients.

1.4.1. Dose response study(ies)

No dose-response studies were submitted in this application.

For dose reduction in newly diagnosed MM patients who receive the lenalidomide therapy in combination with melphalan and prednisone followed by a lenalidomide maintenance therapy, the MAH proposed that the 7.5 mg daily dose and the 2.5 mg daily dose continue to be included as the step-down dose reductions. The currently proposed 2.5 mg or 7.5 mg dosing regimens will result in comparable daily AUC with less daily fluctuation in the drug concentration and it will also support improved patient compliance in terms of allowing for daily dosing where appropriate. There is no justification for the step-down dose reductions in these patients. The argument of improving patient compliance with daily dosing could be a justification but the absence of pharmacodynamic difference has not been demonstrated.

1.4.2. Main studies

<u>Study MM-015</u>

Methods

This is an ongoing, multicentre, randomised, double-blind, placebo-controlled, 3-arm parallel-group study that investigates the use of standard-dose melphalan/prednisone (MP) plus lenalidomide (R; 10 mg daily dose) in patients with newly diagnosed MM who are 65 years of age or older.

Study Participants

Patients were recruited at 82 sites (70 in Europe; 8 in Australia; and 4 in Israel).

Main inclusion criteria were:

- Age >= 65 years
- Newly diagnosed with symptomatic MM defined by the 3 criteria: 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, and myeloma-related organ dysfunction and have measurable disease
- Karnofsky performance status ≥ 60%
- Women of childbearing potential (WCBP) must have a negative medically supervised pregnancy test prior to start of study therapy. She must agree to ongoing pregnancy testing during the course of the study, and after end of study therapy. Male patients must agree to use a condom during sexual contact with a WCBP, to not donate semen during study drug therapy and for a period after

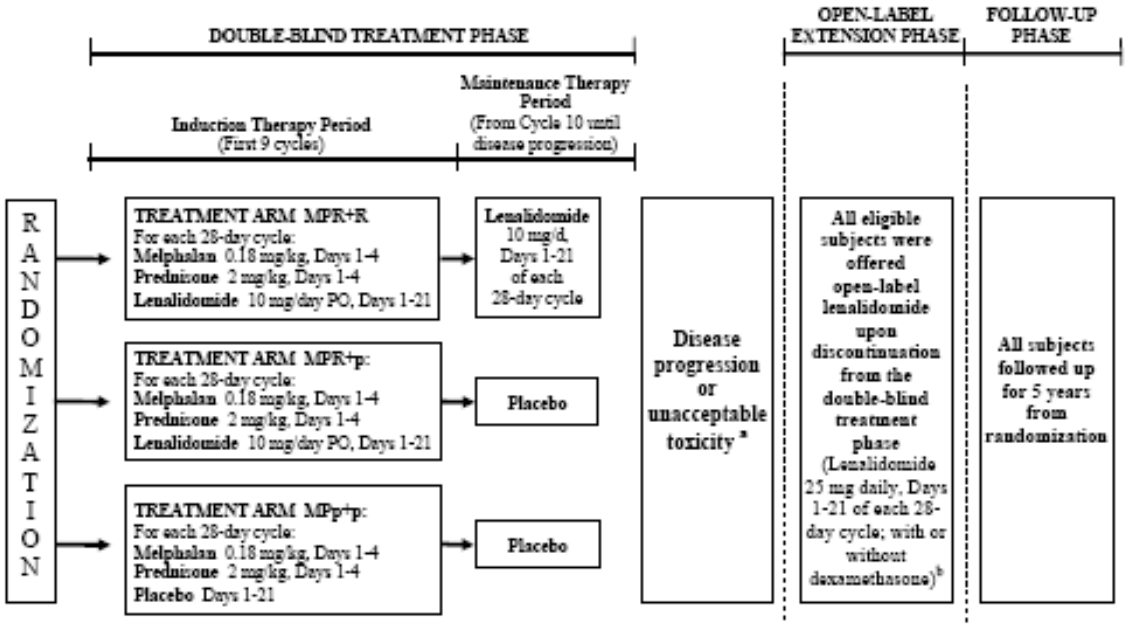
Main exclusion criteria were:

- Previous treatment with antimyeloma therapy
- Any serious medical condition, including the presence of laboratory abnormalities, which places the patient at an unacceptable risk
- Pregnant or lactating females
- Radiotherapy within 14 days of randomisation
- Plasmapheresis within 28 days (4 weeks) of randomisation
- Laboratory abnormalities
- Prior history of malignancies, other than multiple myeloma, unless the subject has been free of the disease for ≥ 3 years, exceptions include the followings:
    - 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 histologic finding of prostate cancer (TNM stage of T1a or T1b)
- Neuropathy of ≥ grade 2 severity
- Known 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, and a follow-up phase.

The overall study design and dosing regimens are presented in the figure below.



[a] Disease progression or unacceptable toxicity can occur during the induction therapy or the maintenance therapy periods.
[b] Dexamethasone was given at the discretion of the treating physician. The recommended dexamethasone dose was 40 mg PO daily on Days 1 to 4, 9 to 12, and 17 to 20 of each 28-day cycle.

Objectives

The primary hypothesis was that the addition of lenalidomide to standard MP induction therapy followed by maintenance therapy with lenalidomide improves PFS in patients with newly diagnosed MM aged 65 years or older. So the primary objective was to determine the efficacy of MPR compared with placebo plus MP in patients 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 this population.

Upon CHMP advice, in order to investigate the risk benefit profile of lenalidomide in both the induction and maintenance therapy periods, the study design was amended to include a third arm containing lenalidomide in the induction combination therapy period only followed by placebo in maintenance. Arm MPR+p was added to the study design of the protocol prior to its finalization.

For that reason, response rates with MPR+p are expected to be higher than those obtained with MPp+p, to justify the interest of lenalidomide use during induction.

Outcomes/endpoints

The primary protocol-planned efficacy endpoint was PFS.

The secondary protocol-planned efficacy endpoints were OS, time to progression (sensitivity analysis for PFS), myeloma response rate, time to response, duration of response, time to next anti-myeloma therapy, and quality of life.

Investigation of cytogenetic abnormalities was an exploratory endpoint.

Safety criteria for evaluation were adverse events, clinical laboratory assessments, vital sign measurements, and electrocardiograms (ECGs).

Sample size

Two pre-planned interim analyses were conducted, when approximately 50% and approximately 70% of the total events required for full statistical power for the primary endpoint, PFS, had occurred (148 PFS events and 207 PFS events across all 3 arms, respectively).

The primary analysis for the study was to compare PFS between Arms MPR+R and MPp+p. For the primary efficacy variable, PFS, a 50% improvement in median time to progression from 15 months in Arm MPp+p to 22.5 months in Arm MPR+R was considered clinically relevant and, therefore, the target difference. A third arm MPR+p, was added for the secondary analyses in order to investigate the effect of lenalidomide maintenance, i.e., comparison of MPR+R with MPR+p and the effect of lenalidomide induction, i.e, comparison of MPR+p with MPp+p. This required a total sample size of 450 patients (150 in each arm). With the adjunction of the third arm MPR+p, the number of events is approximately increased by 1.5.

Randomisation

Patients who met all eligibility criteria were randomised (1:1:1) by a double-blind procedure utilising a validated interactive voice response system (IVRS) 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)

Patients were stratified at randomisation by age (≤ 75 years vs > 75 years) and stage (International Staging System [ISS]; stages I and II vs. stage III).

The start of the double-blind treatment phase (Day 1 of study treatment) was to occur on the same day that the subject was randomised. Each patient continued the double-blind treatment phase until: 1) progressive disease (PD) occurred; or 2) lenalidomide/placebo therapy was discontinued permanently for any reason; or 3) all patients were to be followed in this study for at least 5 years from randomisrandomisation or had died.

Blinding (masking)

The investigator, patient, and Celgene personnel responsible for the conduct of the study were blinded as to each patient's treatment assignments during the patient's participation in the double-blind treatment phase of the study. The blind was broken for patients in the double-blind treatment phase who were assessed by the investigator with progressive disease. Melphalan and prednisone were not blinded.

Statistical methods

The primary efficacy analyses for all endpoints were performed based on the ITT population.

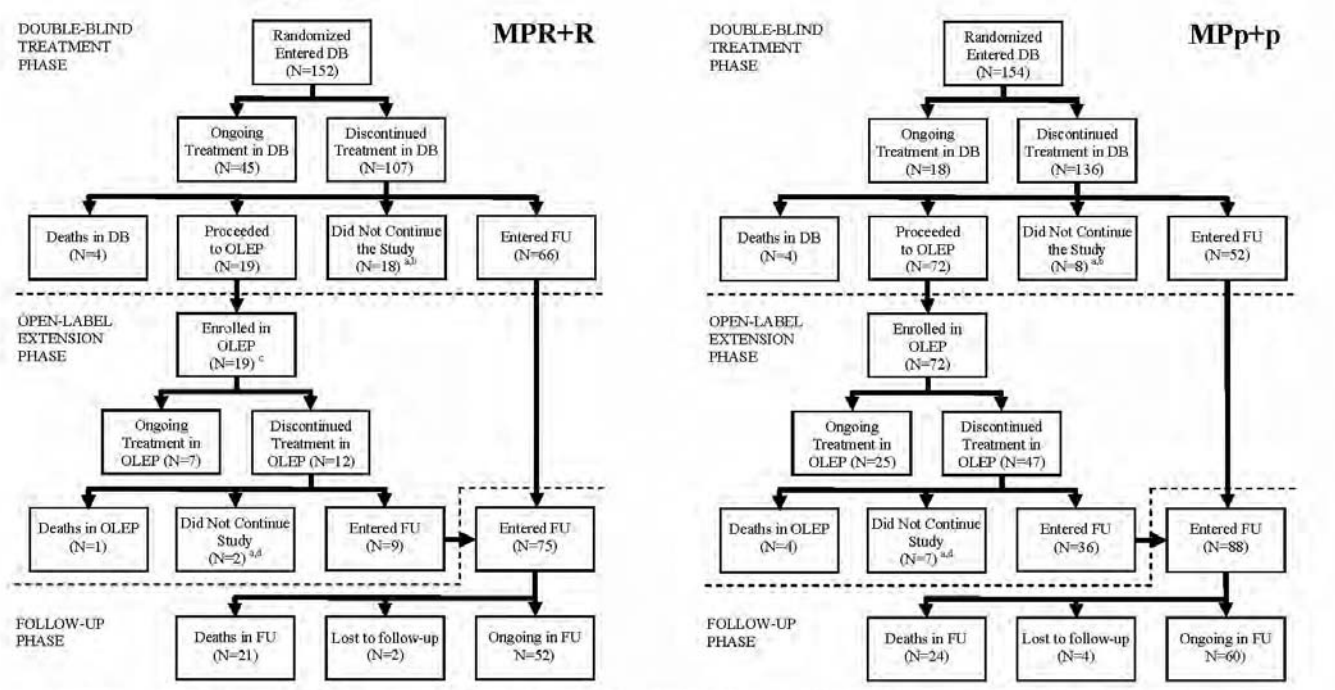
For the efficacy analysis of all endpoints, the primary comparison was arms MPR+R versus MPp+p. The secondary comparisons were arms MPR+R versus MPR+p, and arms MPR+p versus MPp+p and these were conditional on the primary comparison. Therefore, alpha was not adjusted for these secondary

comparisons. Similarly, analyses of the secondary endpoints (including OS) were conditional on the primary comparison of PFS; therefore, alpha was not adjusted for the secondary endpoints.

Results

Participant flow

Of the 459 patients, 152 patients were randomised to the MPR+R treatment arm, 153 to the MPR+p arm and 154 to MPp+p arm. As of 11 May 2010 (date of study unblinding), disposition of patients in arms MPR+R and MPp+p (primary comparison in the efficacy analyses) is given below.



DB = double-blind treatment phase; FU = follow-up phase; ITT = intent to treat; M = melphalan; OLEP = open-label extension phase; P = prednisone; R = lenalidomide.
[a] The number of subjects who did not continue study excludes the number of subjects who died in a study phase.
[b] Subjects chose not to enter the open-label extension phase or the follow-up phase.
[c] Include Subjects 1090009 and 2510005, who were indicated as going into OLEP but were never dosed in OLEP.
[d] Subjects chose not to enter the follow-up phase.
Source: Appendix 1, Table 14.1.1a

As of the 11 may 2010 cut off, 12.5% (19 patients) of patients in Arm MPR+R enrolled in the open-label extension phase compared with 46.8% (72 patients) in Arm MPp+p. Of these, 9 patients in Arm MPR+R and 36 patients in Arm MPp+p remain ongoing.

Recruitment

The first patient was randomised on 01 Feb 2007, the last one on 19 Sep 2008. MM-015 study has completed accrual but there are still patients in the follow up phase. The study will end when all patients have been followed for at least 5 year from randomisation or have died.

Conduct of the study

The protocol was amended 3 times. The Amendment #2, dated 27 Jan 2009, added another interim analysis at 70% information.

Baseline data

Patients in Arm MPp+p tended to have better baseline performance status than those in Arm MPR+R. Disease staging of this population was more advanced since median age was 71 years, 80% of patients were ISS Stage II or Stage III, with approximately 50% of patients categorised as Stage III.

Statistics for cytogenetic abnormalities were removed from the demographic tables due to limited evaluable cytogenetics data, so the planned exploratory analysis on cytogenetic abnormalities could not be performed.

Numbers analysed

The MM-015 study dataset which formed the basis of the original submission had a 01 Dec 2009 cut off date (second pre-planned interim analysis of 70% information for PFS) with a median follow-up of 21.3 months.

The first site was unblinded on 11 May 2010, and the final complete analysis for this study was performed at 76% PFS information (data collected up to study unblinding; cut off date: 11 May 2010). As of this cut off date, 226 of the 296 events originally targeted in the study plan for the final PFS analysis had occurred.

A more recent data cut off, 03 Oct 2011, is being used for all OS analyses, second line therapy and for occurrence of secondary primary malignancies (SPM). Based on this updated data set, the study has now reached a median follow-up of 41.0 months for surviving patients.

Outcomes and estimation

Primary endpoint: PFS

Results of MM-015 clinical study report were presented in the application and derived from the 70% information interim analysis (second IA), using a data cut off of 01 Dec 2009. PFS was significantly longer in arm MPR+R than arm MPp+p. The HR (0.423 (0.294, 0.609), $p < 0.001$, two-sided unstratified Log-rank test) indicated a major decrease in the risk of disease progression for patients treated in arm MPR+R compared to those treated with MPp+p. Results were consistent in the subsequent update where using a data cut off of 11 May 2010, the HR was 0.395 (0.278, 0.560), $p < 0.001$, two-sided unstratified Log-rank test). The censoring rate was higher in the MPR+R arm (the ratio progressed or died/censored is 52/100) compared to MPR+p arm (81/72) and MPp+p arm (93/61).

The updated data showed that as lenalidomide was added as third drug to a standard MP regimen, treatment tolerance was reduced in patients age > 75 years leading to an increased incidence of grade 3/4 toxicities in these patients compared with the stratum of patients age ≤ 75 years. This led to: (1) a higher frequency of dose reductions, (2) a reduced relative dose intensity for melphalan and lenalidomide, and (3) higher frequency of treatment discontinuations compared with the pre-randomisation stratum of patients age ≤ 75 years.

The better treatment tolerance observed in patients ≤ 75 years was associated with better treatment efficacy: For patients ≤ 75 years (N=232), in the primary comparison of MPR+R versus MPp+p, the risk reduction of progression or death amounted to 70% (hazard ratio [HR] = 0.301, 95% confidence interval [CI] = 0.199-0.454), a highly statistically significant and clinically meaningful improvement in this patient population. This translated to an improvement 19.1 month in PFS *(median PFS of 31.4 months for MPR+R vs 12.3 months for MPp+p).

With data cut off date of 01 Dec 2009, PFS on ITT population was not statistically different between Arms MPR+p and MPp+p (p = 0.306, two-sided unstratified Log-rank test). This seemed to show that Revlimid does not provide any benefit in terms of PFS during induction if not followed by maintenance. Whereas, on 11 May 2010 cut off date, excluding patients over 75 years, a 38% risk reduction in disease progression or death was observed in the PFS analysis of MPR+p versus MPp+p (HR [95% CI] = 0.618 [0.436-0.877], p = 0.006, two-sided unstratified Log-rank test). These results point to the contribution of Lenalidomide in the induction period. Also, comparing Arm MPR+R and Arm MPR+p treatment in patients age ≤ 75 years, a 52% risk reduction of progression or death was achieved by adding lenalidomide maintenance (HR [95% CI] = 0.475 [0.315-0.716]).

Secondary endpoints

Response rate and duration

The overall response (comparison of the dichotomized response [CR + PR] vs other, best assessment of response during double blind treatment phase of the study) was significantly higher in arm MPR+R (77.0% [117/152]) than in arm MPp+p (50.0% [77/154]) (p < 0.001, Fisher's exact test).

Statistical difference is also shown favouring lenalidomide for the comparison MPR+p vs MPp+p but no statistical difference was shown for the comparison MPR+R vs MPR+p. These findings seem to show that, in terms of response rates, induction followed by maintenance offers no interest as compared to induction only.

Among the responders, the median duration of response was significantly longer in patients treated with MPR+R compared with those treated with MPp+p. Similarly, the duration of response was significantly longer in patients treated with MPR+R compared with those treated with MPR+p.

However, the duration of response was similar between arm MPR+p (12.9 months) and arm MPp+p (12.8 months) (p = 0.503, two-sided unstratified Log-rank test; hazard ratio 0.877; 95% CI: 0.596, 1.290). This finding shows that induction only offers no interest in terms of duration of response. To achieve longer duration of response, induction must be followed by maintenance. This is especially worrying as, in the context of occurrence of SPM, these 9 induction cycles may penalize by increasing toxicity.

With adjunction of lenalidomide to MP, the overall response rate during induction is increased in the whole population and this increase is mainly driven by patients ≤ 75 years. In this subgroup, lenalidomide significantly added to the efficacy of the standard MP induction regimen as evidenced by a significant increase in overall response rate (79% and 72% in Arm MPR+R and Arm MPR+p, respectively, versus 46% in Arm MPp+p) and a 3-fold increase in the depth/intensity of response (31% and 33% of very good partial responses [VGPRs]/complete responses [CRs] in Arm MPR+R and Arm MPR+p versus 10% in Arm MPp+p).

Overall survival

No statistical differences were observed in overall survival in the comparisons of the 3 treatment arms. As of a 01 Dec 2009 data cut off date (2nd interim analysis), a HR of 0.726 (95% CI, 0.381 - 1.382) was noted.

During the procedure, OS analyses were updated using a data cut off of 3 October 2011. With a median follow-up of 41.0 months, the median OS has not been reached in either arm. The OS time was not significantly different in the primary comparison between Arms MPR+R and MPp+p with an HR (95% CI) of 0.898 (0.613-1.315) and a 2-sided unstratified log-rank test p-value = 0.579.

In patients age ≤ 75 years, HR for survival in the primary comparison MPR+R versus MPp+p has further improved and the 95% CI has narrowed (HR [95% CI] = 0.706 [0.446-1.115] but still, no significantly difference in OS in favour of MPR+R is observed at this point.

Time to progression

TTP was significantly longer in arm MPR+R than arm MPp+p ($p < 0.001$, two-sided unstratified log rank test) as well as versus MPR+p arm ($p < 0.001$, two-sided unstratified log rank test). Analysis of TTP showed no significant differences between arms MPR+p and MPp+p.

Time to treatment failure

Time to treatment failure was significantly longer in arm MPR+R than in arm MPp+p ($p < 0.001$, two-sided unstratified log rank test). Similarly, TTF was significantly longer in arm MPR+R than arm MPR+p ($p = 0.006$, two-sided unstratified log rank test). Whereas, analysis of TTF showed no significant differences between arms MPR+p and MPp+p.

Salvage therapy (post hoc analysis)

Salvage therapy included all therapies given after first line (ie, treatment received after discontinuation from the double-blind treatment phase), including the open-label extension phase treatment (starting dose of 25 mg of lenalidomide). Among the patients who received salvage therapy, approximately 95% of the patients received novel agent-based therapies with lenalidomide, bortezomib, and/or thalidomide.

Time to the next antimyeloma therapy

The time to the next antimyeloma therapy was significantly longer in patients treated with MPR+R compared with those treated with MPp+p ($p < 0.001$, two-sided unstratified log rank test; hazard ratio 0.399; 95% CI: 0.284, 0.560).

Lenalidomide 25 mg (the standard starting dose for RRMM), with or without dexamethasone, in the OLEP was considered second-line therapy, as well as all second-line anti-myeloma therapies given to patients outside of the protocol. On the whole safety population as of 11 May 2010, 24/75 of patients in Arm MPR+R received lenalidomide (25 mg) as second-line therapy, compared with 66/112 patients in Arm MPR+p and 88/123 patients in Arm MPp+p. As expected, the highest proportion of patients who received lenalidomide 25 mg in the open label extension phase was observed in the MPp+p arm.

For patients who received second-line therapies outside of the protocol across treatment arms (N= 158), 92 received bortezomib, 118 received glucocorticoids, and 26 received thalidomide.

Time from second-line antimyeloma therapy to third-line antimyeloma therapies (post hoc analysis)

The median time between second- and third-line antimyeloma therapies was similar in arms MPR+R and MPp+p (54.6 weeks and 54.1 weeks, respectively), When reducing to patients age ≤ 75 years, for patients who received any second-line AMT, as of 11 May 2010 the median time from second-line to third-line AMT was somewhat lower in Arm MPR+R compared with Arm MPp+p (59.6 weeks versus 64.3 weeks); however, the confidence intervals overlap.

Health-related Quality of life

Comparisons between treatment arms show that, there were no statistically significant or clinically meaningful differences in the changes from baseline between treatment groups in the 6 selected scales (QLQ-C30 global health status, physical functioning, fatigue, pain, and disease symptoms; and QLQ-MY20 disease symptoms, side effects related to treatment).

There was no statistical difference between treatment arms in regard to HRQoL in responding patients. The lack of statistical or even clinically meaningful difference between treatment arms is not promising. The gain of MPR triple therapy over MP is once again questioned

Study IFM 2005-02

Methods

This was a phase III, multicentre, randomised, double-blind, placebo-controlled 2-arm parallel study investigating lenalidomide therapy following ASCT for the treatment of multiple myeloma. The study was conducted in patients < 65 years old by the Intergroupe francophone du myeloma (IFM) and was sponsored by the University Hospital in Toulouse, France. It consisted of 2 treatment phases for each patient: a consolidation phase, and a maintenance phase.

Study Participants

This was conducted in 78 centres in France, Belgium and Switzerland. Patients were only eligible for enrollment into Study IFM 2005-02 if they had already completed successful induction chemotherapy and ASCT for the treatment of multiple myeloma.

Main inclusion criteria were:

- Age 18 to 65 years
- No signs of progression after transplant
- Effective contraception if necessary (oral contraception for females and barrier methods of contraception for sexually active males).
- No active severe infection.
- Satisfactory restoration of the haematological parameters defined by: PN >1,000/mm^3 and Platelets > 75,000/mm^3.
- Bilirubin < 35 umol/l and GOT/GPT/PAL< 3N.
- Creatinine < 160 µmol/l.

Main exclusion criteria were:

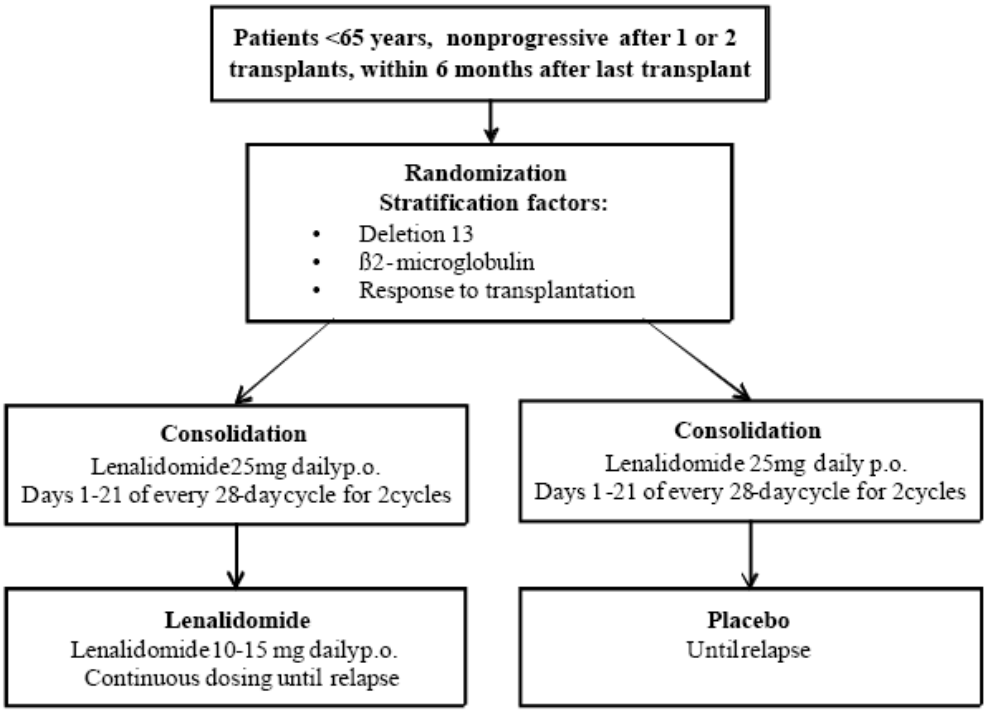
- Pregnant women or women of childbearing potential not using a reliable contraceptive method
- Past or current history of malignancy
- History of symptomatic cardiac failure or coronary disease VEF >40%.
- History of liver disorder: bilirubin >35µmol/L and AST, ALT and alkaline phosphate >4 ULN.
- History of lung disorder: ventilation tests and DLCO >50% N.
- History of renal disorder not related to the disease and defined by a creatinine >160 µmol/L.
- Active chronic infection
- Signs of progression after transplant

Inclusion and non-inclusion criteria are appropriate for transplant-eligible (TE) patients. Patients included are representative of those likely to be treated with the experimental compound.

Treatments

Patients were randomised in the study following confirmation of entry criteria and within 6 months after ASCT, if there was hematological recovery and no disease progression.

The study starts after MM patients have undergone 1 to 2 ASCT. The study design is given below.



All patients withdrawn from the study were followed-up every 3 months until death for survival and late complications, except for patients who withdrew their consent. In addition, data for further antimyeloma treatment was collected.

Objectives

The primary objective of this study was to evaluate the efficacy of a maintenance treatment with lenalidomide following autologous stem cell transplantation in extending post-transplantation PFS.

Secondary objectives were to assess PFS from the date of diagnosis, OS, TTP, response rates and duration and safety of Lenalidomide in post-transplantation consolidation and maintenance treatment chemotherapy.

Outcomes/endpoints

The primary endpoint was post-transplantation PFS calculated for all patients from the date of randomisation to the date of progression or death (whatever the cause).

Secondary endpoints were:

- PFS from diagnosis calculated for all patients from the date of diagnosis to the date of progression or death (whatever the cause).
- OS calculated from the date of randomisation to the date of death.
- Response duration calculated for all randomised patients with a complete or partial response from the date of randomisation to the date of progression.
- Complete response duration calculated for all randomised patients with a complete response from the date of randomisation or the date of complete response to the date of progression.
- TTP calculated for all patients from the date of randomisation to the date of progression.
- Time to the best response calculated for all patients from the date of randomisation to the date of the best response.

Sample size

For the primary efficacy variable, PFS, sample size calculation were based on the assumption that a 42% improvement in median time to progression from 37.5% at 4 years after randomisation for placebo to 50% at 4 years for lenalidomide was to be considered clinically relevant. With α = 5% (one-sided) and β= 10%, 300 events, i.e. 267 randomised patients in each arm were required. Expecting a drop out of 15%, 614 patients enrolled at diagnosis were required. As the one-sided α error should be more stringently defined at 2.5%, updated sample size calculation purportedly required a similar number of patients (263 progressions or deaths) for a one sided log rank test at 2.5% adjusted for 1 interim analysis, which was unreasonable.

Randomisation

After transplantation, patients were randomised (1:1) to 1 of 2 arms, lenalidomide arm or placebo arm. The comparator (placebo) is considered adequate since after SCT there is no reference maintenance treatment.

Randomisation was stratified based on 3 parameters:

- Chromosome 13 deletion (del 13+ or del 13-), if screening for chromosome 13 deletion at diagnosis was unsuccessful, it was considered as negative for the stratification
- β2-microglobulin at diagnosis (≤ 3 mg/L or > 3 mg/L)
- Response to latest transplantation (≥ VGPR or < VGPR)

Initial stratification also comprised the number of transplants (1 or 2). Amendment 4 modified this stratum which became post-transplantation response. In total, 334 patients were randomised before amendment 4.

Blinding (masking)

This was a double blind study.

Statistical methods

This study was designed to have 1 interim analysis performed after 60% of events (progression and/or deaths) had been observed. An independent DMC evaluated safety and efficacy data at the time of the interim analysis. Upper and lower bounds based on O'Brien-Fleming stopping rules were used in the interim efficacy analysis. The primary efficacy variable PFS, was compared between arms using a group sequential log-rank test corresponding to 2 analyses one interim at 60% information and one final at 100% information. The upper boundary for superiority of lenalidomide over placebo was based on an α spending function of the O'Brien-Fleming type with overall one-sided α=0.025. If at the interim analysis (at 60%), a log rank statistic is above the upper boundary a recommendation to stop the study and claim superiority for the lenalidomide to be considered.

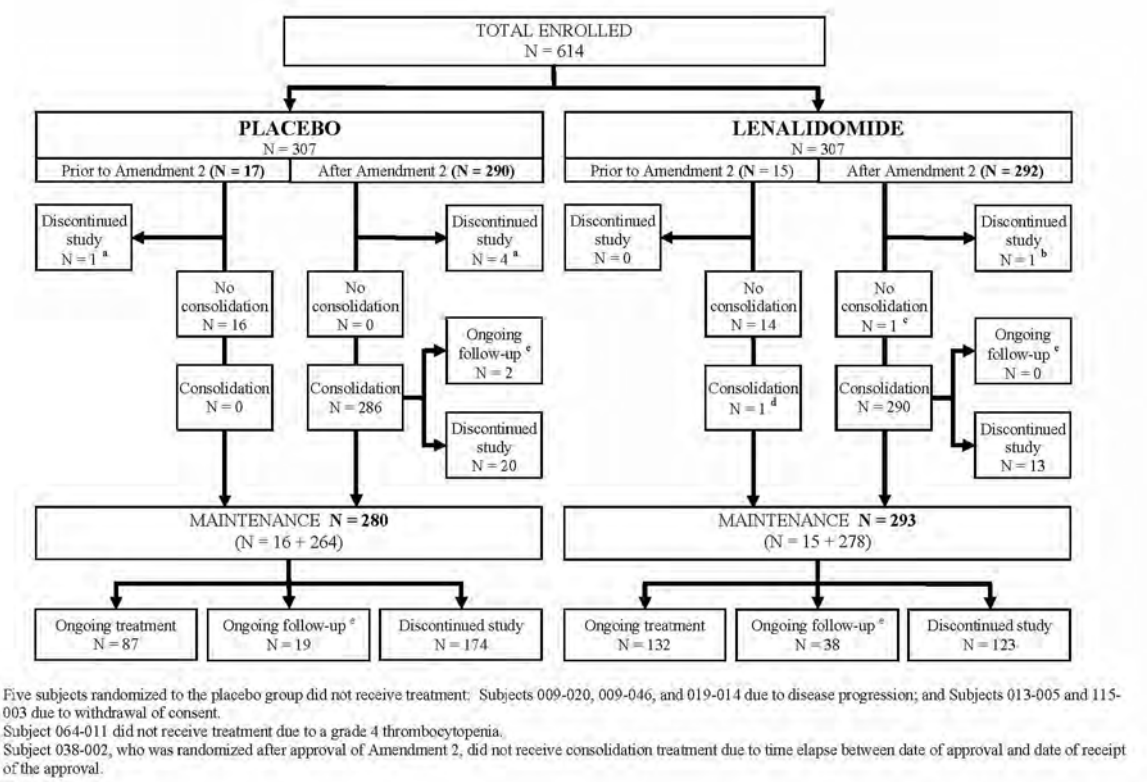
If the ITT population and the PP population differed by more than 10% in size, the analysis of the primary efficacy variable was to be repeated using the PP population to provide evidence of sensitivity/robustness of the primary analysis results.

Efficacy analyses were performed on the ITT population which prevents from attrition bias. Subgroup analyses for the primary endpoint (PFS) were performed based on stratification parameters.

Results

Participant flow

Of the 614 patients enrolled, 307 patients were randomised in Len arm and 307 in Pbo arm. The figure below describes the disposition of patients as of 07 July 2010 whether they receive or not post-transplant consolidation required by protocol amendment 2.



a Five subjects randomized to the placebo group did not receive treatment: Subjects 009-020, 009-046, and 019-014 due to disease progression; and Subjects 013-005 and 115-003 due to withdrawal of consent.
b Subject 064-011 did not receive treatment due to a grade 4 thrombocytopenia.
c Subject 038-002, who was randomized after approval of Amendment 2, did not receive consolidation treatment due to time elapse between date of approval and date of receipt of the approval.

Recruitment

The study started on June 2006. The fist patient was randomised on February the 1st 2007, the last randomised on September 19th, 2008.

Conduct of the study

Treatment compliance was not formally analysed since dose reductions and interruptions were allowed for each patient based on tolerability. Relative dose intensity is used as a surrogate for compliance.

Nine amendments to the study protocol were made.

This first interim analysis was carried out at the end of December 2009 by an independent statistician. This analysis was submitted to the DMC whose recommendation was the study should be unblinded but pursued until its term and that the decision to use Lenalidomide maintenance in patients of the placebo arm be made after discussing with patients the risks and benefits associated with such intervention. The study was unblinded on 07 July 2010. Whereas the interim PFS analysis was based on assessments of response and PD by the investigator, the final PFS analysis was based on assessments performed by an Independent Review Committee (IRC).

Baseline data

No clinically meaningful differences in demographic baseline characteristics were observed between the treatment arms in the ITT population. The type of prior induction chemotherapy was homogenous, >90% of patients having received either VAD or Velcade+dexamethasone. The number of ASCT was well balanced between lenalidomide and placebo arms with 79% of patients in both arms having undergone one ASCT.

Patient characteristics at diagnosis based on stratification factors were similar in both arms. Approximately 75% of the patients had stage III disease according to the Durie Salmon Staging System.

Response after transplant was better than VGPR in approximately 50% of patients in the placebo as well as in the lenalidomide arm. This means that consolidation was proposed to patients who, in the majority, are very good responders. This subpopulation should skip to the maintenance phase. There is no justification as why the whole population should undergo consolidation.

After observing an imbalance of SPMs in the lenalidomide arm, a safety measure was initiated, by the sponsor, on 26 Jan 2011 which resulted in the immediate treatment discontinuation of patients in the lenalidomide arm who were still receiving study maintenance treatment at that time.

Numbers analysed

In the initial application, the PFS results were based on an interim analysis (04 Sep 2009 data cut off) at 60% (180/300) of the planned PFS events for the final analysis specified in the original study design.

The final PFS analysis was conducted using data up to study unblinding on 07 July 2010 at 88% (264/300) PFS events. Whereas the interim PFS analysis included in the original submission was based on assessments of response and PD by the investigator, the final PFS analysis was based on assessments performed by an Independent Review Committee (IRC).

A more recent data cut off, 07 Oct 2011, is being used for all OS analyses, second line therapy and for occurrence of SPM. Based on this updated data set, the study has now reached a median follow-up of 41.4 months for surviving patients.

Outcomes and estimation

Primary endpoint: PFS

At the cut-off date of 04 September 2009, the median PFS, estimated from univariate Kaplan-Meier curves, was 99.29 weeks (95% CI 89.14; 119.14) for the Placebo arm and had not been reached for the Lenalidomide arm ($p<0.0000001$; HR 0.45).

The final PFS analysis was conducted using data up to study unblinding on 7 July 2010 at 88% (264/300) PFS events. The event rates were 52.1% for the placebo arm and 33.9% for the lenalidomide arm. The median PFS time was 177.7 weeks in the lenalidomide arm and 100.1 weeks in the placebo arm. The observed HR (95% CI) of 0.50 (0.39-0.65) with log-rank test p-value < 0.0000001 represents a 50% reduction in the risk of progression or death for the lenalidomide arm as compared to the placebo arm. The 2-, 3-, and 4-year progression-free survival rates for the lenalidomide-treated patients were 74.1%, 59.4%, and 39.1%, respectively. In comparison, the 2-, 3-, and 4-year PFS rates for the placebo-treated patients are lower (48.4%, 35.2%, and 19.5%, respectively). The PFS gain is numerically unquestionable.

The induction therapies administered in this trial were predominantly VAD and [bortezomib+ dexamethasone]. Randomised studies have shown that combinations of novel agents (bortezomib or thalidomide) plus dexamethasone are superior to the classical VAD regimen. Nowadays, VAD is still used as induction regimen but, in order to avoid alkylating agents, VD is preferred as well as [vincristine + dexamethasone] or [thalidomide + dexamethasone]. With the latest, the response rates achieved after induction may be different from the ones obtained with IFM 2005 induction regimens. Moreover, for ASCT, the current practice requires higher level of response (VGPR or CR) than the transplant procedure for IFM 2005-02 trial required. All these parameters may have an impact on subsequent benefit from lenalidomide maintenance.

When analysing by stratification prognostic factor, the subgroup of patients with beta 2 microglobulin below 3 mg/dL at baseline seems to be associated with a larger treatment effect (PFS advantage).

There were 115 patients in the lenalidomide arm and 131 in the placebo arm who had best responses of PR/SD post-transplant. Among these patients with a less robust response to ASCT, a lower proportion of patients in the lenalidomide arm had progressed/died compared with the placebo arm (37.4% [43/115] versus 61.1% [80/131]). The HR (95% CI) was 0.44 (0.30 – 0.64), representing a 56% reduction in the risk to progression in the lenalidomide arm. Also in the subgroup of patients who had best responses of CR/VGPR post-transplant, a lower proportion of patients in the lenalidomide arm (31.2% [59/189]) had progressed/died compared with the placebo arm (45.5% [80/176]). The HR (95% CI) was 0.57 (0.41 – 0.80), representing a 43% reduction in the risk to progression in the lenalidomide arm.

In conclusion, patients who had only achieved a PR/SD after ASCT (40% of the population) benefited earlier and to a greater extent from lenalidomide maintenance than those who had already achieved a CR/VGPR.

Secondary endpoints

Overall survival

The original submission used a data cut off date of 04 Sep 2009, representing a median duration of follow-up time of OS for all patients of 21.8 months. At that time, the median OS had not been reached in both treatment arms and no statistical difference on OS had been demonstrated between the lenalidomide arm and the placebo arm. (HR=0.95; 95%IC= (0.54-1.65); p=08536).

An update on OS was presented during the evaluation with a cut off date of 7 October 2011, representing a median duration follow-up time of OS for all patients of 41.4 months: the median OS was 259.1 weeks in the lenalidomide arm and 251.9 weeks in the placebo arm. The survival was not significantly different between the 2 arms with an HR (95% CI) of 1.12 (0.81-1.55) and a 2-sided unstratified log-rank test p-value = 0.505. The event rates were of 68/307 (22%) for placebo and 76/307 (25%) for lenalidomide.

Progression free survival from the date of diagnosis

The median PFS from the date of diagnosis, estimated from univariate Kaplan-Meier curves, was 146.57 weeks (95% CI 128.29; 156.71) for the placebo arm and had not been reached for the lenalidomide arm ($p < 0.0000001$; HR 0.440).

Time to progression

Median time to progression was significantly longer in the lenalidomide arm compared with the placebo arm ($p < 0.0000001$; HR 0.44). Median time to progression was not reached in the lenalidomide arm and was 99.29 weeks (~23 months) in the placebo arm.

Overall Best Response Rate

The overall myeloma response rate (≥ PR i.e., CR or VGPR or PR) was similar in both treatment arms: 99.3% (305/307) in the lenalidomide arm and 99.0% (304/307) in the placebo arm.

The comparison of response rates between the pre-consolidation and the post-consolidation shows that the rate of patients with complete response or VGPR was statistically significantly higher during the post-consolidation period (68.7%) versus the pre-consolidation period (63.6%), p=0.0002. So the MAH states that consolidation with lenalidomide monotherapy for 2 months statistically significantly improved the depth of response. However response was improved in all patients after transplant at randomisation versus after consolidation. The imputability to lenalidomide is groundless.

Data were not available on all patients for the IRC to determine response at baseline and after consolidation; however, the best response and date of PD could be determined for all treated patients.

The 2 courses of lenalidomide consolidation therapy improved the quality of response (CR/VGPR) from 53% of patients at baseline (160/361) to 66% of patients (181/274) after consolidation therapy in the Pbo arm and from 55% at baseline (162/294) to 66% after consolidation (179/269) in the Len arm.

During the subsequent course of maintenance treatment, the quality of response (CR/VGPR) improved further in both arms but more so with lenalidomide (84%) than with placebo (73%).

Duration of Response

Median response duration for patients who achieved at least a VGPR was significantly longer in the lenalidomide arm compared with the placebo arm (p<0.0001; HR 0.45). Median response duration was not reached in the lenalidomide arm and was 110.14 weeks (~25.4 months) in the placebo arm. Median duration of complete response was not reached in both treatment arms.

Second line anti-myeloma therapy

There was an imbalance in the number of patients who had received second-line therapy in the placebo and lenalidomide treatment arms (177 [57.7%] versus 123 [36.8%] patients, respectively). Of the patients in the lenalidomide treatment arm who received second-line therapy, 36.8% had received bortezomib and 5.9% had received lenalidomide. In the placebo treatment arm, 29.6% had received lenalidomide, 10.4% had received bortezomib, and 8.8% had received combinations of novel drugs as second-line therapies.

There is no evidence that Lenalidomide maintenance therapy may not adversely affect the activity of the second-line antimyeloma therapy other than lenalidomide.

For any second-line therapy including lenalidomide, there was a prolonged PFS observed in favour of the group that had received placebo in maintenance (median of 39.1 weeks for the placebo arm versus 33.3 weeks for the lenalidomide arm; HR [95% CI] = 1.41 [1.03-1.92]). This finding has to be interpreted with caution based on the imbalance of patients who were initiated on second-line therapy (limited size of subpopulations) and on the fact that the second line anti-myeloma therapy was not allocated on a randomised scheme. So, the concern whether the efficacy of second-line therapy could potentially affect OS can not be addressed.

In other words, if administering lenalidomide as first line treatment prevents from using it as subsequent line, it limits the options of second and further lines of treatment.

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 2. Summary of Efficacy for trial CC-5013-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	CC-5013-MM-015		
Design	Phase III, Multicentre, Randomised, Double-blind, Placebo-controlled 3-Arm parallel study		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		Induction of up to 9 cycles followed by maintenance therapy until disease progression or treatment discontinuation not applicable not applicable
Hypothesis	Superiority		
Treatments groups	MPR+R		*Induction* (9 cycles): For each 28 day cycle Melphalan 0.18 mg/kg, Days 1-4 Prednisone 2 mg/kg, Days 1-4 Lenalidomide 10 mg/day PO, Days 1-21 *Maintenance* (from cycle 10 until progression) Lenalidomide 10 mg/d, Days 1-21 of each 28-day cycle
	MPR+p		*Induction* (9 cycles): For each 28 day cycle Melphalan 0.18 mg/kg, Days 1-4 Prednisone 2 mg/kg, Days 1-4 Lenalidomide 10 mg/day PO, Days 1-21 *Maintenance* (from cycle 10 until progression) Placebo
	MPp+p		*Induction* (9 cycles): For each 28 day cycle Melphalan 0.18 mg/kg, Days 1-4 Prednisone 2 mg/kg, Days 1-4 Placebo, Days 1-21 *Maintenance* (from cycle 10 until progression) Placebo
Endpoints and definitions	Primary endpoint	Progression free survival (PFS)	time from randomisation to the first documentation of progressive disease based on the EBMT/IBMTR/ABMTR criteria, or death due to any cause during the treatment phase
	Secondary endpoint	Overall Survival (OS) to 5 years	time from randomisation to death due to any cause
	Secondary endpoint	Response rate	complete response [CR] and partial response [PR] using EBMT/IBMTR/ABMTR criteria
	Secondary endpoint	Duration of response	time from randomisation to the first documented objective response including CR and PR
Database lock	11 May 2010 (76% PFS events)		

Results and Analysis					
Analysis description	**Primary Analysis**				
Analysis population and time point description	Intent to treat Primary efficacy comparison: MPR+R vs MPp+p Secondary efficacy comparisons: MPR+R vs MPR+p and MPR+p vs MPp+p				
Descriptive statistics and estimate variability	Treatment group	MPR+R	MPR+p	MPp+p	
	Number of patient	152	153	154	
	Progressed/Died N (%)	52 (34.2)	81 (52.9)	93 (60.4)	
	Censored N (%)	100 (65.8)	72 (47.1)	61 (39.6)	
	Median PFS (weeks)	136.1	62.1	56.1	
	[95% CI]	(86.14, NE)	(56.14, 72.14)	(52.14, 68.14)	
Effect estimate per comparison	Primary endpoint PFS	Comparison groups	MPR+R vs MPp+p		
		HR [95% CI]	0.395 (0.278,0.560)		
		P-value (unstratified log rank)	< 0.001		
		Comparison groups	MPR+R vs MPR+p		
		HR [95% CI]	0.494 (0.347,0.702)		
		P-value (unstratified log rank)	< 0.001		
		Comparison groups	MPR+p vs MPp+p		
		HR [95% CI]	0.796 (0.589,1.075)		
		P-value (unstratified log rank)	0.134		

NE Not estimable

Summary of Efficacy for trial IFM 2005-02

Title: Benefit of a maintenance treatment with lenalidomide following autologous stem cell transplantation in patients with myeloma aged less than 65 years		
Study identifier	Protocol no. 04.004.01 / IFM 2005-02	
Design	Phase III, multicenter, randomised, double-blind, placebo-controlled 2-arm parallel study	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	Consolidation phase (2 cycles of 28 days) followed by maintenance phase until relapse not applicable not applicable
Hypothesis	Superiority	
Treatments groups	Placebo (Arm A)	Consolidation: lenalidomide 25 mg/day (day 1-21 every 28 day cycle, 2 cycles) Maintenance: placebo until progression

	Lenalidomide (Arm B)		Consolidation: lenalidomide 25 mg/day (day 1-21 every 28 day cycle, 2 cycles) Maintenance: lenalidomide 10 mg/day (if tolerated, could be increased to 15 mg/day) until progression
Endpoints and definitions	Primary endpoint	Post-transplantation progression free survival (PFS)	Time from the date of randomisation to the date of progression or death (whatever the cause)
	Secondary endpoint	PFS from diagnosis	Time from the date of diagnosis to the date of progression or death (whatever the cause).
	Secondary endpoint	Overall survival	Time from the date of randomisation to the date of death
	Secondary endpoint	Response duration	Time for all randomised patients with a complete or partial response from the date of randomisation to the date of progression
Database lock	7 July 2010 (88% interim analysis)		

<u>Results and Analysis</u>

Analysis description	**Primary Analysis**			
Analysis population and time point description	Intent to treat			
Descriptive statistics and estimate variability	Treatment group	Placebo	Lenalidomide	Total
	Number of patient	307	307	614
	Censored	147 (47.9%)	203 (66.1%)	350 (57.0%)
	Progressed or died	160 (52.1%)	104 (33.9%)	264 (43.0%)
	Overall Post-transplantation PFS (weeks) Median	100.1	177.7	
	95% CI	(92.1; 121.7)	(166.4;NE)	

Effect estimate per comparison	Primary endpoint Post-transplantation PFS	Comparison groups	Placebo vs Lenalidomide
		HR [95% CI]	0.50 (0.39-0.65)
		P-value (stratified log rank)	<0.0000001

NE Not estimable

Supportive studies

Study CALGB 100104

Methods

This study was a phase 3 randomised, double-blind study of maintenance therapy with lenalidomide or placebo following ASCT for multiple myeloma. It was sponsored by the US Cancer and Leukemia Group B (CALGB). It is submitted as a supportive study.

Study Participants

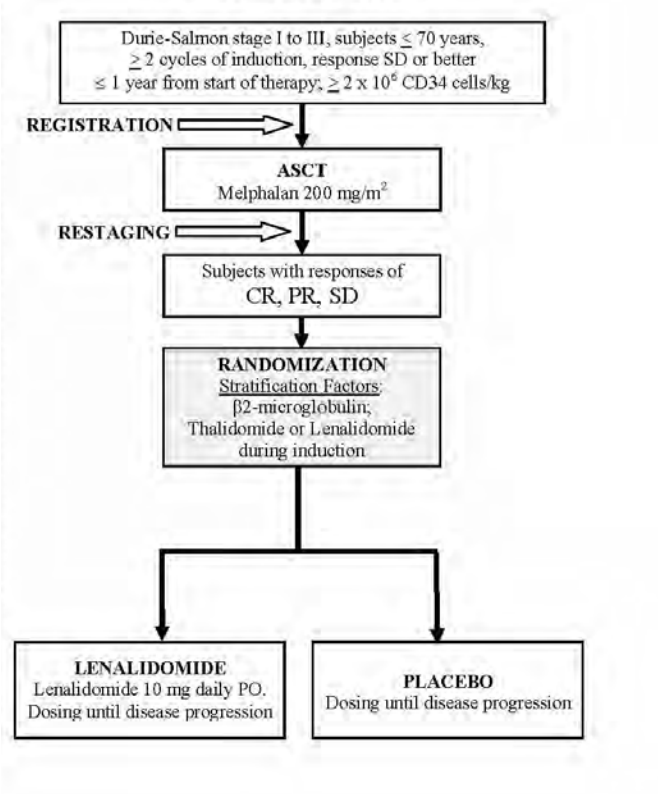
The patient population of Study CALGB 100104 was similar to Study IFM 2005-02 with the exception that the study did not have a consolidation period and patients went directly to maintenance therapy.

Treatments

Patients were registered prior to ASCT. During registration, the patients signed the informed consent form and were assigned a patient identification number. The ASCT had to occur 4 to 6 weeks after registration. There was no consolidation treatment post-transplantation. Patients with stable disease or better were randomised at Day 100 to 110 post-transplant in a double-blind fashion to maintenance treatment with lenalidomide or placebo. The starting dose was 10 mg/day, escalated to 15 mg/day after 3 months, and continued until disease progression. Maintenance treatment was stopped and/or dose reduced as needed to manage toxicity.

Patients in the CALGB study were stratified prior to randomisation according to 2 parameters: β2 microglobulin at diagnosis (≥ 2.5 mg/dL versus normal) and type of induction therapy (thalidomide-containing versus lenalidomide-containing versus other).

The study design is given below.



Objectives

The primary objective of the CALGB 100104 study was to determine if maintenance treatment with lenalidomide would prolong TTP after a single ASCT.

Outcomes/endpoints

In the CALGB 100104 study, the primary endpoint was called TTP. However, by definition, the TTP calculation censoring rules used in this study were essentially equivalent to those for the standard calculation of PFS (progression or death for any reason count as an event from Day 0 of ASCT).

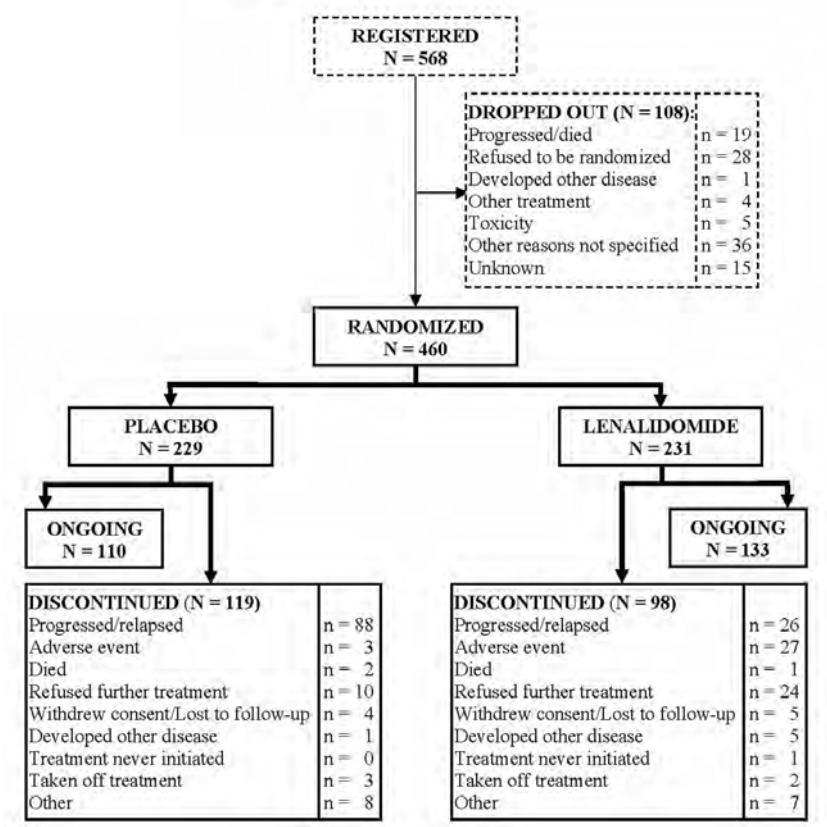
Results

Full analysis of results from the CALGB 100104 study, prior to unblinding, uses 17 December 2009 as cut off date. A more recent data cut off, 07 Oct 2011, is being used for second line therapy and for occurrence of SPM analysis (cut off date 17 August 2011) and for OS analyses (cut off date 15 September 2011). Based on this updated data set, the study has now reached a median follow-up of 32.7 months for surviving patients.

Participant flow

Of the 460 patients randomised, 229 were allocated to placebo and 231 to lenalidomide.

The figure below describes the disposition of patients as of the 17 Dec 2009 cut off date.



After randomisation, in the placebo arm, more patients discontinued treatment due to disease progression or relapse (38.4%) than for any other reason whereas in the Len arm only 11.3% discontinued treatment due to PD or relapse.

As of the 17 Dec 2009 cut off date for unblinding, 133 (57.6%) patients in the lenalidomide arm and 110 (48.0%) patients in the placebo arm were still on treatment. As per the most recent data cut off, 95 of the 231 patients randomised to the lenalidomide arm were still on lenalidomide therapy as of 17 August 2011.

Conduct of the study

The first planned interim analysis of the CALGB 100104 study was reviewed by the DSMB in June 2009. The DSMB requested an update. The update included an interim analysis of data which was performed after 28% (87/309) of the PFS events required for the planned final analysis had occurred (September 2009 cut off date), and was reviewed by the DSMB in November 2009. This DSMB review led to the release of the results in December 2009 as the efficacy results had surpassed the prespecified boundary. Analyses prior to unblinding were performed with the 17 December 2009 cut off date. At the time of unblinding, patients who were receiving placebo were allowed to cross over to open-label lenalidomide.

Baseline data

The demographic and baseline characteristics of the patients in the IFM 2005-02 and CALGB 100104 studies were balanced between the lenalidomide and placebo arms in each respective study and between the 2 studies. However the following differences were observed:

- Patients in the CALGB study had less advanced disease (approximately 52% Durie-Salmon stage III in CALGB compared to 76% in IFM) and lower tumor burden (β2- microglobulin levels ≥ 3.0 mg/L),

- 64% of patients in the CALGB 100104 study had responses of PR/SD post-transplantation prior to randomisation, whereas only 40% of patients in the IFM 2005-02 study had achieved a PR/SD after ASCT,

- None of the patients in the CALGB 100104 study had received a second ASCT,

- In the CALGB 100104 study, patients had more exposure to lenalidomide- or thalidomide-containing regimens as prior induction MM therapy (~74%).

Outcomes and estimation

Primary endpoint: PFS

The PFS results reported in the original submission (D80) were based on data presented at the 2010 Annual ASCO Meeting. That analysis was done when 28% (87/309) of the planned PFS events had occurred.

The present update corresponds to the final PFS analysis that was conducted using the database updated to study unblinding (17 Dec 2009) when 47% (147/309) of the events planned had occurred.

As of 17 Dec 2009, the event rates were 21.2% for the lenalidomide arm and 45.0% for the placebo arm. The median PFS was 175.0 weeks in the lenalidomide arm and 79.1 weeks in the placebo arm. The observed HR (95% CI) of 0.353 (0.250-0.498) with log-rank test p-value <0.001 represents a 65% reduction in the risk of progression or death for the lenalidomide arm as compared to placebo arm. So, the treatment effect is large.

The 2- and 3-year PFS rates for the lenalidomide-treated patients are 74.0% and 51.0%, respectively. In comparison, the 2- and 3-year PFS rates for the placebo-treated patients were lower (43.1% and 19.5%, respectively).

There were 156 patients in the lenalidomide arm and 140 patients in the placebo arm who had only achieved PR/SD post-transplant. Among these patients, a lower proportion in the lenalidomide arm had progressed/died compared with the placebo arm (21.2% [33/156] versus 52.1% [73/140]). The HR (95% CI) was 0.300 (0.198-0.454), representing a 70% reduction in risk of progression/death in favour of the lenalidomide arm. In the subpopulation of patients who achieved PR/SD post-transplant, lenalidomide significantly prolongs PFS.

In comparison, for patients who had achieved a CR/VGPR post-transplant, the HR (95% CI) was 0.650 (0.314-1.344), representing a 35% reduction in risk of progression/death in favour of the lenalidomide arm, but without statistical significance. However the limited size of this subgroup of patients, even decreasing with follow up, make hazardous the interpretation of PFS curves.

CALGB and IFM studies follow the same design (with the exception of 2 months consolidation in both arms of IFM). Hence PFS results in CALGB are supportive for the maintenance part of the IFM.

Secondary endpoints

Overall survival

The present update of OS has a data cut off date of 15 Sep 2011, representing a median duration of follow-up time of 32.7 months. As of the 15 Sep 2011 cut off date, the number of deaths included 32 patients (13.9%) in the lenalidomide arm and 49 patients (21.4%) in the placebo arm. The median OS time has not been reached in the lenalidomide arm or in the placebo arm. The survival was significantly different between the 2 arms with an HR (95% CI) of 0.613 (0.393-0.958) and a 2-sided unstratified log-rank test p-value = 0.030. This represents a 39% reduction in risk of death in favour of lenalidomide maintenance therapy. However the CI is wide and the upper limit almost reaches 1.

No conclusion can be drawn from the analysis of OS per subgroup (patients with post-transplant response of PR/SD or CR/VGPR) since the population size is too small.

Second line anti-myeloma therapy

The type of subsequent therapy in the CALGB 100104 study was analysed using the most recent data cut off date of 17 Aug 2011. As of the 17 Aug 2011 cut off, a total of 76 patients in the placebo arm had crossed over to receive lenalidomide treatment prior to PD. Therefore, the time from second-line to third-line therapy does not represent a good surrogate for PFS of the second-line therapy. As off 17 Aug 11, there was an imbalance in the number of patients who had received subsequent therapy in the lenalidomide and placebo treatment arms (20/231 [8.7%] versus 124/229 [54.1%] patients, respectively), reflective of the efficacy (PFS) of the maintenance therapy prior to unblinding and the patients who crossed over to receive active treatment.

Study ECOG E4A03

Study ECOG E4A03 was a randomised phase 3 study of lenalidomide plus standard-dose dexamethasone versus lenalidomide plus low-dose dexamethasone in previously untreated multiple myeloma with thalidomide plus dexamethasone salvage therapy for non-responders.

It was a National Cancer Institute-sponsored study, which was conducted by the Eastern Cooperative Oncology Group (ECOG) and enrolled 445 patients at 138 sites in the US.

The primary objective of the study was to compare response rates after 4 cycles of treatment between the 2 treatment arms (randomised 1:1): 223 patients were randomised to arm len/D (lenalidomide 25 mg daily for 21 days every 28-day cycle combined with standard-dose dexamethasone [40 mg daily on Days 1 to 4, 9 to 12, and 17 to 20 every 28-day cycle]) and 222 patients were randomised to arm len/d (lenalidomide 25 mg daily for 21 days every 28-day cycle combined with low-dose dexamethasone [40 mg daily on Days 1, 8, 15, and 22 every 28 day cycle]).

The protocol-planned primary endpoint was the response rate in the first 4 cycles of the first phase of the study. Response was assessed by an Independent Response Adjudication Committee (IRAC).

This submission included the following ad hoc analyses (which were not protocol-planned): overall response rate (i.e., response assessments over the treatment period) based on the IRAC review, duration of response, time to first response, TTP, PFS, and OS.

The DSMB recommended termination of enrollment after an interim analysis showed a survival advantage for combination lenalidomide plus low-dose dexamethasone therapy over combination lenalidomide plus standard-dose dexamethasone therapy. Following this recommendation, enrollment was suspended on 27 Mar 2007, and the study was terminated on 01 Jun 2007.

The overall response rate in the first 4 cycles (comparison of the dichotomized response [CR + nCR + PR]) was significantly lower in the len/d arm (64.4% [143/222]) than the len/D arm (77.1% [172/223]) ($p = 0.0035$; Fisher's exact test). Among the responders, the duration of response was not significantly different between treatment arms ($p = 0.0761$), however was numerically longer in the len/d arm than the len/D arm, as shown with the hazard ratio favouring the len/d arm (hazard ratio 1.506; 95% CI: 0.955, 2.375). The proportion of responders who continued to respond at the time of analysis was higher in the len/d arm than the len/D arm (80.1% vs 72.6%, respectively).

PFS was not significantly different between treatment arms ($p = 0.1350$, unstratified log rank test; hazard ratio 1.321; CI [0.916, 1.904]), however a trend was observed that PFS was longer in the len/d arm than the len/D arm.

Overall survival was defined as the number of weeks between the registration/randomisation and death, regardless of cause. As of the date of data release (26 Mar 2007), 17 of the 222 patients (7.7%) in len/d arm and 43 of the 223 patients (19.3%) in the len/D arm had died. Median OS had not been reached for either treatment arm. Based on the unstratified log rank test, OS was significantly longer in the len/d arm than in the len/D arm (p = 0.0003). Based on the hazard ratio (assuming proportional hazard ratio over time), the patients in the len/D arm were approximately 2.7 times as likely to die at anytime as those in the len/d arm (CI: 1.528, 4.706).

Using data up to the extended follow-up cut off (as of 01 Jul 2008), 48 of the 222 patients (21.6%) in the len/d arm, and 54 of the 223 patients (24.2%) in the len/D arm had died (p = 0.2895). The median OS could not be estimated for either treatment arm because too few deaths had occurred.

ECOG E4A03 trial is submitted as a supportive study. Its results were requested by the CHMP as a safety follow up measure (FUM) following granting of marketing authorisation to Revlimid in second line treatment MM to propose management of thromboprophylaxy in MM patients.

As for efficacy, results have shown that low dose dexamethasone provides benefit in terms of efficacy (longer overall survival) and safety (lower toxicity of dexamethasone). But first-line therapy in MM differs whether patients are candidates to transplant or not. Unfortunately, ECOG study included mixed population as regards transplant status.

In the claimed indication (NDMM), lenalidomide is not proposed in combination with dexamethasone. Lenalidomide dosage in ECOG study was higher (25 mg) than the one proposed for NDMM whatever the scheme is.

For all these reasons, the contribution of this supportive trial to the extension of variation is poor.

Study SWOG S0232

Methods

Study SWOG S0232 was a double-blind, placebo-controlled, phase 3 trial comparing the standard-dose of dexamethasone to the combination of lenalidomide plus dexamethasone in patients with previously untreated multiple myeloma who were not immediately undergoing ASCT. Patients could continue on study and delay ASCT if treatment was successful.

Study SWOG S0232 was sponsored by the Southwest Oncology Group (SWOG) and enrolled 198 patients with previously untreated multiple myeloma in 41 US centres.

The primary objective of the study was to compare PFS between the 2 treatment arms: lenalidomide +dexamethasone (len/D) or placebo+dexamethasone (pbo/D).

The secondary objectives were to compare between the 2 treatment arms:

- Overall response rate (ORR)
- Major response rate (> 75% decrease in monoclonal protein [M-protein])
- Time to best response
- OS
- Toxicity profile, including thrombotic complications

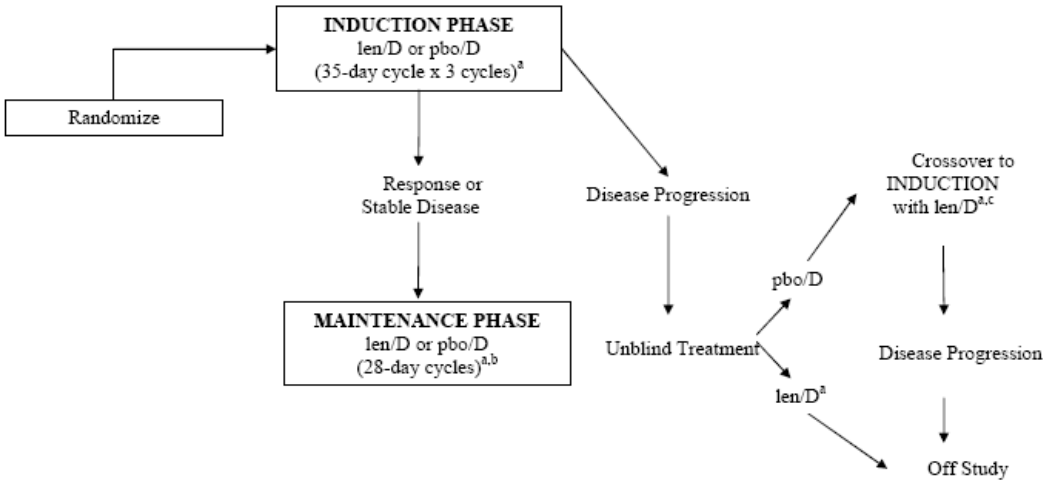
At registration into the study, patients were randomised in a 1:1 ratio into the len/D arm or the pbo/D arm. Randomisation was stratified by International Staging System (ISS) disease stage at registration into the study (Stage I vs Stage II versus Stage III) and performance status (0 and 1 vs 2 and 3).

Dosage regimen used during induction phase (35-Day Cycles) was 25 mg of lenalidomide or placebo orally once daily on Days 1 to 28 plus 40 mg of dexamethasone orally once daily on Days 1 to 4, 9 to 12, and 17 to 20 every 35 days for 3 cycles.

Dosage regimen used during maintenance phase (28-Day Cycles) was 25 mg of lenalidomide or placebo orally once daily on Days 1 to 21 plus 40 mg of dexamethasone orally once daily on Days 1 to 4 and 15 to 18 every 28 days until disease progression or the patient discontinued from the study for another reason.

Patients in both treatment arms were to receive prophylaxis for thrombo-embolic events (325 mg/day of aspirin orally or 40 mg/day of enoxaparin subcutaneously if the patient had an allergy to or intolerance to aspirin) on each day of each cycle during the induction and maintenance phases.

The figure below gives the study design.



a All patients were to take 325 mg/day of aspirin during the double-blind phase of the study and while taking open-label lenalidomide.
b Patients received repeated 28-day cycles of lenalidomide or placebo (25 mg/d on Days 1-21) and dexamethasone (40 mg/d on Days 1-4 and 15-18) until documented disease progression or until discontinuation from the study for another reason.
c The dosage schedule of lenalidomide for patients who crossed over from placebo/dexamethasone (pbo/D) to lenalidomide/dexamethasone (len/D) during the induction phase or during the maintenance phase was the same as that used during blinded therapy for the patients who were randomized to the len/D treatment arm. The dose of dexamethasone that the patient was taking at the time of unblinding was the dose that was used during open-label treatment with lenalidomide and dexamethasone.

The study was planned to include 500 patients. A total of 198 patients were enrolled: 100 patients were randomised to the len/D arm, and 98 patients were randomised to the pbo/D arm. All 198 patients were included in the ITT population for the efficacy analysis; 194 patients (98 patients in the len/D arm and 96 patients in the pbo/D arm) received at least 1 dose of study medication (lenalidomide/placebo or dexamethasone) and were included in the safety analyses.

Main inclusion criteria were:

- Patients aged ≥ 18 years who had a diagnosis of previously untreated multiple myeloma
- no immediate plans to undergo ASCT
- measurable disease, defined as a serum M-protein level of ≥ 1.0 g/dL (≥ 10.0 g/L) as measured by serum protein electrophoresis or immune electrophoresis, a urinary M protein level of ≥ 200 mg/24 hours (≥ 0.2 g/24 hours), or both within 28 days before registration into the study
- Zubrod performance status of 0 to 3
- adequate bone marrow, liver, and renal function.

Main exclusion criteria were:

- Non secretory MM
- Prior treatment for multiple myeloma
- Pregnancy
- Uncontrolled active infection
- New York Heart Association Class III or IV

- Poorly controlled hypertension, poorly controlled diabetes mellitus, or other serious or psychiatric illness
- Prior malignancy
- Unable to take either 325 mg/day of aspirin by mouth or, alternatively, 40 mg of enoxaparin subcutaneously once daily for thrombotic prophylaxis

Patients received treatment until disease progression occurred or until the patient discontinued treatment for another reason.

The primary efficacy endpoint was PFS calculated as the weeks between study registration and documented disease progression or death, whichever occurred first.

The secondary efficacy endpoints were ORR, time to response, duration of response, OS, and TTP.

For the primary efficacy analyses, a blinded Independent Response Assessment Committee (IRAC) assessed the tumor response of each patient using myeloma response criteria as modified from Bladé and the Myeloma Subcommittee of the European Group for Blood and Marrow Transplant (EBMT). The supportive efficacy analyses used the PFS and tumor response based on SWOG's assessments.

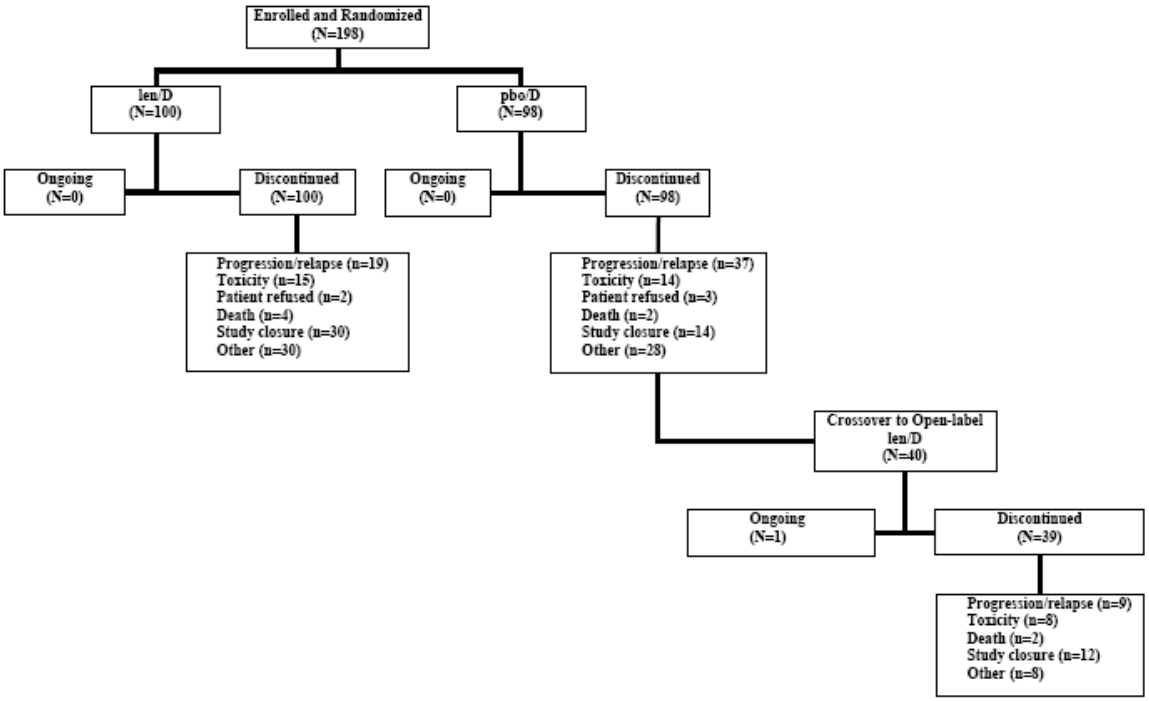
The Kaplan-Meier method was used to estimate the survival distribution functions for PFS, duration of response, OS, and TTP in each treatment arm. A Cox proportional hazards model with treatment term was used to estimate relative risk (len/D over pbo/D) and the 95% confidence interval (CI). Comparison between treatment arms was performed using a 1-sided Fisher's exact test with $\alpha = 5\%$.

Results

The study was initiated on 15 Oct 2004. At the recommendation of the DSMC, accrual to the study was stopped on 02 Apr 2007 after preliminary results of the ECOG E4A03 study suggested a survival advantage for combination lenalidomide plus low-dose dexamethasone therapy over combination lenalidomide plus standard-dose dexamethasone therapy. The treatment assignments for all patients were unblinded on 11 May 2007.

Efficacy results focus on a comparison of blinded data for the 2 treatment arms (len/D and pbo/D) based on data from the start of the study on 15 Oct 2004 up to study unblinding on 11 May 2007.

The disposition of patients in both treatment arms as of 11 May 2007 is summarized in the following figure.



The median duration of follow-up for this analysis was 64.4 weeks for the patients in the len/D arm and 62.5 weeks for the patients in the pbo/D arm.

PFS

As of the date of study unblinding on 11 May 2007, PFS was significantly longer in the len/D treatment arm than in the pbo/D treatment arm ((HR = 0.369 [0.199, 0.684], p = 0.001, unstratified log rank test).

Overall Response Rate, Time to Response, and Duration of Response

Based on the IRAC assessment of myeloma response, the overall response rate (comparison of the dichotomized response [CR + nCR + PR]) was significantly higher in the len/D treatment arm than in the pbo/D treatment (67.0% versus 40.8%; p=0.0003, Fisher's exact test). Based on the odds ratio, the patients in the len/D treatment arm were approximately 2.9 times as likely to respond to therapy as those in the pbo/D treatment arm. Of note, 40 of the 100 patients (40.0%) in the len/D treatment arm, compared with 8 of the 98 patients (8.2%) in the pbo/D treatment arm, achieved a CR or nCR to therapy.

No significant differences were observed between the treatment arms in the time to response or in the duration of response.

OS

As of study unblinding on 11 May 2007, 8 of the 100 patients (8.0%) in the len/D treatment arm and 18 of the 98 patients (18.4%) in the pbo/D treatment arm had died. Median OS had not been reached in either treatment arm (i.e., too few deaths had occurred). Based on the unstratified log rank test, OS was significantly longer in the len/D treatment arm than in the pbo/D treatment arm (p = 0.0342).

Extended follow-up data included data up to 23 Oct 2008 for the patients who received blinded therapy with len/D or pbo/D from 15 Oct 2004 through 11 May 2007 (date of study unblinding). The median duration of follow-up for this analysis was 129.2 weeks for the patients in the len/D treatment arm and 120.8 weeks for the patients in the pbo/D treatment arm. As of 23 Oct 2008, 21 of the 100 patients (21.0%) who had received blinded treatment with len/D and 24 of the 98 patients (24.5%) who had

received blinded treatment with pbo/D had died. Median OS could not be estimated for either of the treatment arms because too few deaths had occurred. No statistically significant difference was observed between the len/D and pbo/D treatment arms in OS as of 23 Oct 2008 based on the unstratified log rank test (primary analysis method). However, it should be noted that patients in the pbo/D treatment arm received, after study discontinuation, alternative therapies, including lenalidomide -based therapies.

The lack of estimation of OS due to too short follow up time makes the results of SWOG S0232 study less informative than expected. Benefit in terms of PFS is not yet confirmed by an advantage in OS.

TTP

As of the date of study unblinding (11 May 2007), TTP was significantly longer in the len/D treatment arm than in the pbo/D treatment arm ($p = 0.0007$, unstratified log rank test). Based on the hazard rate ratio (0.302), patients in the pbo/D treatment arm were approximately 3.3 times as likely as those in the len/D treatment arm to progress at any time during the treatment period.

First-line therapy in MM differs whether patients are candidates to transplant or not but SWOG S0232 study included mixed population as regards transplant status.

In the claimed indication (NDMM), lenalidomide is not proposed in combination with dexamethasone. Lenalidomide dosage in SWOG study was higher (25 mg) than the one proposed for NDMM whatever the scheme is.

1.4.3. Discussion on clinical efficacy

Statistically significant difference in terms of PFS in favour of treatment using lenalidomide alone or in combination has been shown in pivotal and supportive studies in the different settings (induction+maintenance in TNE population or maintenance in TE population). However, in both populations, the duration of maintenance phase was not justified.

In the TNE population

In MM015, lenalidomide was studied as part of combination during induction and as monotherapy during maintenance. PFS was significantly longer in arm MPR+R than arm MPp+p (HR=0.395 (0.278, 0.560), $p < 0.001$, two-sided unstratified Log-rank test). A lower percentage of patients in arm MPR+R experienced disease progression during the double-blind treatment phase than those in arm MPp+p (34% versus 60%, respectively).

With regard to baseline age stratification subgroups, there was a highly significant PFS advantage in arm MPR+R as compared with arm MPp+p in patients ≤ 75 years old, whereas no difference in PFS was observed between arms MPR+R and MPp+p in the > 75 years subgroup. This suggested that in combination with MP, Revlimid provided a better advantage to patients 65-75 years old. This justified that the Applicant only pursued an indication in patients aged ≤ 75 years.

MPR induction demonstrated more effective tumour volume debulking than MP as evidenced by a significant increase in overall response rate and a tripling of the rate of CR/VGPR responses. This confirmed the contribution of lenalidomide to induction in the MPR+R regimen.

Considering that for the primary comparison (MPR+R vs MPp+p), the risk reduction in progression/death is 60%, a 51% risk reduction in progression/death in the MPR+R versus MPR+p comparison indicated that lenalidomide maintenance contributes to a large part of the overall PFS benefit of the MPR+R regimen.

The primary comparison Arm MPR+R versus Arm MPp+p, in the ≤75 years of age group showed a trend in OS benefit in favour of lenalidomide but this gain was not statistically significant. Acknowledging the limits of cross-trial comparisons, other novel agents like bortezomib or thalidomide in association with MP exhibited, in a similar setting, a lesser gain in PFS than MPR+R but a statistically prolonged survival. There is no confirmation or invalidation that the lack of significance of the HR for overall survival in MM 015 study is mainly due to the identified safety risk occurrence of second primary malignancies causing death. As a result, the only benefit of MPR+R combination may be to postpone progression.

Long-term outcomes, including overall survival, might be impacted based on the imbalance of patients in second-line therapy and the crossover effect of lenalidomide in second-line after placebo treatment.

When assessing PFS on second line therapy, lenalidomide was less effective in the patients who received second-line lenalidomide after lenalidomide maintenance. So, patients proposed to be treated with lenalidomide as first line will not get the opportunity to be treated with the same agent as second line therapy.

In the TE population:

Patients who had only achieved a PR/SD after ASCT (40% of the population in the IFM 2005-02 study and > 60% of the population in the CALGB 100104 study) benefited earlier and to a greater extent from lenalidomide maintenance than those who had already achieved a CR/VGPR. As stratification on post transplant response was planned by protocol, subgroup analyses on stratum were allowed. Patients who achieved PR/SD post-transplant may benefit to a greater extent of lenalidomide maintenance than those who had already achieved a CR/VGPR.

Patients in CALGB study did not receive 2 courses of lenalidomide consolidation, as in the IFM 2005-02 study. PFS improvements were nevertheless in the same range (respectively 65% and 50%). The consolidation step did not enhance the gain in PFS and is of no benefit.

No statistically significant prolongation of OS was shown with lenalidomide maintenance.

1.4.4. Conclusions on the clinical efficacy

Clinical benefit in terms of PFS is indubitable. Efficacy analyses by subgroups have identified subpopulations that may, in a greater extent, benefit from lenalidomide as induction+maintenance in TNE population or maintenance in TE population. However, the duration of maintenance phase until progression was not justified.

Given the safety profile reported in the studies (see clinical safety section), the lack of benefit in OS is a major deficiency. As a consequence, a gain in PFS (as primary endpoint) needs to be confirmed by a benefit in overall survival.

In the TNE population, the lack of benefit in OS for MPR+R is of particular concern since other combinations like MPT or MPB, compared to MP, are associated with high statistically significant differences in OS (study IFM 99 06, MPT vs. MP (HR 0.59 (0.46, 0.81)); study VISTA, MPV vs. MP (HR 0.65 (0.51, 0.84)).

The lack of significance of the HR for survival may be explained by the switch from placebo to lenalidomide but also by the occurrence of second primary malignancies. The extent of each cause remains unknown as there was no confirmation or invalidation that the lack of significance of the HR

for survival in MM 015 study is mainly due to the occurrence of second primary malignancies causing death.

In the TE population where the life expectancy is per se longer, prolonged survival is even more expected but IFM 2005 02 study did not show statistically significant benefit in OS and CALGB 100104 study was borderline statistically significant.

Taken together, the provided data do not allow to clearly define the efficacy profile of Revlimid as induction and/or maintenance therapy in NDMM patients.

1.5. Clinical safety

Safety results of the 2 ongoing main studies (CC-5013-MM-015 and IFM 2005-02) as well as safety data from the 3 supportive studies (CALGB 100104, ECOG E4A03 and SWOG S0232) constitute the safety dataset. The patient populations and treatment regimens were different in these studies, thus the safety data have not been integrated and all data were presented separately by study.

A total of 2699 NDMM patients have been enrolled in these studies (1,361 on lenalidomide and 1,338 on placebo). However, this safety analysis has been focused on the safety data from the two main studies. Therefore, the safety population analysed in this report included 1,063 patients (608 on lenalidomide and 455 on placebo).

CC-5013-MM-015 Study (Interim analysis)

Of the 459 newly diagnosed MM patients randomised, 4 did not receive the study drug. Finally, there were 150 MPR+R patients, 152 MPR+p patients, and 153 MPp+p patients. Overall, 24% were ≥ 75 years.

As of the 03 Oct 2011, there were a total of 22 patients still on-study and receiving lenalidomide treatment in Arm MPR+R.

During induction phase, approximately twice as many Revlimid patients experienced AEs that led to dose reduction, or to discontinuation of treatment compared with placebo patients.

A total of 152 patients (33%) experienced at least 1 SAE during the induction. SAEs reported more frequently in the lenalidomide arms arm were anemia, febrile neutropenia, and pneumonia.

Globally, 38% of patients did not enter the maintenance phase: 40% of Revlimid patients and 33.7% of placebo patients. Importantly, 64% of the Revlimid patients ≥75 years discontinued lenalidomide versus 28.9% in the placebo arm. The reasons for discontinuation were mainly due to adverse events and withdraw of consents.

Among the 15 fatal cases reported during induction, 13 (87%) were ≥ 75 years old, but the number of deaths was comparable between Lenalidomide arms and placebo arm. However, four cardiac deaths in lenalidomide patients occurred during the induction period versus one in placebo arm.

During maintenance phase, 27.3% of MPR+R patients had ≥1 dose reduction versus 7.4% MPR+p and 1.0% MPp+p patients. However, the median treatment duration was longer in MPR+R arm. The percentage of patients ≥75 years who discontinued study drug due to AE was similar between lenalidomide arms and placebo arm. Globally, the data regarding this maintenance monotherapy with Revlimid do not raise concern, and 128 patients entered the study phase as of the 01Dec2009 cut-off.

During the double-blind treatment phase, at least 1 adverse event was reported for almost all patients in all 3 treatment arms. The frequency of patients with reported grade 3/4 adverse events was higher in Arms MPR+R (91.3%) and MPR+p (84.9%) than in Arm MPp+p (69.9%). The frequency of patients

with reported grade 5 adverse events during the induction and maintenance periods was similar in all 3 treatment groups (7, 6 and 7, respectively). The frequency of patients with reported serious adverse events that the investigator considered related to lenalidomide/placebo was higher in Arms MPR+R (25.3%) and MPR+p (21.7%) than in Arm MPp+p (7.2%)

The frequency of patients with reported adverse events leading to withdrawal of lenalidomide/placebo also was higher in patients in Arms MPR+R (17.3%) and MPR+p (15.8%) than in Arm MPp+p (9.2%).

There were no deaths in patients while receiving lenalidomide maintenance therapy, whereas the 2 deaths that occurred in patients while receiving placebo maintenance were due to disease progression. Most deaths occurred during the follow-up phase (>30 days after last dose of study medication), with the majority being due to disease progression.

During the conduct of this study and evaluation of this application, a new safety event has emerged. As of 6 February 2011, 18 secondary primary malignancy (SPM) cases have been reported out of 302 patients treated with Revlimid versus 5 out of 153 patients treated with placebo (6% in lenalidomide arm versus 1% in placebo arm).

As of the 3 October 2011, the cumulative number and frequency (number of patients with ≥ 1 SPM/total number of patients) of patients with secondary malignancies in each treatment arm, as well as the pooled lenalidomide-containing arms, of MM-015 is shown in the table below.

Table 14: Cumulative Incidence and Incidence Rates of Second Primary Malignancies in Study MM-015 as of 03 Oct 2011 (Safety Population)

			Subjects with at Least 1 SPM, n (%)									
			Invasive Malignancies								Non-melanoma Skin Cancer	TOTAL[a]
			Hematologic Malignancies						Solid Tumors	Overall		
Study	Treatment	No. of Subjects	AML	MDS	MDS to AML	B-ALL and Hodgkin Lymphoma	Other[b]	Overall				
MM-015	MPR+R	150	4 (2.7)	1 (0.7)[b]	1 (0.7)	0 (0.0)	1 (0.7)	7 (4.7) **1.75•**	5 (3.3) **1.26•**	12 (8.0) **3.04•**	2 (1.3) **0.50•**	14 (9.3) **3.56•**
	MPR+p	152	3 (2.0)	2 (1.3)	1 (0.7)	0 (0.0)	0 (0.0)	6 (3.9) **1.54•**	5 (3.3) **1.28•**	10 (6.6)[c] **2.57•**	5 (3.3) **1.29•**	14 (9.2)[c,d] **3.64•**
	Len–containing arms	302	7 (2.3)	3 (1.0)	2 (0.7)	0 (0.0)	1 (0.3)	13 (4.3) **1.65•**	10 (3.3) **1.27•**	22 (7.3)[c] **2.81•**	7 (2.3) **0.89•**	28 (9.3)[c,d] **3.60•**
	MPp+p	153	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7) **0.24•**	3 (2.0) **0.74•**	4 (2.6) **0.98•**	6 (3.9) **1.50•**	10 (6.5) **2.51•**
	Overall	455	7 (1.5)	4 (0.9)	2 (0.4)	0 (0.0)	1 (0.2)	14 (3.1) **1.17•**	13 (2.9) **1.09•**	26 (5.7)[c] **2.18•**	13 (2.9) **1.09•**	38 (8.4)[c,d] **3.23•**

Studies in the Transplant-eligible Population (Studies IFM 2005-02 and CALGB 100104)

Overall, the tolerability of Revlimid in maintenance treatment in NDMM patients after SCT in study IFM 2005-02 was similar to the known safety profile, notwithstanding the new safety signal regarding second primary malignancies that emerged during assessment of this application.

At the time of the original submission, data from an interim analysis (IFM 2005-02) and an ASCO presentation (CALGB 100104) were available.

As of January 14th, 2011, a total of 23 second malignancies were reported in study IFM 2005-02 of which 3 in the placebo arm (302 patients) and 20 in the lenalidomide arm (306 patients), i.e., the 36-month follow-up cumulated incidences of second cancers are 1% in placebo arm versus 7% in lenalidomide arm ($p < 0.0003$). In contrast, the 18-month follow-up cumulated incidences were similar between the two arms.

6 B-cell malignancies (2 ALL, 4 Hodgkin), which were all observed after at least 2 years of maintenance with Lenalidomide are of particular concern. With the overall imbalance observed in this

trial and the fact that a significant number of Cases (esp. B-cell malignancies) were observed after 2 years of lenalidomide exposure. The DMC reviewed the data and noted that there was a higher incidence of second cancers in the lenalidomide arm compared with placebo, including AML/MDS 5 versus 2 ; AL 2 versus 0; Hodgkin disease 4 versus 0 and solid tumors excluding basal cell skin cancers 6 versus 1. Overall second cancers are higher, 20 versus 3 (excluding basal cell 17 versus 3). AML/MDS deaths were higher 5 versus 1. As a consequence of the DMC review, the IFM 2005-02 study was discontinued by its sponsor.

The most recent data cutoffs for secondary malignancies were 7 October 2011 for the IFM 2005-02 study and 17 Aug 2011 for the CALGB 100104 study. As of the data cutoff for the 2 transplant-eligible studies, a total of 225 patients died in the study (108 in the lenalidomide-based regimens arms and 117 in the control arms). Of these, 25 have died who were diagnosed with an invasive SPM during the course of the study (18 patients in the lenalidomide-based regimens arms and 7 in control arms).

Table 27: Cumulative Incidence and Incidence Rates of Second Primary Malignancies in the Transplant-eligible Newly Diagnosed Multiple Myeloma Studies (Safety Population)

			Subjects with at Least 1 SPM, n (%)									
			Invasive Malignancies									
			Hematologic Malignancies									
Study	Treatment	No. of Subjects	AML	MDS	MDS to AML	B-ALL and Hodgkin Lymphoma	Other [d]	Overall	Solid Tumors	Overall	Non-melanoma Skin Cancer	TOTAL[a]
OVERALL	Lenalidomide-based regimen	523	5 (1.0)	4 (0.8)	3 (0.6)	10 (1.9)[c]	0 (0.0)	22 (4.2) **1.45** [f,g]	19 (3.6) **1.25** [f,g]	41 (7.8) **2.74** [f,g]	8 (1.5) **0.52** [f,g]	47 (9.0)[e] **3.16** [f,g]
	Control	512	3 (0.6)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)[d]	5 (1.0) **0.33** [f]	10 (2.0) **0.66** [f]	15 (2.9) **1.00** [f]	6 (1.2) **0.40** [f]	21 (4.1) **1.40** [f]

1.5.1. Discussion on clinical safety

Overall the tolerability of Revlimid as single-agent maintenance treatment in NDMM patients non eligible to SCT appeared acceptable. However, occurrence of secondary invasive malignancies was of major concern.

At the start of the evaluation, a new safety concern emerged, where cases of second primary malignancies occurred in the pivotal trials MM 015 and IFM 2005-02. The cases reported haematological malignancies (AML, MDS, T-cell ALL, B-cell malignancies and Hodgkin) and non haematological malignancies (skin cancers and solid tumours).

The MAH was consequently requested to provide a thorough safety review of all second primary malignancies, including haematological and non haematological, received for lenalidomide in multiple myeloma, from clinical trials, post-marketing reports, and the literature, with an emphasis on randomised trials.

As of 6th February 2011, 67 secondary cancers, were reported out the 839 patients treated in the pooled lenalidomide treatment arms compared with 13 second cancers out the 684 patients treated in the pooled placebo arms (i.e. 8% versus 1.9%, , $p < 0.0001$).

IFM 2005-02: 7% in lenalidomide arm versus 1% in placebo arm
CC-5013-MM015: 6% in lenalidomide arm versus 1% in placebo arm
CALGB 100104: 8.2% in lenalidomide arm versus 2.1% in placebo arm

Based on the review of cases of secondary malignancies in NDMM patients which concluded that on the basis of preliminary data, it appeared that the rate of second primary cancers, including invasive cancers and non melanoma skin cancers, in Revlimid arms was 4-fold increased as compared with placebo arms.

Therefore, the benefit risk ratio of Revlimid in the approved indication was reviewed in the context of a procedure under Article 20 of Regulation (EC) No 726/2004. On 23 September 2011, having assessed all available information from studies and post-marketing data in the authorised indication on the risk of SPMs, as well as data from clinical trials in unauthorised indications, the Committee concluded that the benefits continue to outweigh the risks and that as a consequence the benefit/risk balance of lenalidomide in the approved indication was positive under normal conditions of use with update of the product information to include a new warning included in section 4.4 of the SmPC (EMEA/H/C/717/A20/0048, Commission Decision on 13 January 2012). A Direct Healthcare Professional Communication was also agreed with this respect.

As of the most recent cutoff dates, 63 patients out of 825 patients treated with len-containing regimen had a secondary invasive cancer versus 19 placebo treated patients (i.e., 7.63% versus 2.8%). A lessening of the difference in the incidence between lenalidomide-treated patients and placebo-treated patients is claimed by the MAH. However, 5 placebo-treated patients had received a salvage therapy with lenalidomide and one had received thalidomide within a compatible timeframe before the occurrence the second invasive cancer. Furthermore, at least 2 additional Placebo-randomised patients (CALGB110532 and CALGB108711) had received lenalidomide for the induction prior to initiate placebo. Finally, at least 7 out of the 19 placebo patients have been exposed to lenalidomide with a compatible time frame before the occurrence of their second invasive cancer.

Taking into account only lenalidomide exposure, 70/825 patients exposed to lenalidomide with a compatible timeframe had a secondary invasive cancer versus 12/665 placebo randomised patients who never received lenalidomide (i.e., 8.48% versus 1.8%). However, the percentage of placebo patients who received lenalidomide before randomisation is likely underestimated since the previous chemotherapies are not always documented in CIOMS. The MAH should have addressed this important issue, since previous exposure and/or salvage therapy with len has likely contributed to the lessening of the imbalance between the two groups.

The ITT analysis of pooled data shows that lenalidomide is associated with a 2.75 increased risk of secondary invasive cancers. However, in per protocol analysis, taking into account only lenalidomide exposure with a compatible time frame with the occurrence of the second invasive cancer, lenalidomide is associated with a 4.7-fold increased risk.

Of note, at least 8 out of the 12 placebo-treated patients have been exposed to lenalidomide with a compatible time frame before the occurrence of their non-melanoma skin cancer. Finally 23/825 patients exposed to lenalidomide had a second non invasive cancer versus 4/665 placebo randomised patients (i.e., 2.78% versus 0.6%).

The competing risk analysis (based on Gray's method) with death as the competing risk was performed on the pooled NDMM population (Studies MM-015, IFM 2005-02, and CALGB 100104) using the most recent data cutoff dates. These data continue to indicate that the occurrence of SPMs following lenalidomide therapy in this setting is higher than the occurrence with placebo therapy. In this context, even a trend to a stabilisation of occurrence of invasive SPMs over time is not reassuring.

Univariate and multivariate analyses were repeated using the updated data, and similar findings were observed.

- Neither the cumulative dose of lenalidomide nor the duration of lenalidomide treatment was found to be associated with an increased incidence of invasive SPM in the multivariate analyses.

- One variable associated with a lower risk of SPM at a significance level of $p < 0.05$, was attainment of a CR at start or during maintenance therapy (HR = 0.258; p = 0.041).

- Increasing age was associated with an increased risk of SPM (HR = 1.077; p = 0.027).

- Additionally, there was 1 other variable with an apparent trend toward an increased risk of SPM, including increasing time from ASCT to first dose of study treatment (HR = 1.007; p = 0.060).

- An additional analysis was conducted on the cumulative incidence of SPMs using lenalidomide treatment duration as a dichotomized variable (lenalidomide treatment for ≤ 2 years versus > 2 years) in the transplant-eligible studies. The incidence rate of invasive SPMs was similar for patients who received lenalidomide therapy for ≤ 2years or > 2 years.

Eight patients in the IFM 2005-02 study developed B-cell malignancies including B-ALL (3 patients), diffuse large B-cell lymphoma (1 patient), and Hodgkin's disease (4 patients). Of these, 5 patients had received either an additional high-dose chemotherapy/transplant procedure (3 patients -2 Hodgkin's disease and 1 B-ALL) or additional DCEP (dexamethasone, cyclophosphamide, etoposide, cisplatin; 2 patients - 1 Hodgkin's disease and 1 B-ALL) chemotherapy following standard induction therapy prior to initiating maintenance therapy with single-agent lenalidomide.

In addition, 4 of the 5 patients from the IFM 2005-02 and CALGB 100104 studies who developed Hodgkin's disease during lenalidomide maintenance therapy were found to have a reactivated Epstein-Barr virus (EBV) status (EBV positive).

Among the 10 patients diagnosed with a B-cell malignancy, 3 received ≤ 2 years of lenalidomide treatment (2 have died) and 7 received > 2 years of lenalidomide treatment.

1.5.2. Conclusions on the clinical safety

Occurrence of secondary invasive malignancies is a major concern in particular in the applied indication. For the time being, no minimization of the risk of second invasive cancers can be discussed since no risk factors have been identified. Neither the cumulative dose of lenalidomide nor the duration of lenalidomide treatment was found to be associated with an increased incidence of invasive SPM in the multivariate analyses.

1.6. Pharmacovigilance

Detailed description of the pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

Risk Management Plan

The applicant submitted a risk management plan, which included a risk minimisation plan.

The CHMP, having considered the data submitted in the application was of the opinion that the proposed risk minimisation activities were not able to reduce the risks to an acceptable level.

Further to the withdrawal of the proposed indication, the RMP remains consequently unchanged.

2. Benefit-Risk Balance

Benefits

Beneficial effects

Clinical data as well as in vitro dissolution profile were submitted and considered acceptable to demonstrate bioequivalence and support the new 2.5 and 7.5 mg strengths.

Pivotal studies (CC-5013-MM-015, IFM 2005-02 and CALGB 100104) intended to show the benefit of maintenance in 2 different settings for patients with newly diagnosed multiple myeloma. Study CC-5013-MM-015 was conducted in elderly patients (≥ 65 years old) who are not eligible for ASCT (TNE patients), to show the benefit of maintenance after 9 cycles of induction with MP +/- R. Studies IFM 2005-02 and CALGB 100104 were conducted in the younger population (respectively < 65, ≤ 70 years old), to show the benefit of maintenance after ASCT (TE patients).

In the TNE population:

In study MM015, PFS was significantly longer in arm MPR+R than arm MPp+p (HR=0.395 (0.278, 0.560), p < 0.001, two-sided unstratified Log-rank test), corresponding to a median difference of about 80 weeks (136 w. vs. 56 w). A lower percentage of patients in arm MPR+R experienced disease progression during the double-blind treatment phase than those in arm MPp+p (34% versus 60%, respectively).

With regard to baseline age stratification subgroups, there was a highly significant PFS advantage in arm MPR+R as compared with arm MPp+p in patients ≤ 75 years old, whereas no difference in PFS was observed between arms MPR+R and MPp+p in the > 75 years subgroup. This suggested that in combination with MP, Revlimid provided a better advantage to patients 65-75 years old.

MPR induction demonstrated more effective tumour debulking than MP as evidenced by a significant increase in overall response rate and a tripling of the rate of CR/VGPR responses. This confirmed the contribution of lenalidomide to induction in the MPR+R regimen.

Considering that for the primary comparison (MPR+R vs MPp+p) the risk reduction in progression/death is 60%, a 51% risk reduction in progression/death in the MPR+R versus MPR+p comparison indicated that lenalidomide maintenance contributes to a large part of the overall PFS benefit of the MPR+R regimen.

In the TE population:

The use of lenalidomide maintenance post-ASCT was associated with a highly statistically significant and clinically meaningful improvement of PFS in the IFM 2005-02 and CALGB 100104 studies. The reduction in risk of progression or death was respectively 50% and 65%. This, however, refers to low event rates in the experimental arm (34% in IFM, 21% in CALGB).

Uncertainty in the knowledge about the beneficial effects

In the TNE population:

In the TNE population, a fourth arm MPp+R in the pivotal trial MM015 would have been of interest to assess the contribution of lenalidomide in the maintenance phase only.

Overall survival data are still immature and did not provide the reassurance actually warranted to exclude a relevant negative effect (HR 0.9 95%CI 0.6; 1.3), especially when put into context of secondary invasive malignancies. Moreover, the lack of benefit in OS for MPR+R is of particular concern since other combinations like MPT or MPB, compared to MP, prolong OS.

In the TE population:

The lack of control during consolidation makes evaluation of interest of this phase difficult as both arms in the IFM 2005-02 study received two courses of full-dose lenalidomide consolidation therapy after ASCT. Moreover, lenalidomide maintenance in CALGB 100104 study provided as high improvement of PFS in a similar population without any prior consolidation. The value of the consolidation step was not demonstrated. In addition, the immaturity of PFS data, especially in the CALGB 100104 study, contributes to the overall uncertainty.

In the TE population where the life expectancy is per se longer, prolonged survival is even more expected but none of the two studies (IFM 2005 02 and CALGB 100104) showed statistically significant benefit in OS.

In the IFM 2005-02 study, with event rates of 68/307 (22%) in placebo arm and 76/307 (25%) in lenalidomide arm, the reported HR is 1.12 (85% CI 0.8; 1.6). This is not reassuring as regards putative negative effects.

In the CALGB 100104 study a formally significant survival benefit was demonstrated (HR=0.6, p=0.03). However, as the vast majority of the patients are expected to succumb to the underlying disease, with event rates of 21% (49/229) in placebo arm and 14% (32/231) in lenalidomide arm, no claims related to "statistical significance" are considered well founded. Altogether and at this stage, in the TE study also, reassurance as regards absence of putative negative effect on survival is a remaining major issue.

Overall, the lack of benefit in OS is a major limitation to the observed impressive PFS superiority and this contrast must find an explanation. In addition, relevance to patients of an isolated PFS benefit is doubtful.

The neutral effect of lenalidomide on OS could correspond to contrasted effects on efficacy (such a prolonged PFS would logically result in a prolonged OS) and on safety (the observed increase in secondary malignancies may at least in part suppress this advantage).

Another explanation could be found in a high rate of cross-over from placebo to lenalidomide in the control group at progression. This cross-over is nothing else than the application of an approved indication.

The two explanations are not mutually exclusive.

If a long-term negative effect of lenalidomide is accepted to explain the neutral effect on OS, this would mean that this important safety concern could affect mainly patients with a relatively long life expectancy. This would result in recommending the use of lenalidomide at the latest stages of the disease. The benefit of moving indication from second line to NDMM becomes uncertain.

If cross-over is the main explanation, the logical consequence is that the effect of lenalidomide on survival is the same when the drug is used early (NDMM at maintenance) or later (at relapse). This would question the benefit of an early treatment.

If we consider the direct benefit to patients, any significant delay in progression is expected to provide a delay in symptoms (re)appearance, to allow a longer free-of-treatment period and to prolong survival. There is no strong demonstration in this application that maintenance with lenalidomide would alleviate the symptomatic burden of the disease. Patients submitted to maintenance therapy are not free of treatment and even receive earlier a therapy that would otherwise be prescribed only after relapse. For patients that would be treated with another regimen at relapse, the analysis of the time from second-line to third-line AMT is limited (only qualitative data, limited number of events). So it cannot be stated that lenalidomide maintenance therapy may not adversely affect the activity of the second-line antimyeloma therapy other than lenalidomide. Survival does not appear to be affected by maintenance. It results that the benefit of a prolonged PFS without any effect on OS is uncertain in this context.

Risks

Unfavourable effects

In TNE population, patients >75 years comprised about 25% of the randomised patients in each of the treatment arms. Patients in this age group did not tolerate the 3-drug (MPR) regimen as well as they did the standard 2-drug (MP) standard therapy. This led to earlier and more frequent dose reductions and treatment discontinuations, which had an adverse impact on treatment outcome.

In both TNE and TE populations, the major safety risk is occurrence of secondary invasive malignancies.

Uncertainty in the knowledge about the unfavourable effects

Regarding secondary invasive malignancies, neither the cumulative dose of lenalidomide nor the duration of lenalidomide treatment was found to be associated with an increased incidence of invasive SPM in the univariate or multivariate analyses. Competing risk analyses based on Gray's method were performed on the pooled transplant studies (IFM 2005-02 and CALGB 100104) to examine the incidence of invasive SPM over time with death as the competing risk. Despite the apparent lessening of the difference in the incidence between the lenalidomide- and placebo-treated patients, there is still an increased risk of SPMs with lenalidomide (10-15% of deaths are due to SPMs). As a matter of fact, at least 7 out of the 19 placebo patients have been exposed to lenalidomide with a compatible time frame before the occurrence of their second invasive cancer. The pooled data ITT analysis shows that lenalidomide is associated with a 2.75 increased risk of second invasive cancers. However, in per protocol analysis, taking into account only lenalidomide exposure with a compatible time frame with the occurrence of the second invasive cancer, lenalidomide is associated with, at least, a 4.7-fold increased risk of secondary invasive malignancies..

There is still no justification for the duration of lenalidomide maintenance until progression. Taking into account the risk of occurrence of secondary invasive malignancies and the lack of benefit in OS, prolonged exposure to lenalidomide may be detrimental in both populations (TNE and TE).

Benefit-risk balance

Importance of favourable and unfavourable effects

Multiple myeloma is a highly symptomatic disease in stages of progression. Therefore delay in progression is per se valuable to the patient. Normally, a delay in progression would be expected to

result in improved survival; if not the treatment effect is diluted due to long survival after progression or due to negative effects on the activity of next-line therapies.

Available anti-cancer therapies are in most cases associated with tolerability issues and severe and sometimes fatal adverse reaction, whether due to infections, vascular events or secondary malignancies.

In light of updated results with recent cut off dates, efficacy of lenalidomide in either induction +maintenance for transplant non eligible myeloma patients or in maintenance for transplant eligible patients has been confirmed.

Subpopulations that may, in a greater extent, benefit from lenalidomide have been identified. This efficacy is however not clearly understood since impressive effect to prevent progression does not result in survival advantages.

The risk of occurrence of secondary invasive malignancies has not been fully appreciated. Some tracks regarding risk factors (duration of lenalidomide exposure and cumulative dose) have been investigated but ruled out. The Applicant has not explored any other potential risk factor. Still this major risk has not been discarded.

Benefit-risk balance

An undoubtedly clinically relevant delay in PFS has been documented both in treatment naïve patients unsuitable for stem cell transplantation (ASCT) and as maintenance therapy after ASCT. There are some uncertainties related to the relative immaturity of PFS data in all studies, but major changes are considered unlikely.

With respect to tolerability and toxicity, including secondary malignancies, the observed profile would be acceptable if a clear survival benefit was demonstrated. This, however, is not the case; data are not even reassuring from the perspective of excluding with reasonable certainty negative effects. Whether this is due to data immaturity or actual negative effects of maintenance therapy on the activity of next-line therapies remain at this stage speculative.

The impressive efficacy of lenalidomide to delay progression is difficult to translate in terms of unequivocal benefit to the patients. A favourable effect on symptoms is not established. Further therapies may be delayed, but this is obtained by maintenance of a toxic treatment and the advantage is far from clear. Finally, there is no OS advantage which considerably limits the relevance of the PFS advantage. This neutral OS effect may reflect an equivalent efficacy of maintenance and treatment at progression (if true, this would favour a delayed treatment) or a negative effect of lenalidomide on cancer risk (which would justify delaying lenalidomide as much as possible not to expose patients at relatively good prognosis). Results taken from other clinical studies should be taken into consideration when drawing the benefit risk balance of Revlimid in the TNE population: Alternative options including Bortezomib and Thalidomide are associated with high statistically significant differences in OS (Mateos, 2010; Facon, 2007). The lack of significance of the HR for survival in all pivotal studies could be mainly due to the occurrence of second primary malignancies causing death.

Discussion on the benefit-risk balance

On the basis of the data provided at this timepoint, the suspected and established risks affect all populations included in the sought indication(s), especially when life expectancy is longer. There is no efficacy marker that could identify, in the submitted application for NDMM, a group in whom the benefit would make the risk worth taking. Revlimid remains however an efficient drug in multiple

myeloma, but its use is probably safer and at least equally beneficial when it is used for later stages of the disease, e.g. as late as in the already approved second-line indication.

There is no indication that maintenance could offer any benefit as compared to the already accepted indication for Revlimid (as a second line at progression). Considering the concerns related to a causal relationship with new invasive malignancies, lenalidomide should be more easily recommended at late stages of the disease.

As a consequence, mature overall survival data and further follow-up were needed in order to conclude on the benefit–risk of Revlimid in the proposed indication. Subsequent to this CHMP conclusion, the MAH has decided to withdraw the new indication part of this application.

However, clinical as well as in vitro dissolution profile data demonstrate bioequivalence to authorised strengths and support the new 2.5 and 7.5 mg strengths which can be used in the current indication and future developments.

3. Recommendations

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Revlimid is not similar to Thalidomide Celgene 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 that the risk-benefit balance of Revlimid 2.5mg and 7.5 mg hard capsules in combination with dexamethasone for the treatment of multiple myeloma patients who have received at least one prior therapy is favourable and therefore recommends the granting of the extension of the marketing authorisation subject to the conditions of the marketing authorisation.