28 March 2019
EMA/232212/2019
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Revlimid

International non-proprietary name: lenalidomide

Procedure No. EMEA/H/C/000717/II/0102/G

Note

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

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List of abbreviations

Abbreviation	Explanation
ADR	Adverse drug reaction
AE	Adverse event
AESI	Adverse event of special interest
AMT	Antimyeloma therapy
ANC	Absolute neutrophil count
ASH	American Society of Hematology
auto-HSCT	Autologous hematopoietic stem cell transplantation; for the purpose of this document, auto-HSCT is synonymous with autologous stem cell transplantation (as
B-ALL	B-cell acute lymphocytic leukemia
Bu-Mel	Busulfan with melphalan
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CLcr	Creatinine clearance
CR	Complete response
CRAB	**C**: hypercalcemia (serum calcium > 10.5 mg/dL or upper limit of normal); **R**: renal insufficiency (serum creatinine > 2 mg/dL); **A**: anemia (hemoglobin < 10 g/dL or > 2 g/dL below the lower limit of normal); or
CrCl	Creatinine clearance
CSR	Clinical study report
DLT	Dose-limiting toxicity
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
EMN	European Myeloma Network
ESMO	European Society for Medical Oncology
EU	European Union
FDA	United States Food and Drug Administration
G-CSF	Granulocyte colony-stimulating factor
GCP	Good Clinical Practice
HDM	High-dose melphalan
HR	Hazard ratio
HSC	Hematopoietic stem cells
IA	Integrated Analysis
ICH	International Council for Harmonisation
IFM	Intergroupe Francophone du Myélome
IMWG	International Myeloma Working Group
IRAC	Independent Response Adjudication Committee
ISS	International Staging System
ITT	Intent to treat
IV	Intravenous or intravenously
KM	Kaplan-Meier
LDH	Lactate dehydrogenase
M-protein	Monoclonal protein
MAH	Marketing Authorisation Holder
MedDRA	Medical Dictionary for Regulatory Activities
MEL200	Melphalan 200 mg/m^2; for the PETHEMA GEM2012 study, MEL200 = melphalan 100 mg/m^2 on Days -3 and -2, or melphalan 200 mg/m^2 on Day -2,
MM	Multiple myeloma
MPp+p	Melphalan, prednisone, and placebo for induction followed by placebo for
MPR	Melphalan, prednisone, and lenalidomide
MPR+p	Melphalan, prednisone, and lenalidomide for induction followed by placebo for

MPR+R	Melphalan, prednisone, and lenalidomide for induction followed by lenalidomide for
MPT	Melphalan, prednisone, and thalidomide
MRD	Minimal residual disease
NCCN	National Comprehensive Cancer Network
NDMM	Newly diagnosed multiple myeloma; also previously untreated multiple
OS	Overall survival
PD	Progressive disease
PFS	Progression-free survival
PFS2	Progression-free survival after next-line therapy
PO	Oral or orally
PS	Performance status or propensity score, depending on context
PT	Preferred term
RCT	Randomized controlled trial
Rd	Lenalidomide and dexamethasone; in Study MM-020, Rd = lenalidomide and dexamethasone
Rd18	In Study MM-020, lenalidomide and dexamethasone given for ≤ 18 four-week
RMP	Risk Management Plan
RRMM	Relapsed or refractory multiple myeloma
RVd	Lenalidomide, bortezomib, and dexamethasone
SAE	Serious adverse event
SAP	Statistical analysis plan
SC	Subcutaneous or subcutaneously
SCE	Summary of Clinical Efficacy
SCS	Summary of Clinical Safety
SmPC	Summary of Product Characteristics
SMQ	Standardized MedDRA Query
SOC	System organ class
SPM	Second primary malignancy
SWOG	Southwest Oncology Group (until 2010; thereafter referred to as SWOG)
TE	Transplant eligible
TEAE	Treatment-emergent adverse event
TNE	Transplant noneligible
US	United States
VCD	Bortezomib, cyclophosphamide, and dexamethasone
VD	Bortezomib and dexamethasone
VGPR	Very good partial response
VMP	Bortezomib, melphalan, and prednisone
VTD	Bortezomib, thalidomide, and dexamethasone

1. Background information on the procedure

1.1. Type II group of variations

Pursuant to Article 7.2 of Commission Regulation (EC) No 1234/2008, Celgene Europe BV submitted to the European Medicines Agency on 16 July 2018 an application for a group of variations.

The following variations were requested in the group:

Variations requested		Type	Annexes affected
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, IIIB and A
B.II.e.5.a.2	B.II.e.5.a.2 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change outside the range of the currently approved pack sizes	Type IB	I, IIIA, IIIB and A
B.II.e.5.a.2	B.II.e.5.a.2 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change outside the range of the currently approved pack sizes	Type IB	I, II, IIIA, IIIB and A

Extension of indication to include treatment with Revlimid in combination with bortezomib and dexamethasone of adult patients with previously untreated multiple myeloma. As a consequence, the MAH submitted a request to add 7-capsule pack sizes for the 7.5 mg, 20 mg and 25 mg strengths of Revlimid (lenalidomide) to support the proposed posology and lenalidomide dose modification. Sections 4.1, 4.2, 4.4, 4.8, 5.1, 6.5 and 8 of the SmPC are updated; the Package Leaflet is updated in accordance. Additionally, minor editorial changes have been introduced throughout the PI and Annex II key elements of the RMM have been updated to include information on timing of blood and semen donation in line with the SmPC section 4.4. An updated RMP (version 36.1) has also been submitted.

Revlimid was designated as an orphan medicinal product EU/3/03/177 on 19/06/2007.

Revlimid was designated as an orphan medicinal product in the following indication: treatment of multiple myeloma.

The period of orphan market exclusivity for treatment of multiple myeloma has ended on 19/06/2017.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0279/2017 on the granting of a product-specific waiver.

Information relating to orphan market exclusivity

Similarity

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

Protocol assistance

The applicant did not seek Protocol Assistance at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Alexandre Moreau Co-Rapporteur: N/A

Timetable	Actual dates
Submission date	16 July 2018
Start of procedure:	18 August 2018
CHMP Rapporteur Assessment Report	17 October 2018
PRAC Rapporteur Assessment Report	22 October 2018
PRAC members comments	24 October 2018
PRAC Outcome	31 October 2018
CHMP members comments	5 November 2018
Updated CHMP Rapporteur(s) (Joint) Assessment Report	9 November 2018
Request for supplementary information (RSI)	15 November 2018
CHMP Rapporteur Assessment Report	28 February 2019
PRAC Rapporteur Assessment Report	28 February 2019
PRAC members comments	6 March 2019
Updated PRAC Rapporteur Assessment Report	n/a
PRAC Outcome	14 March 2019
CHMP members comments	18 Mach 2019
Updated CHMP Rapporteur Assessment Report	22 March 2019
Opinion	28 March 2019

2. Scientific discussion

2.1. Introduction

About the product

Lenalidomide has a pleiotropic mechanism of action that is cell-type and context dependent, suggesting modulation of multiple biochemical pathways. Lenalidomide physically associates with cereblon, a component of an E3 ubiquitin ligase complex. Cereblon-mediated mechanisms at least partially explain the pleiotropic effects of lenalidomide, including inhibition of tumour cell proliferation, induction of tumour cell apoptosis, and activation of immune effector cells observed in multiple myeloma (MM).

About the disease

Multiple myeloma (MM) accounts for about 10% to 18% of haematologic malignancies (Moreau, 2017; Siegel, 2018). It is a disease of the elderly (San Miguel, 2013a), with an overall median age at manifestation of approximately 72 years (Moreau, 2017). The number of MM patients is increasing in the general population due to aging populations and more patients living longer due to modern drugs (Turesson, 2018). The prevalence of MM varies from c ountry to country in the European Union (EU). Overall, the estimated prevalence of MM in the EU in 2018 ranges from 1.79 to 3.61 in 10,000 persons. In Europe, 38,900 new cases of MM and 24,300 deaths due to MM were estimated in 2012 (Ferlay, 2013).

Multiple myeloma is a B-cell neoplasm that stems from the malignant transformation of plasma cells and is characterized by the accumulation of clonal plasma cells in the bone marrow (Kumar, 2018; Palumbo, 2011). The malignant proliferation of the plasma cell clone causes increasing levels of monoclonal protein (M-protein) in the serum and urine and may result in bone marrow failure, suppression of uninvolved immunoglobulin levels, and skeletal destruction. Clinical complications of progressive MM include recurrent infections, cytopenias, renal failure, hyperviscosity syndrome, hypercalcemia, bone pain, and pathologic fractures (Munshi, 2012).

Clinical presentation, diagnosis

Multiple myeloma typically is detected when reviewing results of routine blood work or by characteristic symptoms (eg, bone pain, fatigue, and weight loss) (Girnius, 2013). The International Myeloma Working Group (IMWG) criteria for the diagnosis of MM require the following: 1) the presence of serum and/or urinary M-protein (in patients without detectable M-protein, an abnormal free light-chain ratio), 2) bone marrow plasma cells > 10%, and 3) evidence of end-organ damage attributable to plasma cell proliferation (including hypercalcemia, renal failure, anemia, or bone lesions) according to the CRAB2 criteria (Durie, 2006). The IMWG guidelines were subsequently updated to include any one or more of the following biomarkers of malignancy as a myeloma-defining event: clonal bone marrow plasma cell percentage $\geqslant$ 60%, involved/uninvolved serum free light chain ratio $\geqslant$ 100, and > 1 focal lesion on magnetic resonance imaging studies (Rajkumar, 2014). The presence of at least one of the CRAB criteria distinguishes symptomatic MM from smoldering (asymptomatic) MM. Symptomatic MM generally requires treatment (Durie, 2006; Kyle, 2009a).

Management

Despite the introduction of therapeutic options with new mechanisms of action and a better understanding of the disease biology, MM is not curable with current therapies. Multiple Myeloma is a heterogeneous disease with a highly variable clinical course (Avet-Loiseau, 2013; Moreau, 2017). Most patients still experience disease relapse and require several lines of therapy (Agarwal, 2017; Larocca, 2017; van de Velde, 2017; Yong, 2016). The course of MM is characterized by subsequently shorter periods of remission and relapse following sequential lines of treatment (Agarwal, 2017; Larocca, 2017; Moreau, 2017). Thus, first-line therapy is generally accepted to be of primary importance in providing long-term benefits for MM patients (Mateos, 2015). Furthermore, many patients only receive 1 or at most 2 lines of treatment (Raab, 2016; Willenbacher, 2018; Yong, 2016). Thus, all patients with newly diagnosed multiple myeloma (NDMM) should receive the most effective therapy available upfront.

For patients with NDMM, the choice of initial therapy is determined by the patient's age, fitness/frailty status, and the presence of comorbidities, and thus the ability to undergo autologous hematopoietic stem cell transplantation (auto-HSCT) (Kumar, 2018; Ludwig, 2014; Moreau, 2017), as well the differing availability of treatment options within each EU member state.

The determinant for auto-HSCT eligibility is shifting from chronological age to biological age/fitness. The

current European Society for Medical Oncology (ESMO) MM guidelines recommend auto-HSCT for patients < 65 years or fit patients < 70 years in good clinical condition (Moreau, 2017). Similarly, the European Myeloma Network (EMN) guideline for transplant-eligible (TE) MM patients recommends auto-HSCT for non-frail patients < 65 years; auto-HSCT should still be considered for patients ⩾ 65 years who have reduced performance status (PS) or comorbidities when the benefit of transplant outweighs the risk (Gay, 2018). The recently published EMN guidelines for elderly MM patients note that non-frail, elderly MM patients up to the age of 70 years (or even 75 years) without prohibitive comorbidities and adequate organ function may benefit from high-dose melphalan (HDM) followed by auto-ASCT (Larocca, 2018). Consistent with the recommendation in MM guidelines, a more individualized approach is currently being used in routine clinical practice.

High-dose therapy followed by auto-HSCT has demonstrated superior outcomes compared with other options and is the treatment of choice for patients with NDMM, provided they are eligible. The goal of initial treatment in TE patients with NDMM is to achieve the deepest and longest possible first remission while ensuring that patients can proceed to stem cell collection and auto-HSCT (Multiple Myeloma Research Foundation, 2017). The depth of response needed to achieve optimal long-term disease control is an area of active investigation. The rates of complete response (CR) and very good partial response (VGPR) remain important prognostic indicators of long-term outcome in patients with NDMM (Harousseau, 2007, 2009). To allow subsequent stem cell collection, a further important consideration is the choice of agents without stem cell toxicity (ie, a melphalan-free combination).

More recent studies using more sensitive methods of disease detection have demonstrated that MM patients who achieve minimal residual disease (MRD)-negative status following initial treatment have improved progression-free survival (PFS) and overall survival (OS) compared with those who do not achieve MRD-negative status, further demonstrating the importance of a deep response (Lahuerta, 2017; Landgren, 2016a; Martinez-Lopez, 2014a; Munshi, 2017; Paiva, 2008, 2011a; Puig, 2014; Rawstron, 2013, 2015). As a result, IMWG has included MRD in the most recent criteria for response (Kumar, 2016). Ongoing strategies to deepen response also include use of triplet or quadruplet regimens (if tolerable).

Treatment of MM has changed substantially during the last 10 to 15 years, predominantly due to the introduction of bortezomib, lenalidomide, and thalidomide (San-Miguel, 2017). In the last 5 years, 6 additional therapies for MM have been approved for the treatment of relapsed or refractory multiple myeloma (RRMM). This has been associated with a steady improvement in clinical outcomes, including the duration of survival (Bergin, 2017; San-Miguel, 2017).

In the TE NDMM setting, bortezomib is authorized in combination with dexamethasone (VD) or with thalidomide and dexamethasone (VTD) as initial treatment for adult patients with previously untreated MM who are eligible for transplant. In addition, lenalidomide is authorized for the maintenance treatment of adult patients with NDMM who have undergone autologous stem cell transplant.

In the TNE NDMM setting, the below drugs are authorized as initial treatment: 1) lenalidomide in combination with dexamethasone (Rd) or lenalidomide in combination with melphalan and prednisone followed by lenalidomide for maintenance (MPR+R), 2) bortezomib in combination with melphalan and prednisone is indicated for the treatment of adult patients with previously untreated multiple myeloma who are not eligible for high dose chemotherapy with haematopoietic stem cell transplantation and 3) thalidomide in combination with melphalan and prednisone is indicated as first line treatment of patients with untreated multiple myeloma, aged ⩾ 65 years or ineligible for high dose chemotherapy.

As new treatment options become available, with the promise of achieving deeper responses during initial therapy, the guidelines for the treatment of MM continue to evolve. A summary of treatment options that are currently recommended for patients with NDMM by the ESMO (Moreau, 2017), EMN (Engelhardt, 2014 [TNE]; Gay, 2018 [TE]; Larocca, 2018 [elderly]); and National Comprehensive Cancer Network (NCCN; Kumar, 2018) is presented in next table.

Table 1 : Currently Recommended Initial Treatment Options for Previously Untreated Patients With NDMM: ESMO, EMN, and NCCN Treatment Guidelines

ESMO (Moreau, 2017)	EMN (Engelhardt, 2014 [TNE]; Gay, 2018 [TE]; Larocca, 2018 [Elderly][a])	NCCN, Version 3.2018 (Kumar, 2018)
Not Eligible for Transplant		
First Option • Rd • RVd • VMP *Second Option* • MPT • VCD *Other Options* • CTD • MP • BP	*6 to 9 Cycles* • VMP (1A)[a,b] • MPT (1A)[b] • RVd[a] • Rd (2B)[a,c] • Vd[a] • Reduced-dose triplet regimens[a] • rd[a] • vd[a]	*Preferred Regimens*[d-g] • Bortezomib/lenalidomide/dexamethasone (RVd) (Category 1)[h] • Lenalidomide/low-dose dexamethasone (Rd) (Category 1)[h,i,j] • Bortezomib/cyclophosphamide/dexamethasone (Category 2A)[k,l] *Other Recommended Regimens*[d-g] • Carfilzomib[m]/lenalidomide/dexamethasone (Category 2A)[k] • Carfilzomib[m]/cyclophosphamide/dexamethasone (Category 2A)[k] • Ixazomib/lenalidomide/dexamethasone (Category 2A)[k] *Useful in Certain Circumstances*[d-g] • Bortezomib/dexamethasone (Category 2A)[i,k]
Eligible for Transplant		
4 to 6 Cycles of 3-Drug Regimens • RVd • VTD • VCD • PAD	*3 to 4 Cycles of 3-Drug Regimens* • VTD (1A)[b] • VRD (1B)[n] • PAD (1A)[b] • VCD (1B)[n]	*Preferred Regimens*[d-g,o] • Bortezomib/lenalidomide[p]/dexamethasone (RVd) (Category 1)[h] • Bortezomib/cyclophosphamide/dexamethasone (Category 2A)[k,l] *Other Recommended Regimens*[d-g,o] • Bortezomib/doxorubicin/dexamethasone (Category 1)[h] • Carfilzomib[m,q]/lenalidomide[p]/dexamethasone (Category 2A)[k] • Ixazomib/lenalidomide[p]/dexamethasone (Category 2B)[r] *Useful in Certain Circumstances*[d-g,o] • Lenalidomide[p]/dexamethasone (Rd) (Category 1)[h,i] • Bortezomib/dexamethasone (Category 1)[h,i] • Bortezomib/thalidomide/dexamethasone (Category 1)[h] • VTD-PACE (Category 2A)[k]

ASCT = autologous stem cell transplantation; BP = bendamustine and prednisone; CTD = cyclophosphamide, thalidomide, and dexamethasone; EMN = European Myeloma Network; ESMO = European Society for Medical Oncology; MP = melphalan and prednisone; MPT = melphalan, prednisone, and thalidomide; NCCN = National Comprehensive Cancer Network; NDMM = newly diagnosed multiple myeloma; PAD = bortezomib, doxorubicin, and dexamethasone; rd = reduced dose lenalidomide and dexamethasone; Rd = lenalidomide and dexamethasone; RVd = lenalidomide, bortezomib, and dexamethasone; TE = transplant eligible; TNE = transplant noneligible; VCD = bortezomib, cyclophosphamide, and dexamethasone; vd = reduced dose bortezomib and dexamethasone; Vd = bortezomib and dexamethasone; VMP = bortezomib, melphalan, and prednisone; VRD = bortezomib, lenalidomide, and dexamethasone; VTD = bortezomib, thalidomide, and dexamethasone; VTD-PACE = bortezomib/ thalidomide/ dexamethasone-cisplatin/ doxorubicin/ cylclophosphamide/etoposide.

[a] The EMN guideline for elderly NDMM patients (Larocca, 2018) recommends treatment based on patient fitness level: full-dose regimens for fit patients (ASCT, VMP, VRD, Rd), full-dose doublet (Rd, Vd) or reduced-dose triplet regimens for patients with intermediate fitness, and reduced-dose doublet regimens (rd, vd) or palliative + supportive care for frail patients.

[b] 1A: Evidence strongly suggests that the benefit outweighs potential risks, or risks outweigh potential benefits; consistent evidence from systemic reviews of high-quality randomized studies or from high-quality observational studies.

[c] Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.

[d] Selected regimens are included but are not inclusive of all regimens.

[e] Herpes zoster prophylaxis for patients treated with proteasome inhibitors or daratumumab.
[f] Subcutaneous bortezomib is the preferred method of administration.
[g] Full-dose aspirin recommended with immunomodulator-based therapy. Therapeutic anticoagulation recommended for those at high risk for thrombosis.
[h] Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
[i] Triplet regimens should be used as the standard therapy for patients with multiple myeloma; however, elderly or frail patients may be treated with doublet regimens.
[j] Continuously until progression.
[k] Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
[l] Preferred initial treatment in patients with acute renal insufficiency. Consider switching to bortezomib/ lenalidomide/ dexamethasone after renal function improves.
[m] Can potentially cause cardiac and pulmonary toxicity, especially in elderly patients.
[n] 1B: Evidence strongly suggests that the benefit outweighs potential risks, or risks outweigh potential benefits; evidence from randomized and observational studies with important methodological flaws.
[o] Exposure to myelotoxic agents (including alkylating agents and nitrosoureas) should be limited to avoid compromising stem-cell reserve before stem-cell harvest in patients who may be candidates for transplants.
[p] Consider harvesting peripheral blood stem cells before prolonged exposure to lenalidomide.
[q] Optimal dosing in this regimen has not been defined.
[r] Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.
Sources: Engelhardt, 2014; Gay, 2018; Kumar, 2018; Larocca, 2018; Moreau, 2017

The current indication for Revlimid is the following:

Multiple myeloma

Revlimid as monotherapy is indicated for the maintenance treatment of adult patients with newly diagnosed multiple myeloma who have undergone autologous stem cell transplantation.

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

Revlimid in combination with dexamethasone is indicated for the treatment of multiple myeloma in adult patients who have received at least one prior therapy.

Myelodysplastic syndromes

Revlimid as monotherapy is indicated for the treatment of adult patients with transfusion-dependent anemia due to low- or intermediate-1-risk myelodysplastic syndromes associated with an isolated deletion 5q cytogenetic abnormality when other therapeutic options are insufficient or inadequate.

Mantle cell lymphoma

Revlimid as monotherapy is indicated for the treatment of adult patients with relapsed or refractory mantle cell lymphoma (see sections 4.4 and 5.1).

The indication proposed by the MAH was as follows: Revlimid in combination with bortezomib and dexamethasone is indicated for the treatment of adult patients with previously untreated multiple myeloma.

The final indication approved by the CHMP is as follows: Revlimid as combination therapy with dexamethasone, or bortezomib and dexamethasone, or melphalan and prednisone (see section 4.2) is indicated for the treatment of adult patients with previously untreated multiple myeloma who are not eligible for transplant.

2.2. Non-clinical aspects

No new clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.2.1. Ecotoxicity / environmental risk assessment

Substance (INN / Invented Name): Lenalidomide			
CAS-number (if available): 191732-72-6			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107 or …	Log Kow -0.6 (pH 4) and -0.5 (pH 7 and 9)	N
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}	-0.6 (pH 4), -0.5 (pH 7 and 9)	not B
	BCF	3.2 L/kg (Estimated)	not B
Persistence	DT50 or ready biodegradability		NA
Toxicity	NOEC or CMR		NA
PBT-statement :	The compound is not considered as PBT nor vPvB		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surfacewater}$, default or refined (e.g. prevalence, literature)	0.0069 µg/L	µg/L	< 0.01 threshold
Other concerns (e.g. chemical class)			(N)

An updated Environmental Risk Assessment (ERA) for lenalidomide was provided which covers the following: diffuse large B-cell lymphoma, follicular lymphoma, mantle cell lymphoma, marginal zone lymphoma, multiple myeloma, and myelodysplastic syndromes.

The partition coefficient (n-octanol/water) for lenalidomide was experimentally determined at several concentrations and pH values. The resulting logKow for lenalidomide was -0.34 at pH 4.5-7.5 from a non-GLP non-guideline study (Celgene, 2003) and -0.6 (pH 4) and -0.5 (pH 7 and 9) in a GLP compliant OECD 107 study (Ciric, 2016).

As the logKow for lenalidomide is below the trigger of 4.5, a PBT assessment is not required. Based on the logKow of -0.5 and the structural formula, a BCF was estimated using BCFBAF of EPIWEB 4.11. The resulting estimated value for lenalidomide was 3.2 L/kg wwt (logBCF = 0.5).

Calculation of the Predicted Environmental Concentration (PEC)

In Phase I, the PEC calculation is restricted to the aquatic compartment. The calculation of the PEC in surface water further assumes that the predicted amount used per year is evenly distributed over the year and throughout the geographic area, the sewage system is the main route of entry, there is no biodegradation or

retention of the drug substance in the sewage treatment plant (STP) and metabolism in the patient is not taken into account. Thus, a PEC is only calculated for the active substance (the parent compound or the active metabolite for prodrugs).

PECSURFACEWATER (expressed in mg/L) is calculated as

$$PEC_{SURFACEWATER} = \frac{Dose_{ai} \times F_{pen}}{WASTEW_{inhab} \times DILUTION}$$

Pregion prevalence for particular region
ttreatment duration of one treatment period (days)
ntreatment,p number of treatment periods/year
Nd number of days/year, i.e., 365 days/year

In a summary of the IQVIA 21 May 2018 (IQVIA, 2018) report the Sponsor indicates a prevalence value for MM of 36.1/100,000 be utilized.

The calculation of Fpen per indication is:

Table 2 : Calculation of refined F_{pen} per indication

Indication	Prevalence in EU (/100,000)			Treatment regime	Refined F_{pen}
	Inserm, 2013	Inserm, 2018	IQVIA, 2018		
MM	17.5	11.9	36.1	0.75 [c]	0.00027
MDS	20	9.0 [b]	-	0.75 [c]	0.000067
MCL	4	3.5	-	0.75 [c]	0.000026
FL	Not applicable [a]	28.0	-	0.75 [c]	0.00021
MZL	Not applicable [a]	7.0	-	0.75 [c]	0.000052
DLBCL	Not applicable [a]	16.0	-	0.23 [d]	0.000037

The PEC surface water has been calculated for lenalidomide in each disease:
multiple myeloma: 0.0034 µg/L
myelodysplastic syndromes: 0.00034 µg/l
mantle cell lymphoma: 0.000033 µg/l
follicular lymphoma: 0.0021 µg/l
marginal zone lymphoma: 0.00052 µg/l
diffuse large B-cell lymphoma: 0.00028 µg/l

The total $PEC_{SURFACEWATER}$ of lenalidomide for all indications in Phase I is the sum of the 6 separate $PEC_{SURFACEWATER}$ values and amounts to 0.0069 µg/L.

Action Limits

Based on the calculated market penetration factors for MM, MDS, MCL, FL, MZL and DLBCL and the maximum daily doses per indication, the total $PEC_{SURFACEWATER}$ of lenalidomide is 0.0069 µg/L and thus below the action limit of 0.01 µg/L. A Phase II environmental assessment is not triggered.

2.2.2. Discussion and conclusions on non-clinical aspects

The Applicant provided an updated ERA for lenalidomide in diffuse large B-cell lymphoma, follicular lymphoma, mantle cell lymphoma, marginal zone lymphoma, multiple myeloma, and myelodysplastic syndromes. The logkow was experimentally determined and was inferior to 4.5 which does not require a PBT assessment.

The Applicant has refined the Fpen for each indication based on refined prevalence data and calculated the corresponding $PEC_{surface\ water}$. The sum of the $PEC_{surfacewater}$ for the 6 indications is 0.0069µg/l. The Phase I $PEC_{SURFACEWATER}$ of lenalidomide does not exceed the action limit of 0.01µg/L, so a Phase II environmental fate and effects assessment is not triggered. The intended medicinal uses of lenalidomide are considered to be of low risk to the environment, according to current guidelines.

The updated data submitted in this application do not lead to a significant increase in environmental exposure further to the use of Lenalidomide.

2.3. Clinical aspects

2.3.1. 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

Table 3 : Studies and analyses supporting the RVd application

Study / Analysis	Description
Main Study: NDMM – Subjects Not Intended to Undergo Immediate Auto-HSCT	
SWOG S0777 (NCI)	RVd versus Rd for initial treatment, followed by continued Rd, in subjects with previously untreated MM not intended to undergo immediate auto-HSCT
Main Studies and Analyses: TE NDMM	
PETHEMA GEM2012 (PETHEMA Foundation)	RVd followed by high-dose therapy with MEL200 versus Bu-Mel and consolidation with RVd in patients 18 to 65 years old with NDMM
IFM 2009	RVd versus RVd + HDM/auto-HSCT in the initial management of NDMM patients 18 to 65 years of age
Integrated Analysis	Integrated efficacy/safety analysis of 4 RCTs evaluating an RVd (PETHEMA GEM2012 and IFM 2009) or VTD (PETHEMA GEM2005 and IFM 2013-04) initial treatment regimen in TE NDMM patients

auto-HSCT = autologous hematopoietic stem cell transplantation; Bu-Mel = busulfan with melphalan; HDM = high-dose melphalan; IFM = Intergroupe Francophone du Myélome; MEL200 = melphalan 200 mg/m2 (Note: For the PETHEMA GEM2012 study, MEL200 = melphalan 100 mg/m2 on Days -3 and -2, or melphalan 200 mg/m2 on Day -2, relative to infusion of hematopoietic stem cells, according to each site's standard practice.); MM = multiple myeloma; NCI = National Cancer Institute; NDMM = newly diagnosed multiple myeloma; RCT = randomized controlled trial; Rd = lenalidomide and dexamethasone; RVd = lenalidomide, bortezomib, and dexamethasone; TE = transplant eligible; VTD = bortezomib, thalidomide, and dexamethasone.

2.4. Clinical efficacy

2.4.1. Dose response studies

The recommended starting dose is lenalidomide 25 mg orally once daily on either: a) days 1-14 of each 21-day cycle or b) days 1-21 of each 28-day cycle. Bortezomib should be administered via subcutaneous injection (1.3 mg/m2 body surface area) twice weekly on days 1, 4, 8, and 11 of each 21-day or 28-day cycle.

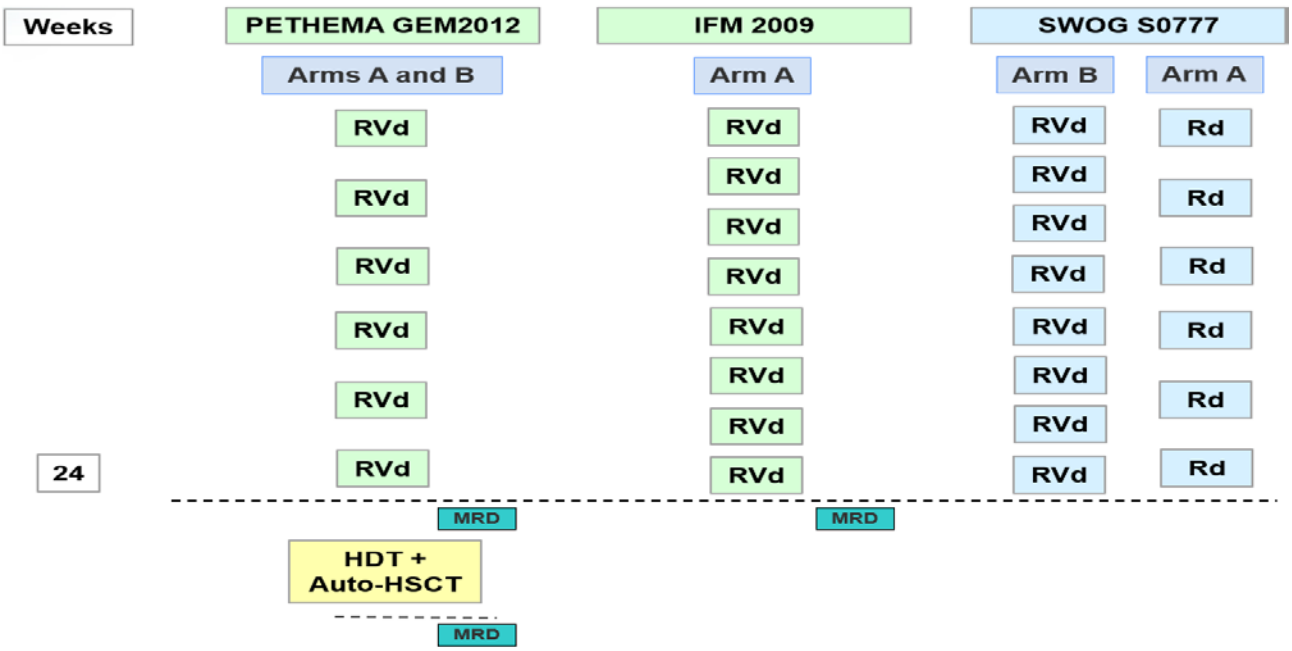
This recommended dose and schedule is per the RVd arms of the SWOG S0777, PETHEMA GEM2012, and IFM 2009 studies. The continued Rd dosing is consistent with the recommended dosing of Rd until disease progression in the current EU SmPC.

The applicant's rationale for RVd in study SWOG S0777 was based on the results of a Phase 1, dose-finding study of lenalidomide plus bortezomib in 17 subjects with relapsed/refractory multiple myeloma (RRMM) that had been reported, including subjects who had failed with each agent separately; the response rate (complete response [CR] + partial response [PR]) was 59% (Richardson, 2005). Preliminary data from a Phase 1/2 study in 33 subjects with NDMM suggested that the triplet therapy of bortezomib, lenalidomide, and dexamethasone was active and well tolerated in subjects with NDMM (Richardson, 2007).

The rationale for study PETHEMA GEM2012 is that the combination RVd has been shown to be highly effective as induction treatment in previous Phase 2 trials (Richardson, 2010; Roussel, 2010) (using a 21-day cycle regimen), which was the basis for its use in this Phase 3 clinical trial.

For study IFM2009, the choice of RVd was based on the results from DFCI (Dana-Farber Cancer Institute) team with 100% PR and 74% VGPR (Richardson, 2007; Richardson, 2008, Roussel, 2014).

Figure 1 : Overview of the design of Studies PETHEMA GEM2012, IFM 2009 (Arm A), and SWOG S0777



auto-HSCT = autologous hematopoietic stem cell transplantation; HDT = high-dose therapy; MRD = minimal residual disease; Rd = lenalidomide and dexamethasone; RVd = lenalidomide, bortezomib, and dexamethasone; TE = transplant eligible.
Notes: 1) Each box represents one 4-week cycle of RVd in the PETHEMA GEM2012 study and Rd in Arm A of the SWOG S0777 study, one 3-week cycle of RVd in the IFM 2009 study, and one 3-week cycle of RVd in Arm B of the SWOG S0777 study.
2) Bortezomib was given subcutaneously in the PETHEMA GEM2012 study and intravenously in the IFM 2009 and SWOG S0777 studies.

Table 4 : Overview of RVd Dosing Regimens Used for Initial Treatment – Studies PETHEMA GEM2012, IFM 2009, and SWOG S0777

	PETHEMA GEM2012 (4-week cycles x 6 = 24 weeks)	IFM 2009[a] (3-week cycles x 8 = 24 weeks)	SWOG S0777 (3-week cycles x 8 = 24 weeks)
Study Dates	2013 to 2015	2010 to 2012	2008 to 2012
Dose, Route of Administration, Schedule, and Dose Intensity[b]			
Lenalidomide	25 mg/day Oral Days 1-21 131 mg/week	25 mg/day Oral Days 1-14 117 mg/week	25 mg/day[c] Oral Days 1-14 117 mg/week
Bortezomib	1.3 mg/m^2 Subcutaneous Days 1, 4, 8, 11 1.3 mg/m^2/week	1.3 mg/m^2 Intravenous Days 1, 4, 8, 11 1.73 mg/m^2/week	1.3 mg/m^2 Intravenous Days 1, 4, 8, 11 1.73 mg/m^2/week
Dexamethasone	40 mg/day Oral Days 1-4 and 9-12 80 mg/week	20 mg (10 mg[d])/day Oral Days 1, 2, 4, 5, 8, 9, 11, 12 53 mg (26.7 mg[d])/week	20 mg/day Oral Days 1, 2, 4, 5, 8, 9, 11, 12 53 mg/week

RVd = lenalidomide, bortezomib, and dexamethasone.
a For the purpose of comparison to the PETHEMA GEM2012 and SWOG S0777 studies, the 8 cycles (24 weeks) of initial RVd therapy for Arm A in the IFM 2009 study are referred to as "initial treatment."
b Dose intensity = (daily dose) x (number of daily doses per cycle) / (number of weeks per cycle).
c For subjects with serum creatinine ≥ 2 mg/dL before Cycle 1, the recommended starting dose of lenalidomide was 5 mg/day with dose escalation as tolerated (related to potential myelosuppression) at the treating physician's discretion (CSR SWOG S0777 Section 9.4.5.1).
d Starting at Cycle 4, the dose of dexamethasone was reduced from 20 mg/day to 10 mg/day, which reduced the dose intensity from 53 mg/week to 26.7 mg/week.

2.4.2. Main studies

Study SWOG SO777

Methods

Study SWOG SO777 was a randomized, multicenter, Phase III clinical study studying lenalidomide and low dose dexamethasone (LLD) versus bortezomib, lenalidomide and low dose dexamethasone (BLLD) for induction, in patients with previously untreated multiple myeloma without an intent for immediate autologous stem cell transplant.

Methods

Study participants

Main inclusion criteria

1. Subjects must have had NDMM[1], with measurable disease[2]. Subjects with non-secretory MM based upon standard M-component criteria (ie, measurable serum/urine M-component) were not eligible for this study. Exception: Subjects with non-secretory MM were eligible only if the baseline serum Freelite was elevated (see Section 10.1 of the protocol; Appendix 16.1.1). (Note that serum Freelite must have been drawn; serum light chains were not acceptable.) All tests for establishing baseline disease status must have been completed within 28 days prior to registration and documented on the Baseline and Follow-up Tumour Assessment Form for Multiple Myeloma
2. Subjects must have received no prior chemotherapy for this disease. Subjects must have received no prior radiotherapy to a large area of the pelvis (more than half of the pelvis). Prior steroid treatment was allowed provided treatment was not more than 2 weeks in duration. Subjects must not have received any prior treatment with bortezomib or lenalidomide

3. Subjects must have been ≥18 years of age at the time of registration
4. Subjects must have had adequate marrow function as defined herein:

   a. Platelet count ≥ 80 x 10^3/mcL,

   b. Absolute neutrophil count (ANC) ≥ 1 x 10^3/mcL, and

   c. Hemoglobin (including subjects who had been either transfused or treated with erythropoietin) ≥ 9 g/dL
5. Subjects with pathologic fractures, pneumonia at diagnosis, or symptomatic hyperviscosity must have had these conditions attended to prior to registration (ie, intramedullary rod, intravenous [IV] antibiotics, plasmapheresis).
6. Subjects must have had a calculated or measured creatinine clearance (CrCl) > 30 cc/min. Measured CrCl or serum creatinine used in calculation must be obtained within 28 days prior to registration
7. Females of childbearing potential (FCBP) must have had a negative serum or urine pregnancy test with a sensitivity of at least 25 mIU/mL within 10 to 14 days and again within 24 hours prior to starting Cycle 1 of lenalidomide. Further, they must have either committed to continued abstinence from heterosexual intercourse or started 2 acceptable methods of birth control: one highly effective method and one additional effective method at the same time, at least 28 days before starting lenalidomide. FCBP must have also agreed to ongoing pregnancy testing. Men must have agreed to use a latex condom during sexual contact with a FCBP, even if they have had a successful vasectomy.

[1] Diagnostic 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 (1 or more of the following: calcium elevation in the blood [serum calcium > 10.5 mg/dL or upper limit of normal; renal insufficiency [serum creatinine > 2 mg/dL; anemia [hemoglobin < 10 g/dL or 2 g < normal]; and lytic bone lesions or osteoporosis).
[2] Serum M protein ≥ 1 g/dL (≥ 10 g/L), quantified using densitometry on serum protein electrophoresis and/or urine M-protein (Bence-Jones protein) ≥ 200 mg/24 h (≥ 0.2 g/24 h), quantified by 24-hour urine protein electrophoresis and/or bone marrow plasma cells, or subjects with both serum M protein level < 1 g/dL and urine M protein levels < 200 mg/24 h at baseline may have been followed by serum free light chain assay if the free light chain level involved was ≥ 10 mg/dL (≥ 100 mg/L).

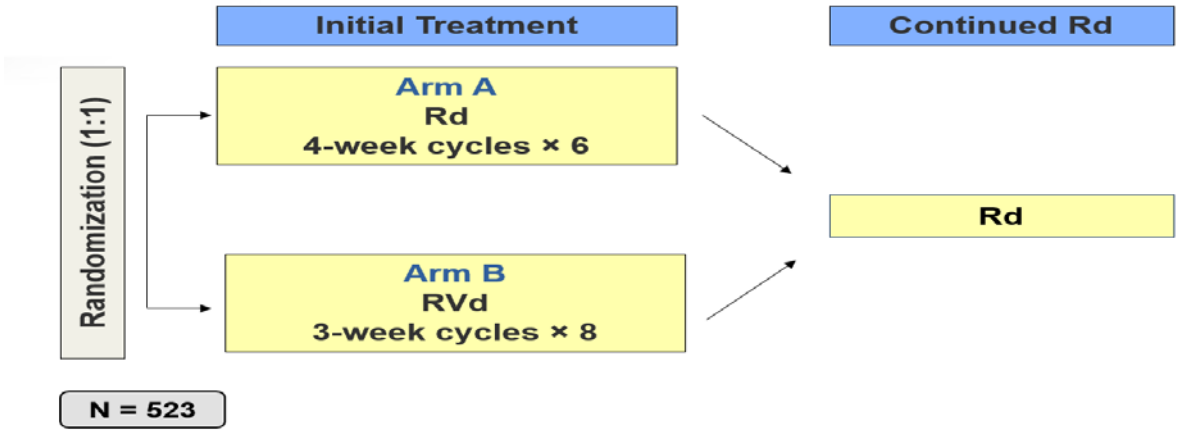
Main exclusion criteria

1. Subjects must not have had uncontrolled, active infection requiring IV antibiotics, New York Heart Association Class III or Class IV heart failure, myocardial infarction within the last 6 months, history of treatment for clinically significant ventricular cardiac arrhythmias, poorly controlled hypertension, or poorly controlled diabetes mellitus
2. Subjects must not have been hepatitis B, hepatitis C or human immunodeficiency virus (HIV) positive as these conditions could interfere with endpoint assessment. Subjects must have had a negative hepatitis B and HIV test performed within 28 days prior to registration. Exception: Subjects with treatment-sensitive HIV infection were eligible provided that immunological and virologic indices were indicative of favorable long-term survival prospects on the basis of HIV infection, but whose life expectancy was limited predominantly by MM rather than HIV infection in the judgment of the treating physician.
3. Subjects must not have had a history of cerebral vascular accident with persistent neurologic deficits
4. No prior malignancy was allowed except for adequately treated basal cell (or squamous cell) skin cancer, in situ cervical cancer, or other cancer for which the subject had been disease-free for 5 years.

Treatments

This study consisted of 2 parts: 1) initial treatment with RVd compared with Rd and 2) continued Rd for all subjects.

Figure 2 : Treatment schema overview SWOG S07777



R = lenalidomide; Rd = lenalidomide and dexamethasone; RVd = lenalidomide, bortezomib, and dexamethasone; V = bortezomib.

Initial treatment

- Arm A:

Six 28-day cycles (24 weeks) of Rd (initial treatment); subjects who completed treatment continued Rd therapy until PD. ☐ 4 cycles of R

- Lenalidomide (R) 25 mg/day per os once daily on Days 1 to 21

- Dexamethasone (d) 40 mg/day per os on Days 1, 8, 15, and 22 in each 28-day cycle for up to 6 cycles

- Arm B:

Eight 21-day cycles (24 weeks) of RVd (initial treatment); subjects who completed able to tolerate a total of 8 cycles of initial treatment continued Rd (same regimen as for treatment therapy for Arm A) until PD. ☐ 6 cycles b

- Lenalidomide (R) 25 mg/day per os once daily on Days 1 to 14

- Dexamethasone (d) 20 mg/day per os on Days 1, 2, 4, 5, 8, 9, 11 and 12

- Bortezomib (V) 1.3 mg/m2 intravenous on Days 1, 4, 8, and 11 in each 21-day cycle for up to 8 cycles

Continued Rd

For both arms, the planned duration of treatment was 24 weeks for initial treatment and until PD for continued Rd treatment.

Objectives

The primary objective was to compare the PFS in subjects with NDMM treated with RVd versus Rd.

The secondary objectives included:

- Assess response using the new IMWG response criteria
- Bank specimens for future translational medicine research
- Follow subjects to assess overall survival (OS) and other long-term outcomes.

Outcomes / endpoints

- Primary Efficacy Endpoint
    - Progression-free survival (PFS) defined as the time from the date of randomization to date of first documentation of progression (including symptomatic deterioration), or death due to any cause, whichever occurred earlier (as per investigator assessment).
- Secondary Efficacy Endpoints
    - Overall survival (OS) defined as the time from randomization to death due to any cause
    - Response rate (CR, VGPR, PR, SD, and PD) based on IMWG criteria
- Exploratory Endpoints
    - Time to response (PR or better), time to CR or better, time to VGPR or better
    - Duration of response
    - Time to subsequent antimyeloma therapy (AMT)
- Safety Endpoints
    - AEs, clinical laboratory tests, deaths, and SPMs

Sample size

The determination of sample size was based on hypotheses about the difference of RVd versus Rd for the primary endpoint PFS: H0: HR (RVd versus Rd) = 1 versus H1: HR (RVd versus Rd) ≠ 1 where HR (RVd versus Rd) is the hazard ratio (HR) between RVd arm and Rd.

A PFS of 64% at 2 years was anticipated by the applicant in the Rd arm, based on data from the SWOG S0232 study. This corresponds to a median PFS of approximately 3 years, assuming an exponential distribution of PFS. With 4 years of subject accrual, and 2.5 years of follow-up, a sample size of 220 eligible subjects per arm and 276 PFS events results in a study with 87% power to detect an increase of PFS of 50%, from a median of 3 years to 4.5 years, which corresponds to an HR of 0.67 (RVd versus Rd) and an increase in PFS at 2 years from 64% to 74%. These calculations were based on a 1-sided stratified log-rank test at level 0.025 with 2 interim analyses.

Randomisation

Subjects who meet all eligibility criteria were randomized (1:1) utilizing a dynamic allocation scheme to receive 1 of 2 treatment arms: lenalidomide, bortezomib, and low-dose dexamethasone for eight 3-week cycles (RVd) or lenalidomide and low-dose dexamethasone for six 4-week cycles (Rd)
Subjects were stratified at randomization by:
1. Stage (International Staging System [ISS] Stages I, II, or III)
2. Intent to transplant at progression: Yes versus No.

Blinding (masking)

This was an open-label study.

Statistical methods

Analysis population

- Intent-to-treat (ITT) population: includes all subjects who are randomized and with valid consent prior to the randomization, and is used for the primary efficacy analysis
- Safety population: includes all subjects who are randomized and received at least one dose of study drug.

- Eligible population: defined as ITT subjects who met eligibility criteria, and is used for analyses of PFS, OS and overall response rate (ORR).

Primary Efficacy analysis

The applicant's intention of the planned primary analysis for PFS is to use the same data cutoff date (5 November 2015) as published by SWOG. The analysis for the primary endpoint PFS was based on disease assessment by IRAC using the IMWG criteria and the applicable PFS censoring rules (per SWOG S0777 protocol, FDA and EMA guidelines). This analysis used the ITT population. In addition, PFS was updated using data available as of the new data cutoff date of 1 Dec 2016 (based on IRAC assessment).

PFS was to be compared between RVd and Rd treatment arms using the stratified log-rank test, stratified by the 2 strata used in the randomization (ISS stage and Intent to transplant at progression).

Additional analysis

Subgroup analysis were planned to be performed for PFS and secondary efficacy endpoints on age ≤ 65 years and > 65 years), sex, race (Caucasian and non-Caucasian), ISS stage at randomization (I, II and III) and Intent to transplant (Yes or No).

The efficacy endpoints were planned to be compared between treatment arms based on the eligible population, using the same methods as those used for the ITT analyses.

Interim analysis

Two formal interim analyses were planned after one third (92 of 276) and two thirds (184 of 276) of the total targeted PFS events (276) had occurred. The first interim analysis was at approximately 36 months (3 years), after approximately 75% of subjects had been accrued. The second interim analysis was at approximately 54 months (4 and a half years), after all subjects had been accrued.

A Haybittle-Peto approach was used for alpha spending, and a 1-sided alpha of 0.0025 was used for each interim analysis. If the null hypothesis was rejected at this level of significance, it would have suggested early termination of the trial and a conclusion that the RVd arm is better than the Rd arm. In addition, the alternative hypothesis of a 50% improvement of PFS for the RVd arm would be tested at the 1-sided level of 0.0025, using an extension of the log-rank test that allows for testing a relative risk not equal to 1. Rejection of this alternative hypothesis would lead to early termination and a conclusion that the RVd arm is not better than the Rd arm. The actual decision to terminate the study early was to be made by the data safety monitoring committee (DSMC), and would consider response rates, OS, toxicities and other factors in addition to PFS.

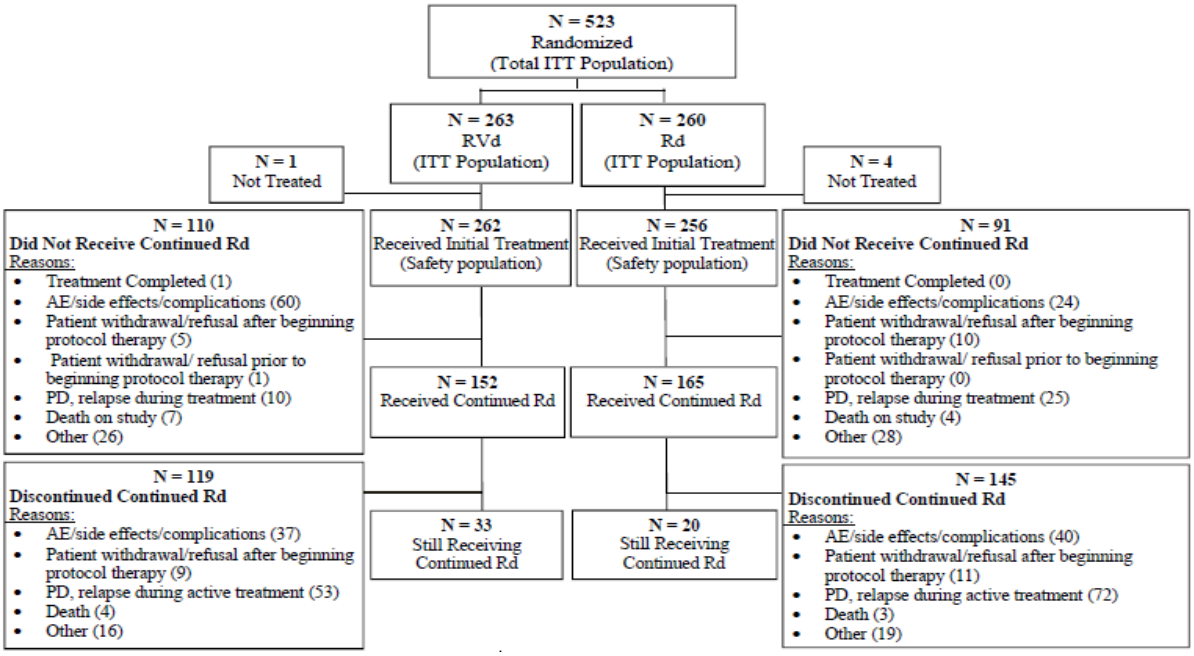
Protocol deviations

The definition of major deviation was as follows: a major deviation occurs when a deviation for a specific modality was also considered a major deviation for the protocol overall: 1) a required modality was omitted; 2) modalities were not administered in the correct sequence; 3) treatment modalities that were not allowed by the protocol were given; or 4) study coordinator identified a major surgical or RT deviation on a study that did not require discipline review.

Results

Participant flow

Figure 3 : SWOG S0777 participant flow



AE = adverse event; ITT = intent to treat; PD = progressive disease; Rd = lenalidomide and dexamethasone; RVd = lenalidomide, bortezomib, and dexamethasone
Data cutoff date = 1 Dec 2016.

Recruitment

First subject randomized = 28 July 2008

Last subject randomized = 2 February 2012

Data cut-off date for the final PFS analysis = 5 November 2015

Updated data cut-off date = 1 December 2016

Conduct of the study

Twenty-four protocol amendments or revisions were made throughout the period covered by this study report with no major changes (data not shown).

Changes From Final Protocol to Final Statistical Analysis Plan

Changes from the planned analyses described in the final SWOG S0777 protocol to the final SAP prepared by Celgene are described below:

- In the SWOG S0777 protocol, only eligible subjects were considered as the ITT population in the protocol. In the final SAP, the ITT population includes all subjects (with valid consent) who were randomized. The ITT population, as randomized, was used for the primary efficacy analysis.
- In the SWOG S0777 protocol, the Fisher’s exact test was proposed to compare response rates. However, the stratified Cochran-Mantel-Haenszel test was used in the publication (Durie, 2017). In the final SAP, the same stratified Cochran-Mantel-Haenszel test was used to compare response rate.

Changes From Final Statistical Analysis Plan

- In the final SWOG S0777 SAP (Section 10.1 in the SAP; Appendix 16.1.9), the primary PFS was to be based on the central assessment of PD by the Study Chair; instead, the primary PFS was analyzed using the independent assessment of PD by the IRAC.
- In the final SWOG S0777 SAP, the eligible population was defined as ITT subjects who met eligibility criteria and with valid consent as used in the SWOG S0777 publication (Durie, 2017). In the analyses presented in this report, the eligible population is defined as ITT subjects who met eligibility criteria. This included subjects with laboratory values collected outside the protocol-specified window.

Baseline data

The demographic characteristics of the subjects in the ITT population are summarized in the table below.

Table 5 : Demographic Characteristics as of 1 Dec 2016 (ITT Population-Study SWOG S0777)

Parameter	RVd (N = 263)	Rd (N = 260)	Total (N = 523)
Age (years)			
Median	63.0	63.0	63.0
Min, Max	35.0, 85.0	28.0, 87.0	28.0, 87.0
Age Group 1 (years), n (%)			
≤ 65	167 (63.5)	150 (57.7)	317 (60.6)
> 65	96 (36.5)	110 (42.3)	206 (39.4)
Age Group 2 (years), n (%)			
≤ 65	167 (63.5)	150 (57.7)	317 (60.6)
> 65 and ≤ 75	68 (25.9)	85 (32.7)	153 (29.3)
> 75	28 (10.6)	25 (9.6)	53 (10.1)
Sex, n (%)			
Male	164 (62.4)	137 (52.7)	301 (57.6)
Female	99 (37.6)	123 (47.3)	222 (42.4)
Race Group, n (%)			
Caucasian	210 (79.8)	207 (79.6)	417 (79.7)
Non-Caucasian	46 (17.5)	47 (18.1)	93 (17.8)
Unknown	7 (2.7)	6 (2.3)	13 (2.5)

ITT = intent to treat; Max = maximum; Min = minimum; Rd = lenalidomide and dexamethasone; RVd = lenalidomide, bortezomib, and dexamethasone.
Data cutoff date = 1 Dec 2016.

Baseline clinical characteristics of the subjects in the ITT population as of the 1 December 2016 data cutoff date are summarized in table below.

Table 6 : Baseline Clinical Characteristics as of 1 Dec 2016 (ITT Population-Study SWOG S0777)

Parameter	RVd (N = 263)	Rd (N = 260)	Total (N = 523)
ISS Stage, n (%)			
I	78 (29.7)	75 (28.8)	153 (29.3)
II	99 (37.6)	98 (37.7)	197 (37.7)
III	86 (32.7)	87 (33.5)	173 (33.1)
Revised ISS Stage, n (%)			
I	54 (20.5)	55 (21.2)	109 (20.8)
II	155 (58.9)	161 (61.9)	316 (60.4)
III	26 (9.9)	23 (8.8)	49 (9.4)
Missing	28 (10.6)	21 (8.1)	49 (9.4)
Intent to Transplant at Progression (Stratification Factor), n (%)			
No	81 (30.8)	81 (31.2)	162 (31.0)
Yes	182 (69.2)	179 (68.8)	361 (69.0)
Cytogenetic Risk, n (%)			
High[a]	30 (11.4)	36 (13.8)	66 (12.6)
Not High	210 (79.8)	207 (79.6)	417 (79.7)
Missing[b]	23 (8.7)	17 (6.5)	40 (7.6)
Frailty Group, n (%)			
Not Frail	206 (78.3)	188 (72.3)	394 (75.3)
Frail	56 (21.3)	72 (27.7)	128 (24.5)
Missing	1 (0.4)	0 (0.0)	1 (0.2)
Frailty and Age Group, n (%)			
Age ≤ 65 years and Not Frail	142 (54.0)	120 (46.2)	262 (50.1)
Age > 65 years and/or Frail	121 (46.0)[c]	140 (53.8)	261 (49.9)[c]
Performance Status (ECOG) Category 1, n (%)			
0 - Fully active	106 (40.3)	101 (38.8)	207 (39.6)
1 - Restricted activity	128 (48.7)	120 (46.2)	248 (47.4)
2 - No work, ambulatory	19 (7.2)	32 (12.3)	51 (9.8)
3 - Limited self-care	10 (3.8)	7 (2.7)	17 (3.3)
Creatinine Clearance Group 1, n (%)			
< 60 mL/min	78 (29.7)	79 (30.4)	157 (30.0)
≥ 60 mL/min	185 (70.3)	180 (69.2)	365 (69.8)
Missing	0 (0.0)	1 (0.4)	1 (0.2)
Creatinine Clearance Group 2, n (%)			

< 50 mL/min	46 (17.5)	45 (17.3)	91 (17.4)
≥ 50 mL/min	217 (82.5)	214 (82.3)	431 (82.4)
Missing	0 (0.0)	1 (0.4)	1 (0.2)
Hemoglobin Group, n (%)			
< 10 g/dL	89 (33.8)	76 (29.2)	165 (31.5)
≥ 10 g/dL	174 (66.2)	184 (70.8)	358 (68.5)
B2 Microglobulin Group, n (%)			
≤ 5.5 mg/L	176 (66.9)	174 (66.9)	350 (66.9)
> 5.5 mg/L	85 (32.3)	84 (32.3)	169 (32.3)
Missing	2 (0.8)	2 (0.8)	4 (0.8)
Lactate Dehydrogenase Group, n (%)			
Not High (LDH ≤ 280 IU/L and not missing)	214 (81.4)	224 (86.2)	438 (83.7)
High (LDH > 280 IU/L)	44 (16.7)	32 (12.3)	76 (14.5)
Missing	5 (1.9)	4 (1.5)	9 (1.7)
Albumin Group, n (%)			
≤ 35 g/L	128 (48.7)	129 (49.6)	257 (49.1)
> 35 g/L	135 (51.3)	128 (49.2)	263 (50.3)
Missing	0 (0.0)	3 (1.2)	3 (0.6)

ECOG = Eastern Cooperative Oncology Group; ISS = International Staging System; ITT = intent to treat; Rd = lenalidomide and dexamethasone; RVd = lenalidomide, bortezomib, and dexamethasone; t(4;14) = translocation involving chromosomes 4 and 14; t(14;16) = translocation involving chromosomes 14 and 16.
a High Risk: t(4;14), t(14;16) or del(17p).
b Cytogenetic risk assessment was not required by the protocol.
c One subject in the RVd arm with a missing frailty is counted in the category age > 65 years and/or frail.
Data cutoff date = 1 Dec 2016.

Numbers analysed

Table 7 : Number of subjects included in data sets analyzed as of 5 Nov 2015 and 1 Dec 2016 data cut-off dates (Study SWOG S0777)

Population	RVd n (%)	Rd n (%)	Total n (%)
Intent to treat[a]	263 (100.0)	260 (100.0)	523 (100.0)
Safety[b]	262 (99.6)	256 (98.5)	518 (99.0)
Eligible[c]	247 (93.9)	244 (93.8)	491 (93.9)

ITT = intent to treat; Rd = lenalidomide and dexamethasone; RVd = lenalidomide, bortezomib, and dexamethasone.
a The ITT population includes all subjects who were randomized and gave valid consent prior to randomization.
b The safety population includes all randomized subjects who received at least one dose of study drug.
c The eligible population includes all ITT subjects who met eligibility criteria.
Data cutoff date = 05 Nov 2015 and 01 Dec 2016.

Outcomes and estimation

- ***Primary endpoint- PFS***

Table 8 : Progression-free Survival from randomization (EMA and SWOG Censoring Rules) for the ITT Population-Study SWOG S0777 – (Data cut-off date: 1 Dec 2016 and 15 May 2018)

	As of 01 Dec 2016		As of 15 May 2018	
	RVd (N = 263)	Rd (N = 260)	RVd (N = 263)	Rd (N = 260)
Median Follow-up[a] (All Surviving Subjects), months	69.0		84.2	
PFS (IRAC, EMA Censoring)				
PFS Events, n (%)	170 (64.6)	196 (75.4)	Not Assessed	
Median[b] PFS time (95% CI),[c] months	41.7 (33.1, 51.5)	29.7 (24.2, 37.8)		
HR (95% CI)[d]; p-value[e]	**0.76** (0.62, 0.94); p = 0.00996			
PFS (SWOG Censoring)				
PFS Events, n (%)	170 (64.6)	204 (78.5)	182 (69.2)	211 (81.2)
Median[b] PFS time (95% CI),[c] months	43.9 (39.4, 52.5)	32.8 (25.3, 39.9)	43.9 (39.4, 52.5)	32.8 (25.3, 39.9)
HR (95% CI)[d]; p-value[e]	**0.71** (0.58, 0.86); p = 0.00075		**0.72** (0.59, 0.88); p = 0.00117	

CI = confidence interval; EMA = European Medicines Agency; HR = hazard ratio; IRAC = Independent Response Adjudication Committee; ITT = intent to treat; PFS = progression-free survival; Rd = lenalidomide and dexamethasone; RVd = lenalidomide, bortezomib, and dexamethasone; SE = standard error.
a The median is based on Kaplan-Meier estimate.
b Two-sided 95% CI about the median PFS time.
c Based on unstratified Cox proportional hazards model comparing hazard functions associated with treatment arms (RVd:Rd).
d The p-value is based on unstratified log-rank test.

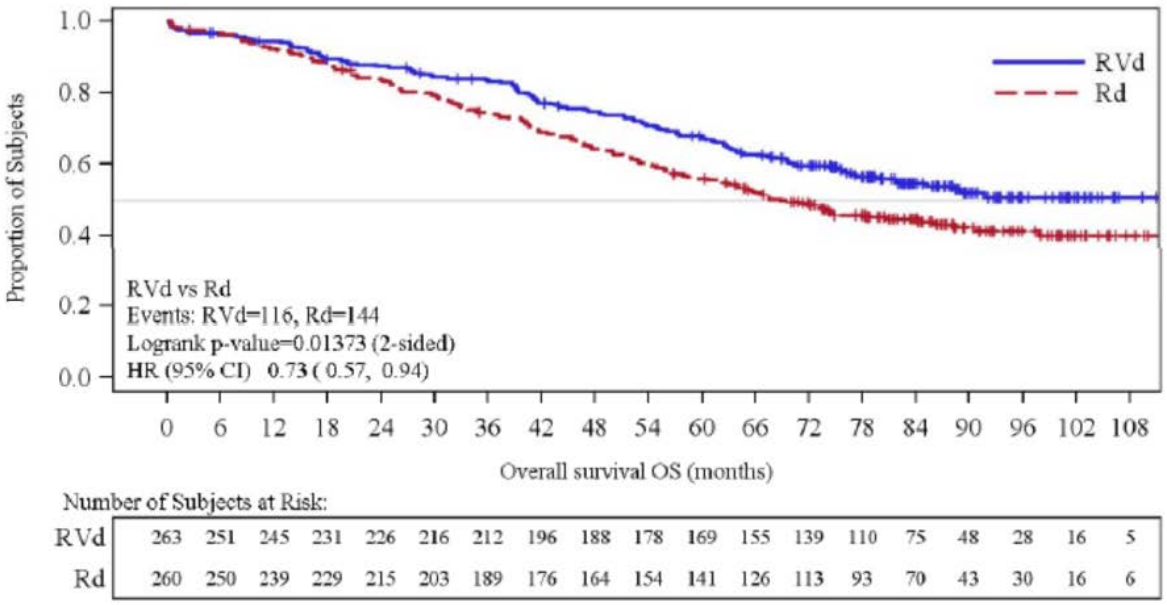
- ***Secondary endpoint-Overall survival (OS)***

As of 15 May 2018 (using SWOG censoring rules), there was a 28% reduction of risk of PD or death for subjects treated with RVd compared with those treated with Rd (HR = 0.72; 95% CI = 0.59, 0.88).

Table 9 Overall survival analysis(ITT population - Study SWOG S0777)- Data cut-off date: 1 Dec 2016 and 15 May 2018

	As of 01 Dec 2016		As of 15 May 2018	
	RVd (N = 263)	Rd (N = 260)	RVd (N = 263)	Rd (N = 260)
Median Follow-up[a] (All Surviving Subjects), months	69.0		84.2	
OS				
OS Events, n (%)	104 (39.5)	132 (50.8)	116 (44.8)	144 (55.4)
Median[b] OS time (95% CI)[c], months	89.1 (76.1, NE)	67.2 (58.4, 90.8)	NE (79.9, NE)	68.9 (59.1, 86.2)
HR (95% CI); p-value	**0.72** (0.56, 0.94); p = 0.01335		**0.73** (0.57, 0.94); p = 0.01373	

Figure 4: Kaplan-Meier Curves of Overall Survival – Study SWOG S0777 (ITT Population) Data Cutoff Date of 15 May 2018



CI = confidence interval; HR = hazard ratio; ITT = intent to treat; OS = overall survival; Rd = lenalidomide and dexamethasone; RVd = lenalidomide, bortezomib, and dexamethasone.
Data cutoff date = 15 May 2018.

- ***Secondary endpoint-Response rate***

Myeloma response rates after the first 9 and 12 weeks of initial treatment and at the end of initial treatment (ie, post-initial treatment) based on disease assessment by IRAC review as of 1 December 2016 are presented in the table below.

Table 10 : Response Rate at Post 9 Weeks, Post 12 Weeks, and Post-initial Treatment Based on IRAC Assessments as of 1 Dec 2016 (ITT Population-Study SWOG S0777)

Parameter	Post 9 Weeks		Post 12 Weeks		Post-initial Treatment	
	RVd (N = 263)	Rd (N = 260)	RVd (N = 263)	Rd (N = 260)	RVd (N = 263)	Rd (N = 260)
Overall Response Rate[a]						
Complete Response (CR), n (%)	0 (0.0)	0 (0.0)	2 (0.8)	0 (0.0)	14 (5.3)	7 (2.7)
Very Good Partial Reponse (VGPR), n (%)	92 (35.0)	26 (10.0)	80 (30.4)	34 (13.1)	139 (52.9)	76 (29.2)
Partial Response (PR), n (%)	91 (34.6)	106 (40.8)	49 (18.6)	68 (26.2)	46 (17.5)	87 (33.5)
Stable Disease (SD), n (%)	25 (9.5)	74 (28.5)	7 (2.7)	23 (8.8)	12 (4.6)	35 (13.5)
Progressive Disease (PD), n (%)	3 (1.1)	11 (4.2)	4 (1.5)	4 (1.5)	15 (5.7)	26 (10.0)
Response Not Evaluable (NE)[b], n (%)	52 (19.8)	43 (16.5)	121 (46.0)	131 (50.4)	37 (14.1)	29 (11.2)
p-value[c]	< 0.00001		< 0.00001		< 0.00001	
Dichotomized Response						
CR or VGPR, n (%) (2-sided 95% CI)	92 (35.0) (29.2, 40.7)	26 (10.0) (6.4, 13.6)	82 (31.2) (25.6, 36.8)	34 (13.1) (9.0, 17.2)	153 (58.2) (52.2, 64.1)	83 (31.9) 26.3, 37.6)
PR or SD or PD or NE, n (%)	171 (65.0)	234 (90.0)	181 (68.8)	226 (86.9)	110 (41.8)	177 (68.1)
p-value[d]	< 0.00001		< 0.00001		< 0.00001	
Odds Ratio (2-sided 95% CI)	4.71 (2.91, 7.63)		3.09 (1.97, 4.85)		2.96 (2.06, 4.26)	

CI = confidence interval; IRAC = Independent Response Adjudication Committee; ISS = International Staging System; ITT = intent to treat; Rd = lenalidomide
and dexamethasone; RVd = lenalidomide, bortezomib, and dexamethasone.
a The best response of a subject.

b Including subjects who did not have any response assessment data, or not evaluable.
c Probability from Wilcoxon rank sum test with normal approximation (1 = CR, 2 = VGPR, 3 = PR, 4 = SD, 5 = PD) which excludes the category - response not evaluable (NE).
d Based on stratified Cochran-Mantel-Haenszel test stratified by ISS stage and intent to transplant at progression.

Table 11 Myeloma response rate post-initial treatment for the ITT population and in subjects without ASCT prior to PD-Study SWOG S0777

	ITT Population		Subjects without ASCT prior to PD	
	RVd (N = 263)	Rd (N = 260)	RVd (N = 216)	Rd (N = 214)
Myeloma Response Post-initial Treatment (IRAC), n (%)				
≥ VGPR	153 (58.2)	83 (31.9)	123 (56.9)	74 (34.6)
ORR (CR, VGPR, or PR)	199 (75.7)	170 (65.4)	159 (73.6)	144 (67.3)

- ***Exploratory endpoint-Subsequent antimyeloma therapy (AMT)***

Table 12 : Summary of First Subsequent Antimyeloma Therapy for Subjects with Subsequent Antimyeloma Therapy as of 1 Dec 2016 (ITT Population-Study SWOG S0777)

	RVd (N = 263)	Rd (N = 260)
Subjects With Subsequent AMT	163 (62.0)	187 (71.9)
Without PD When Received	75 (28.5)	82 (31.5)
With PD When Received	88 (33.5)	105 (40.4)

AMT = antimyeloma therapy; ITT = intent to treat; PD = progressive disease; Rd = lenalidomide and dexamethasone; RVd = lenalidomide, bortezomib, and dexamethasone.

- ***Exploratory endpoint-Time to response***

Among responders, the mean time to response was shorter in the RVd arm than the Rd arm for a response of PR or better (5.8 versus 7.8 weeks) and for response of VGPR or better (10.0 versus 14.3 weeks) as of 01 Dec 2016

- ***Exploratory endpoint-Duration of response***

Among responders, the median duration of response was 48.6 months for RVd and 38.9 months for Rd as of 01 Dec 2016. The observed HR for the comparison between the RVd arm and the Rd arm was 0.83 (95% CI: 0.61 to 1.12; p = 0.21905), indicating a longer duration of response in the RVd arm. Based on the KM estimates, 42% of the responders with RVd compared with 36% with Rd had response lasting at least 6 years.

- ***Exploratory endpoint-Subgroup analysis with intent to transplant***

Based on the IRAC review assessment and using EMA censoring rules for ITT population (cut-off 1 Dec 2016)

Table 13 : Progression-free survival by IRAC review and EMA censoring rules for ITT population, by intent to transplant at progression, data cut-off:1 Dec 2016 (Study SWOG S0777)

Intent to Transplant at progression	Yes (n = 361)		No (n = 162)	
Regimen	RVd (n = 182)	Rd (n = 179)	RVd (n = 81)	Rd (n = 81)
Median PFS (months) (95% CI)	43,0 (33,2 ; 56,4)	35,3 (28,9 ; 43,1)	37,5 (22,6 ; 50,3)	22,5 (15,6 ; 28,6)
HR (95% CI)	0,79 (0,61 ; 1,02) ; p = 0,06582		0,70 (0,49 ; 1,00) ; p = 0,04938	

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 14 Summary of Efficacy for trial SWOG SO777

Title: A randomized phase III trial of CC-5013 (Lenalidomide) and low dose dexamethasone (LLD) versus bortezomib, lenalidomide and low dose dexamethasone (BLLD) for induction, in patients with previously untreated multiple myeloma without an intent for immediate autologous stem cell transplant.			
Study identifier	SWOG S0777		
Design	Phase 3, randomized, active-controlled, open-label, multicenter		
	Duration of initial treatment:	24 weeks	
	Duration of continued RD treatment:	Until disease progression	
Hypothesis	Superiority		
Treatments groups	RVd		Eight 3-week cycles (24 weeks) of RVd (initial treatment); subjects who completed ≥6 cycles of RVd but were not able to tolerate a total of 8 cycles of initial treatment continued Rd until PD. -Lenalidomide 25 mg/day PO on Days 1 to 14 -Bortezomib 1.3 mg/m^2 IV on Days 1, 4, 8, and 11 -Dexamethasone 20 mg/day PO on Days 1, 2, 4, 5, 8, 9, 11, and 12 (N = 263)
	Rd		Six 4-week cycles (24 weeks) of Rd (initial treatment); subjects who completed ≥4 cycles of Rd initial treatment continued Rd until PD. -Lenalidomide 25 mg/day orally (PO) on Days 1 to 21 -Dexamethasone 40 mg/day PO on Days 1, 8, 15, and 22 (N = 260)
Endpoints and definitions	Primary endpoint	Progression free survival (PFS)	time from the date of randomization to date of first documentation of progression (including symptomatic deterioration), or death due to any cause, whichever occurred earlier.
	Secondary endpoint	Overall survival (OS)	time between randomization and death. Subjects who died before or on the date of data cut-off were considered to have had an OS event.
	Secondary endpoint	Response rate	CR, VGPR, PR, SD, and PD based on IMWG criteria
Database lock	5 November 2015 for primary PFS and 1 December 2016 for updated PFS results and other endpoints results.		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat: The ITT population includes all subjects who are randomized and with valid consent prior to the randomization.		
Descriptive statistics and estimate variability	Treatment group	RVd	Rd
	Number of subjects	N=263	N=260
	Median PFS (SWOG censuring rules), months	42.5	29.9
	2-sided 95% CI	34.0-54.8	25.6-38.2

	Updated Median PFS (SWOG censuring rules), months	42.5	29.9
	2-sided 95% CI	34.0-52.5	25.6-38.2
	Median OS(months)	89.1	67.2
	2-sided 95%CI	76.1-NE	58.4-90.8
	CR or VGPR, n (%) (post-initial treatment based on IRAC assessments)	153 (58.2)	83 (31.9)
	2-sided 95% CI	52.2-64.1	26.3-37.6
	2-sided 95% CI	34.8-77.9	28.1-53.6

Effect estimate per comparison **Analysis description** Descriptive statistics and estimate variability	Primary endpoint PFS using SWOG censuring rules	Comparison groups	RVd versus Rd
		HR	0.76
		95%CI	0.61-0.94
		P-value (log-rank test)	0.01038
	Primary endpoint Updated PFS (using SWOGG censuring rules)	Comparison groups	RVd versus Rd
		HR	0.76
		95%CI	0.62-0.93
		P-value	0.00862
	Secondary endpoint OS	Comparison groups	RVd versus Rd
		HR	0.75
		95%CI	0.58-0.97
		P-value (log-rank test)	0.02786
	Secondary endpoint RR≥ VGPR	Comparison groups	RVd versus Rd
		Odds ratio (OR)	2.96
		95%CI	2.06-4.26
		P-value	<0.00001
	Sensitivity analysis (The analysis of PFS from randomization using EMA censoring rules) Intent to treat population Cut-off date: 5 November 2015 for primary PFS and 1 December 2016 for updated PFS results.		
	Treatment group	RVd	Rd
	Number of subject	N=263	N=260
	Median PFS (EMA censuring rules), months	40.5	29.2
	2-sided 95% CI	33.1-50.3	24.1-36.6
	Updated Median PFS (EMA censuring rules), months	41.7	29.7
	2-sided 95% CI	33.1-51.5	24.2-37.8
Effect estimate per comparison	Primary endpoint Primary PFS using EMA censuring rules	Comparison groups	RVd versus Rd
		HR	0.76
		95%CI	0.62-0.94
		P-value (log-rank test)	0.01272
	Primary endpoint Updated PFS (using EMA censuring rules)	Comparison groups	RVd versus Rd
		HR	0.76
		95%CI	0.62-0.94
		P-value	0.00996

Supportive studies

Data from 2 studies (PETHEMA GEM2012 and IFM 2009) have been provided to support the treatment of TE patients (eligible for transplant) with NDMM.

- **Study PETHEMA GEM2012**

This was an open-label, randomized, multicenter, national study that compared 2 pretransplant conditioning regimens (Bu-Mel versus MEL200) in subjects who received RVd as initial (induction) treatment. This study was conducted in Spain. The primary efficacy endpoint of this study was PFS for both conditioning regimens.

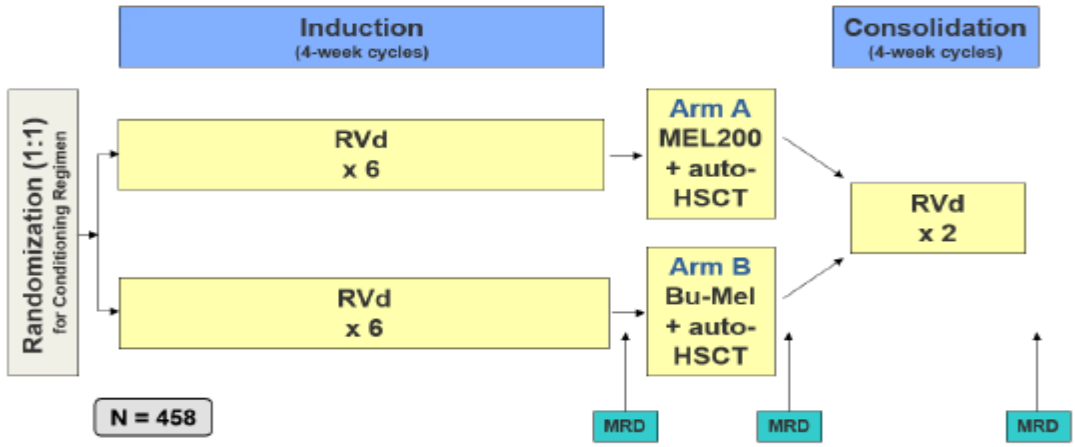
Eligible subjects were randomized in a 1:1 ratio to 1 of 2 arms, which were designed as follows:

- Arm A: Six 4-week cycles (24 weeks) of RVd initial treatment followed by melphalan 200 mg/m2 (MEL200)7 conditioning, auto-HSCT, and two 4-week cycles of RVd consolidation
- Arm B: Six 4-week cycles (24 weeks) of RVd initial treatment followed by busulfan with melphalan (Bu-Mel) conditioning, auto-HSCT, and two 4-week cycles of RVd consolidation

For both treatment arms, the RVd dosing regimen was as follows:

- Lenalidomide 25 mg/day PO on Days 1 to 21
- Bortezomib 1.3 mg/m2 subcutaneously (SC) on Days 1, 4, 8, and 11
- Dexamethasone 40 mg/day PO on Days 1 to 4 and 9 to 12

Figure 5 : Treatment Schema Overview PETHEMA GEM2012



- Primary endpoint: PFS after both conditioning regimens
- Key inclusion criteria: 18 to 65 years, symptomatic NDMM, ECOG PS ≤ 2 (or 3 if the ECOG PS was due to myeloma, eg, pathological fracture), and life expectancy > 3 months
- RVd regimen per cycle: **R** 25 mg/d PO (Days 1-21), **V** 1.3 mg/m^2 SC (Days 1, 4, 8, 11), **d** 40 mg/d PO (Days 1-4, 9-12)

auto-HSCT = autologous hematopoietic stem cell transplantation; Bu-Mel = busulfan with melphalan; MEL200 = melphalan 100 mg/m2 on Days -3 and -2, or melphalan 200 mg/m2 on Day -2, relative to infusion of hematopoietic stem cells, according to each site' s standard practice;
MRD = minimal residual disease; RVd = lenalidomide, bortezomib, and dexamethasone.
Note: Evaluation of MRD in subjects with immunofixation-negative complete response after each phase of treatment (induction, transplant, and consolidation).

Table 15 : Number of Subject included in data sets analyzed – Study PETHEMA GEM2012

Data set	RVd/ Bu-Mel/ RVd (N = 230) n (%)	RVd/ MEL200/ RVd (N = 228) n (%)	Total (N = 458) n (%)
Intent-to-treat population[a]	230 (100.0)	228 (100.0)	458 (100.0)
Safety population[b]	230 (100.0)	228 (100.0)	458 (100.0)
Efficacy evaluable population[c]	226 (98.3)	224 (98.2)	450 (98.3)

Bu-Mel = busulfan with melphalan; ITT = intent to treat; MEL200 = melphalan 100 mg/m2 on Days -3 and -2, or melphalan 200 mg/m2 on Day -2, relative to infusion of hematopoietic stem cells, according to each site' s standard practice; RVd = lenalidomide, bortezomib, and dexamethasone.
a The ITT population is defined as all subjects who were randomized with valid consent, and who were not screen failures. All percentages are calculated based on the ITT population.
b The safety population is defined as all subjects who were randomized and received at least one dose of study drug.
c The efficacy evaluable population is defined as all ITT subjects who had measurable disease at baseline, and were evaluated after receiving at least one dose of study treatment.
Data cutoff date = 31 Mar 2017.

Table 16 : Disease Characteristics at Diagnosis- Study PETHEMA GEM2012

Characteristic	RVd/ Bu-Mel/ RVd (N = 230)	RVd/ MEL200/ RVd (N = 228)	Total (N = 458)
ISS Stage, n (%)			
I	95 (41.3)	84 (36.8)	179 (39.1)
II	78 (33.9)	88 (38.6)	166 (36.2)
III	53 (23.0)	54 (23.7)	107 (23.4)
Missing	4 (1.7)	2 (0.9)	6 (1.3)
Revised ISS Stage, n (%)			
I	37 (16.1)	38 (16.7)	75 (16.4)
II	91 (39.6)	86 (37.7)	177 (38.6)
III	16 (7.0)	16 (7.0)	32 (7.0)
Missing	86 (37.4)	88 (38.6)	174 (38.0)
ECOG performance status, n (%)			
Fully active (Grade 0)	94 (40.9)	101 (44.3)	195 (42.6)
Restricted activity (Grade 1)	94 (40.9)	88 (38.6)	182 (39.7)
No work, ambulatory (Grade 2)	29 (12.6)	33 (14.5)	62 (13.5)
Limited self-care (Grade 3)	11 (4.8)	5 (2.2)	16 (3.5)
Missing	2 (0.9)	1 (0.4)	3 (0.7)
Cytogenetic risk[a], n (%)			
High	50 (21.7)	42 (18.4)	92 (20.1)
Not high	106 (46.1)	107 (46.9)	213 (46.5)
Other	42 (18.3)	52 (22.8)	94 (20.5)
All missing	32 (13.9)	27 (11.8)	59 (12.9)
Creatinine clearance, n (%)			
< 60 mL/min	35 (15.2)	35 (15.4)	70 (15.3)
≥ 60 mL/min	186 (80.9)	184 (80.7)	370 (80.8)
Missing	9 (3.9)	9 (3.9)	18 (3.9)
β2 microglobulin, n (%)			
≤ 5.5 mg/L	179 (77.8)	172 (75.4)	351 (76.6)
> 5.5 mg/L	49 (21.3)	54 (23.7)	103 (22.5)
Missing	2 (0.9)	2 (0.9)	4 (0.9)
Lactate dehydrogenase elevated, n (%)			
Yes	32 (13.9)	33 (14.5)	65 (14.2)
No	188 (81.7)	188 (82.5)	376 (82.1)
Missing	10 (4.3)	7 (3.1)	17 (3.7)

Bu-Mel = busulfan with melphalan; ECOG = Eastern Cooperative Oncology Group; ISS = International Staging System; ITT = intent to treat; MEL200 = melphalan 100 mg/m2 on Days -3 and -2, or melphalan 200 mg/m2 on Day -2, relative to infusion of hematopoietic stem cells, according to each site's standard practice; RVd = lenalidomide, bortezomib, and dexamethasone.
a Cytogenetic high-risk is defined as any of the three following probes being positive: deletion of p53, translocation involving chromosomes 4 and 14 (t[4;14]), or translocation involving chromosomes 14 and 16 (t[14;16]). "Not high risk" is defined as all of the above three probes being negative. The cytogenetic risk is "Other" if the status for the probes are partially available but not sufficient to determine "High" or "Not high". The cytogenetic risk is "All missing" if the status for all three probes are missing.
Data cutoff date = 31 Mar 2017.

The results of the primary PFS analysis are shown in the table below. PFS was assessed by investigators under the review of a central hematologist.

Table 17: Progression-free Survival (EMA Censoring Rules) – ITT Population-Study PETHEMA GEM2012

	Statistic	RVd/ Bu-Mel/ RVd (N = 230)	RVd/ MEL200/ RVd (N = 228)
Progressed/died	n (%)	50 (21.7)	52 (22.8)
Progressed	n (%)	36 (15.7)	45 (19.7)
Died	n (%)	14 (6.1)	7 (3.1)
Censored	n (%)	180 (78.3)	176 (77.2)
PFS time (months)	Median[a]	NE	NE
	(95% CI)	NE, NE	NE, NE
	6 months event-free % (SE)	96.5 (1.21)	92.9 (1.70)
	12 months event-free % (SE)	90.0 (1.98)	87.6 (2.19)
	18 months event-free % (SE)	84.9 (2.40)	84.5 (2.42)
	24 months event-free % (SE)	80.9 (2.72)	80.7 (2.75)
	30 months event-free % (SE)	75.2 (3.38)	72.6 (3.49)
	36 months event-free % (SE)	68.6 (4.81)	72.6 (3.49)

Comparison between treatment arms	Hazard Rate Ratio HR (95% CI)[b]	Log-rank Test p-value[c]
Bu-Mel arm versus MEL200 arm	0.94 (0.64, 1.39)	0.75572

Bu-Mel = busulfan with melphalan; CI = confidence interval; EMA = European Medicines Agency; HR = hazard ratio; ITT = intent to treat; MEL200 = melphalan 100 mg/m2 on Days -3 and -2, or melphalan 200 mg/m2 on Day -2, relative to infusion of hematopoietic stem cells, according to each site' s standard practice; NE = not estimable;
PFS = progression-free survival; RVd = lenalidomide, bortezomib, dexamethasone; SE = standard error.
a The median is based on Kaplan-Meier estimate.
b Based on non-stratified Cox proportional hazards model comparing hazard functions associated with treatment arms (Bu-Mel arm:MEL200 arm).
c The p-value is based on non-stratified log rank test.
Data cutoff date = 31 Mar 2017.

The myeloma response rates (secondary endpoint) were evaluated by the investigators as well as an IRAC. The investigator assessments, per protocol, were according to the IMWG response criteria. The IRAC's assessment was performed retrospectively in a blinded manner and was based on the IMWG criteria. An overview of ≥ VGPR and ≥ CR response rates by IRAC assessment at post-induction, post-transplant, and post-consolidation are presented in table below.

Table 18 : Myeloma Response Rates of VGPR or Better and CR or Better by IRAC Assessment at Post-induction, Post-transplant, and Post-consolidation (ITT Population- Study PETHEMA GEM2012)

Parameter	RVd/ Bu-Mel/ RVd (N = 230) n (%)	RVd/ MEL200/ RVd (N = 228) n (%)	Total (N = 458) n (%)
Post-induction			
≥ VGPR[a] (CR or VGPR)	**156 (67.8)**	**149 (65.4)**	**305 (66.6)**
p-value[b]	0.57443		-
Odds ratio (two sided 95% CI)	1.12 (0.76,1.65)		-
Difference (%) (two sided 95% CI)[c]	2.5 (-6.2,11.1)		-
CR[a]	**85 (37.0)**	**68 (29.8)**	**153 (33.4)**
p-value[b]	0.10566		-
Odds ratio (two sided 95% CI)	1.38 (0.93,2.04)		-
Difference (%) (two sided 95% CI)[c]	7.1 (-1.5,15.7)		-
Post-transplant			
≥ VGPR[d] (CR or VGPR)	**175 (76.1)**	**169 (74.1)**	**344 (75.1)**
p-value[b]	0.62691		-
Odds ratio (two sided 95% CI)	1.11 (0.73,1.70)		-
Difference (%) (two sided 95% CI)[c]	2.0 (-6.0,9.9]		-
CR[d]	**109 (47.4)**	**93 (40.8)**	**202 (44.1)**
p-value[b]	0.15480		-
Odds ratio (two sided 95% CI)	1.31 (0.90,1.89)		-
Difference (%) (two sided 95% CI)[c]	6.6 (-2.5,15.7)		-
Post-consolidation			
≥ VGPR[e] (CR or VGPR)	**175 (76.1)**	**171 (75.0)**	**346 (75.5)**
p-value[b]	0.78670		-
Odds ratio (two sided 95% CI)	1.06 (0.69, 1.62)		-
Difference (%) (two sided 95% CI)[c]	1.1 (-6.8, 9.0)		-
CR[e]	**121 (52.6)**	**109 (47.8)**	**230 (50.2)**
p-value[b]	0.30414		-
Odds ratio (two sided 95% CI)	1.21 (0.84, 1.75)		-
Difference (%) (two sided 95% CI)[c]	4.8 (-4.3, 13.9)		-

Bu-Mel = busulfan with melphalan; CI = confidence interval; CR = complete response; IRAC = Independent Response Adjudication Committee; ITT = intent to treat; MEL200 = melphalan 100 mg/m2 on Days -3 and -2, or melphalan 200 mg/m2 on Day -2, relative to infusion of hematopoietic stem cells, according to each site's standard practice; RVd = lenalidomide, bortezomib, and dexamethasone; VGPR = very good partial response.

a The last valid response assessment (neither missing nor recorded as "not evaluable") on or before the post-Cycle 6 assessment in the induction phase.

b Based on two-sided Chi-square test.

c Response rate difference with 95% Wald confidence interval (Bu-Mel arm minus MEL200 arm).

d Response at post-transplant assessment.

e The last valid response assessment (neither missing nor recorded as "not evaluable") on or before the post-Cycle 2 assessment in the consolidation phase.
Data cutoff date = 31 Mar 2017.

Results of the OS analysis (secondary efficacy endpoint) are presented in the table below.

Table 19 : Overall Survival – ITT Population-Study PETHEMA GEM2012

	Statistic	**RVd/ Bu-Mel/ RVd (N = 230)**	**RVd/ MEL200/ RVd (N = 228)**
Died	n (%)	29 (12.6)	29 (12.7)
Censored	n (%)	201 (87.4)	199 (87.3)
Survival time (months)	Median[a]	NE	NE
	(95% CI)	NE, NE	NE, NE
	6 months event-free % (SE)	99.1 (0.61)	97.4 (1.06)
	12 months event-free % (SE)	95.2 (1.41)	95.6 (1.36)
	18 months event-free % (SE)	91.0 (1.92)	92.3 (1.79)
	24 months event-free % (SE)	87.5 (2.34)	90.6 (2.03)
	30 months event-free % (SE)	85.8 (2.58)	86.2 (2.72)
	36 months event-free % (SE)	84.2 (2.96)	80.2 (4.30)

Comparison between treatment arms	**Hazard Rate Ratio HR (95% CI)[b]**	**Log-rank Test p-value[c]**
Bu-Mel arm versus MEL200 arm	1.01 (0.6, 1.69)	0.96386

Bu-Mel = busulfan with melphalan; CI = confidence interval; HR = hazard ratio; ITT = intent to treat; MEL200 = melphalan 100 mg/m2 on Days -3 and -2, or melphalan 200 mg/m2 on Day -2, relative to infusion of hematopoietic stem cells, according to each site's standard practice; NE = not estimable; RVd = lenalidomide, bortezomib, and dexamethasone; SE = standard error.
a The median is based on Kaplan-Meier estimate.
b Based on non-stratified Cox proportional hazards model comparing hazard functions associated with treatment arms (Bu-Mel arm:MEL200 arm).
c The p-value is based on non-stratified log rank test.
Data cutoff date = 31 Mar 2017.

In the PETHEMA GEM2012 study, bone marrow samples were collected in all subjects at prespecified time points and referred for MRD analysis (secondary efficacy endpoint). MRD studies were carried out after each stage of treatment. The PETHEMA GEM2012 study defined MRD negativity at the 10^{-6} sensitivity level. Results were also analyzed by the applicant with MRD negativity defined at the 10^{-4} sensitivity level. More subjects were MRD negative under the less stringent 10^{-4} cutoff level compared with the more stringent 10^{-6} sensitivity level.

Table 20: Post-initial Treatment MRD Status (10-4 and 10-6 Sensitivity Levels) by Response Category (IRAC Review) – Study PETHEMA GEM2012 (ITT Population)

Response Category MRD Status	RVd[a] (4-week cycles × 6 = 24 weeks) (N = 458) n (%)	
	Negativity Defined at 10^{-4} Sensitivity	Negativity Defined at 10^{-6} Sensitivity
All Subjects	**458 (100.0)**	**458 (100)**
Negative	217 (47.4)	132 (28.8)
Positive	179 (39.1)	264 (57.6)
Missing	62 (13.5)	62 (13.5)
Subjects With ≥ VGPR[b]	**305 (66.6)**	**305 (66.6)**
Negative[c]	196 (42.8)	118 (25.8)
Positive[c]	89 (19.4)	167 (36.5)
Missing[c]	20 (4.4)	20 (4.4)
Subjects With CR[b]	**153 (33.4)**	**153 (33.4)**
Negative[c]	124 (27.1)	83 (18.1)
Positive[c]	25 (5.5)	66 (14.4)
Missing[c]	4 (0.9)	4 (0.9)

CR = complete response; IRAC = Independent Response Adjudication Committee; ITT = intent to treat; MRD = minimal residual disease; RVd = lenalidomide, bortezomib, and dexamethasone; VGPR = very good partial response.
a Both RVd arms combined.
b The last valid response assessment on or before the post-initial treatment visit.
c Percentage is based on the total number of subjects in the treatment arm.
Data cutoff date = 31 Mar 2017.

Table 21: Post-transplant Treatment MRD Status (10-4 and 10-6 Sensitivity Levels) by Response Category (IRAC Review) – Study PETHEMA GEM2012 (ITT Population)

Response Category MRD Status	RVd[a] (4-week cycles × 6 = 24 weeks) (N = 458) n (%)	
	Negativity Defined at 10^{-4} Sensitivity	Negativity Defined at 10^{-6} Sensitivity
All Subjects	**458 (100.0)**	**458 (100)**
Negative	287 (62.7)	193 (42.1)
Positive	73 (15.9)	167 (36.5)
Missing	98 (21.4)	98 (21.4)
Subjects With ≥ VGPR[b]	**344 (75.1)**	**344 (75.1)**
Negative[c]	271 (59.2)	187 (40.8)
Positive[c]	44 (9.6)	128 (27.9)
Missing[c]	29 (6.3)	29 (6.3)
Subjects With CR[b]	**202 (44.1)**	**202 (44.1)**
Negative[c]	175 (38.2)	136 (29.7)
Positive[c]	10 (2.2)	49 (10.7)
Missing[c]	17 (3.7)	17 (3.7)

CR = complete response; IRAC = Independent Response Adjudication Committee; ITT = intent to treat; MRD = minimal residual disease; RVd = lenalidomide, bortezomib, and dexamethasone; VGPR = very good partial response.
a Both RVd arms combined.
b Response is from the post-transplant assessment.
c Percentage is based on the total number of subjects in the treatment arm
Data cutoff date = 31 Mar 2017.

- **Study IFM 2009**

This study was a Phase 3, randomized, controlled, open-label, multicenter study that was sponsored by the Centre Hospitalier Universitaire (CHU) de Toulouse with partnership and close collaboration of the Intergroupe Francophone du Myélome (IFM).

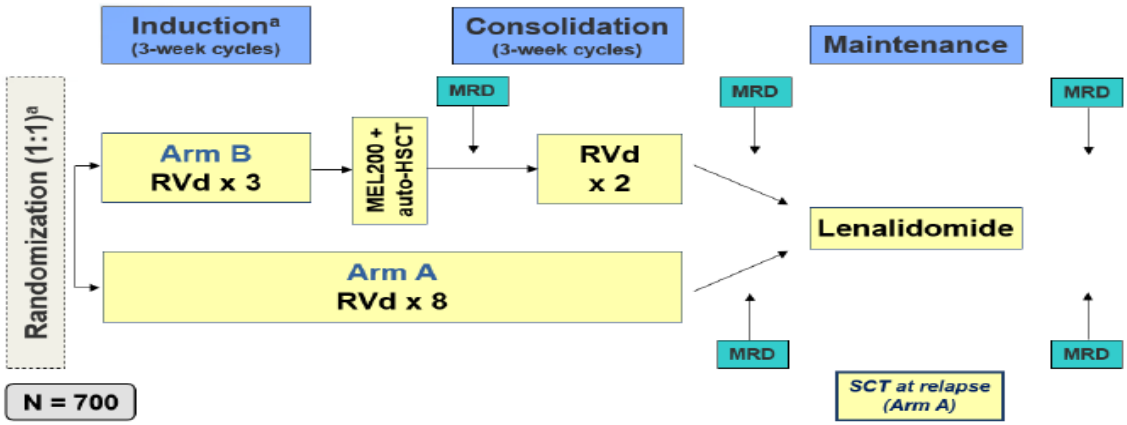
The primary objective of this study was to compare PFS in subjects treated with RVd without immediate high-dose treatment (HDT) followed by lenalidomide maintenance (Arm A, or RVd) to those treated with RVd

plus consolidation with HDT/auto-HSCT and 2 cycles of RVd, followed by lenalidomide maintenance (Arm B, or RVd + auto-HSCT).

Randomization to Arm A or Arm B (1:1) occurred 2 to 3 weeks after the initiation of Cycle 1 of RVd and prior to Cycle 2 of RVd.

- **Arm A (RVd arm):** RVd induction (three 3-week cycles = 9 weeks) without immediate HDM/auto-HSCT followed by 5 cycles of RVd consolidation and lenalidomide maintenance (total of 8 cycles of initial therapy, or 24 weeks, of RVd without transplant)
- **Arm B (RVd + auto-HSCT arm):** RVd induction (three 3-week cycles = 9 weeks) + HDM/auto-HSCT followed by 2 cycles of RVd consolidation and lenalidomide maintenance.

Figure 6: Treatment Schema Overview – Study IFM 2009



- Stratification factors: ISS stage (I vs II vs III) and cytogenetics (standard vs high risk[b] vs FISH failures)
- Primary endpoint: PFS
- Key inclusion criteria: 18 to 65 years, symptomatic NDMM, and ECOG PS ≤ 2 (Karnofsky ≥ 60%)
- RVd regimen per cycle: **R** 25 mg/d PO (Days 1-14), **V** 1.3 mg/m^2 IV (Days 1, 4, 8, 11), **d** 20 mg/d PO (Days 1, 2, 4, 5, 8, 9, 11, 12); during consolidation, the dose of dexamethasone was reduced to 10 mg/d.

auto-HSCT = autologous hematopoietic stem cell transplantation; d = day or dexamethasone; del 17p = deletion in chromosome 17p; ECOG = Eastern Cooperative Oncology Group; FISH = fluorescence in situ hybridization; ISS = International Staging System; IV = intravenously; MEL200 = melphalan 200 mg/m2; MRD = minimal residual disease; NDMM = newly diagnosed multiple myeloma; PFS = progression-free survival; PO = orally; PS = performance status; R = lenalidomide; RVd = lenalidomide, bortezomib, and dexamethasone; SCT = stem cell transplant; t(4;14) = translocation involving chromosomes 4 and 14; t(14;16) = translocation involving chromosomes 14 and 16; V = bortezomib.
a One cycle of induction (initial) therapy was given after registration and before randomization; 2 cycles of induction (initial) therapy were given after randomization.
b High risk was defined as the presence of del 17p, t(4;14), or t(14;16) using FISH.
Note: 1) For Arm A, RVd (without transplant) was given for 24 weeks: three 3-week cycles (9 weeks) of induction followed by five 3-week cycles (15 weeks) of consolidation.
2) Bone marrow used for MRD was collected before or on Day 1 of RVd Cycle 4 (Arm B only), before or on Day 1 of maintenance, and after maintenance (= end of study treatment) or early discontinuation.

The ITT population included 700 subjects (350 subjects in each treatment arm). They were enrolled between November 2010 and November 2012 at 69 sites in France, Belgium, and Switzerland.

Regarding the primary efficacy endpoint, the DMC recommended to release the results early because the difference in PFS met the prespecified stopping criterion ($p < 0.015$) based on results of the second interim analysis. The final/primary PFS results after the second interim analysis (1 Sep 2015 data cut-off date) and an updated PFS analysis (1 Dec 2016 data cut-off date) are presented below. PFS was assessed by investigators and centrally confirmed by medical monitor.

Myeloma response rate (secondary efficacy endpoint) was assessed by the investigator and centrally confirmed by the medical monitor on an ongoing basis based on the IMWG Uniform Response Criteria.

MRD was an exploratory endpoint at post-initial treatment, with negativity defined at the 10^{-4} sensitivity level.

Table 22: Progression-free Survival from randomization (Data Cut-off Date 1 Sep 2015- Study IFM 2009)

PFS Analysis		RVd	RVd + auto-HSCT
PFS from randomization using EMA censoring rules on the ITT population (stratified analysis)	Median (months)[a] (95% CI)[b]	34.8 (31.5, 37.7)	43.9 (41.1, NE)
	HR (95% CI)[c] p-value[d]	0.67 (0.55, 0.82) p = 0.00010	
PFS from randomization using FDA censoring rules on the ITT population (stratified analysis)	Median (months)[a] (95% CI)[b]	35.6 32.1, 38.4	48.5 40.5, NE
	HR (95% CI)[c] p-value[d]	0.65 (0.53, 0.80) p = 0.00005	

Auto-HSCT = autologous hematopoeitic stem cell transplantation; CI = confidence interval; EMA = European Medicines Agency; FDA = Food and Drug Administration; HR = hazard ratio; ISS = international staging system; ITT = intent to treat; NE = not estimable; PFS = progression-free survival; RVd = lenalidomide, bortezomib, and dexamethasone.
a The median is based on Kaplan-Meier estimate.
b 95% confidence interval about the median progression free survival time.
c Based on stratified Cox proportional hazards model stratified by ISS stage and cytogenetic risk factors comparing hazard functions associated with treatment groups (RVd+auto-HSCT:RVd).
d The p-value is based on stratified log-rank test stratified by ISS stage and cytogenetic risk factors.
Data cutoff date: 01 Sep 2015

Table 23: Updated Progression-free Survival from randomization based on Investigator Assessment (and Centrally Confirmed by the Medical Monitor) and using the EMA Censoring Rules – ITT population- Study IFM 2009 (Data Cut-off Date 1 Dec 2016)

	Statistics	RVd (N=350)	RVd + auto-HSCT (N=350)	Total (N=700)
Disease Progression	N	350 (100.0)	350 (100.0)	700 (100.0)
Censored	n (%)	104 (29.7)	141 (40.3)	245 (35.0)
Progressed/Died	n (%)	246 (70.3)	209 (59.7)	455 (65.0)
Progression Free Survival Time (months)	Median[a]	35.0	45.8	39.7
	Two sided 95% CI[b]	[31.5 , 37.8]	[41.1 , 51.0]	[37.1 , 42.7]
	12 Months Event-Free %(SE)	85.28 (1.90)	88.78 (1.69)	87.03 (1.28)
	24 Months Event-Free %(SE)	66.20 (2.54)	77.82 (2.23)	72.02 (1.71)
	36 Months Event-Free %(SE)	48.56 (2.69)	61.91 (2.61)	55.24 (1.89)
	48 Months Event-Free %(SE)	34.31 (2.56)	48.75 (2.69)	41.53 (1.88)
	60 Months Event-Free %(SE)	26.69 (2.72)	36.56 (2.90)	31.68 (1.99)
	72 Months Event-Free %(SE)	NE (NE)	NE (NE)	NE (NE)
Hazard Ratio (Stratified)	HR (95% CI) [d]	0.71 [0.59, 0.86]		
Log-Rank Test (Stratified)	p-value [e]	0.00031		

auto-HSCT = autologous hematopoeitic stem cell transplantation; CI = confidence interval; EMA = European Medicine Agency; ITT = intent to treat; ISS = International Staging System; NE = not estimable; RVd = lenalidomide, bortezomib, and dexamethasone; SE = standard error.
a The median is based on Kaplan-Meier estimate.
b 95% confidence interval about the median progression free survival time.
c The mean and median are the univariable statistics without adjusting for censoring.
d Based on stratified Cox proportional hazards model stratified by ISS stage and cytogenetic risk factors comparing hazard functions associated with treatment groups (RVd+auto-HSCT:RVd).
e The p-value is based on stratified log-rank test stratified by ISS stage and cytogenetic risk factors.
Data cutoff date: 01 Dec 2016

Table 24: Overall Survival from randomization (ITT Population-Study IFM 2009)

	Statistics	RVd (N=350)	RVd + auto-HSCT (N=350)	Total (N=700)
Overall Survival (OS)	N	350 (100.0)	350 (100.0)	700 (100.0)
Censored	n (%)	275 (78.6)	268 (76.6)	543 (77.6)
Died	n (%)	75 (21.4)	82 (23.4)	157 (22.4)
Survival Time (months)	Median[a]	NE	NE	NE
	Two sided 95% CI[b]	[NE , NE]	[NE , NE]	[NE , NE]
	12 Months Event-Free %(SE)	97.42 (0.85)	94.27 (1.24)	95.84 (0.76)
	24 Months Event-Free %(SE)	93.10 (1.36)	90.25 (1.59)	91.68 (1.05)
	36 Months Event-Free %(SE)	89.35 (1.66)	85.65 (1.88)	87.50 (1.25)
	48 Months Event-Free %(SE)	83.53 (1.99)	80.16 (2.14)	81.84 (1.46)
	60 Months Event-Free %(SE)	78.22 (2.43)	75.61 (2.46)	76.90 (1.73)
	72 Months Event-Free %(SE)	68.78 (4.73)	71.92 (3.48)	70.49 (2.91)
Hazard Ratio (Stratified)	HR (95% CI)[d]	1.17 [0.85, 1.60]		
Log-Rank Test (Stratified)	p-value[e]	0.33498		

auto-HSCT = autologous hematopoeitic stem cell transplantation; CI = confidence interval; ISS = International Staging System; ITT = intent to treat; NE = not estimable; RVd = lenalidomide, bortezomib, and dexamethasone; SE = standard error.
a The median is based on Kaplan-Meier estimate.
b 95% confidence interval about the median overall survival time.
c The mean and median are the univariable statistics without adjusting for censoring.
d Based on stratified Cox proportional hazards model stratified by ISS stage and cytogenetic risk factors comparing hazard functions associated with treatment groups (RVd+auto-HSCT:RVd).
e The p-value is based on stratified log-rank test stratified by ISS stage and cytogenetic risk factors.
Data cutoff date: 01 Dec 2016

A summary of the key results for myeloma response rate by investigator assessment is presented in the table below.

Table 25: Summary of Myeloma Response Rates by Investigator Assessment (Centrally confirmed by the Medical Monitor) Post-induction, Post-Cycle 4 (RVd Arm), Post-cycle 6 (RVd Arm), Post-transplant (RVd + auto-HSCT Arm), and Post-consolidation (ITT Population-Study IFM 2009)

	RVd (N=350)				RVd + auto-HSCT (N=350)		
Statistics	Post-cycle 3 (induction)	Post-cycle 4	Post-cycle 6	Post-cycle 8 (consolidation)	Post-cycle 3 (induction)	Post-transplant	Post-consolidation
Myeloma Response Rate[a]							
CR	16 (4.6)	25 (7.1)	38 (10.9)	107 (30.6)	17 (4.9)	65 (18.6)	114 (32.6)
VGPR	164 (46.9)	175 (50.0)	184 (52.6)	130 (37.1)	182 (52.0)	164 (46.9)	148 (42.3)
≥ VGPR	**180 (51.4)**	**200 (57.1)**	**222 (63.4)**	**237 (67.7)**	**199 (56.9)**	**229 (65.4)**	**262 (74.9)**
PR	143 (40.9)	129 (36.9)	115 (32.9)	96 (27.4)	131 (37.4)	74 (21.1)	53 (15.1)
SD	22 (6.3)	16 (4.6)	7 (2.0)	6 (1.7)	15 (4.3)	2 (0.6)	2 (0.6)
PD	2 (0.6)	3 (0.9)	5 (1.4)	10 (2.9)	4 (1.1)	0 (0.0)	2 (0.6)
NE[b]	3 (0.9)	2 (0.6)	1 (0.3)	1 (0.3)	1 (0.3)	45 (12.9)	31 (8.9)

auto-HSCT = autologous hematopoeitic stem cell transplantation; CR = complete response ; ITT = intent to treat; NE = response not evaluable; PD = progressive disease; PR = partial response; RVd = lenalidomide, bortezomib, and dexamethasone;. SD = stable disease; VGPR = very good partial response.
a The last valid response on or before the post-induction, post-cycle 4, post-tarnsplant, and post-consolidation visits.
b Including subjects who did not have any response assessment data, or not evaluable.
Data cutoff date: 01 Dec 2016

During the course of the IRAC review and the inconsistent availability of urine protein electrophoresis (UPEP) results, the IRAC performed a separate assessment based only on the review of available local laboratory data in order to determine maximum tumour volume reduction (Arm A only), see results in table below.

Table 26: Myeloma Response Rate by IRAC based on Maximum tumour volume reduction from local laboratories (ITT population-Study IFM 2009)

	RVd Arm Only n = 350		
	Post-cycle 4 n (%)	**Post-cycle 6 n (%)**	**Post-cycle 8 (consolidation) n (%)**
Myeloma Response Rate[a]			
CR	15 (4.3)	22 (6.3)	65 (18.6)
VGPR	199 (56.9)	212 (60.6)	174 (49.7)
≥ VGPR	**214 (61.1)**	**234 (66.9)**	**239 (68.3)**
PR	104 (29.7)	91 (26.0)	82 (23.4)
SD	19 (5.4)	10 (2.9)	10 (2.9)
PD	5 (1.4)	7 (2.0)	13 (3.7)
NE[a]	8 (2.3)	8 (2.3)	6 (1.7)

CR = complete response; IRAC = independent response adjudication committee; ITT = inten to treat; NE = response not evaluable; PD = progressive disease; PR = partial response; RVd = lenalidomide, bortezomib, and dexamethasone; SD = stable disease; VGPR = very good partial response.
a Including subjects who did not have any response assessment data, or not evaluable.
Data cutoff date: 01 Dec 2016

At the end of 8 cycles of initial treatment in the RVd arm (no transplant), 38.9% of subjects had ≥ VGPR (central review) and were MRD negative, and 23.4% of subjects had CR and were MRD negative.

Table 27: Post-initial Treatment MRD Status (10-4 Sensitivity) by Response Category (Central Review) (ITT population-Study IFM 2009)

Response Category MRD Status	**RVd[a] (3-week cycles × 8 = 24 weeks) (N = 350) n (%)**
All Subjects	Not collected[b]
Negative	
Positive	
Missing	
Subjects With ≥ VGPR[c]	**237 (67.7)**
Negative[d]	136 (38.9)
Positive[d]	55 (15.7)
Missing[d]	46 (13.1)
Subjects With CR[c]	**107 (30.6)**
Negative[d]	82 (23.4)
Positive[d]	11 (3.1)
Missing[d]	14 (4.0)

CR = complete response; IRAC = Independent Response Adjudication Committee; ITT = intent to treat; MRD = minimal residual disease; RVd = lenalidomide, bortezomib, and dexamethasone; VGPR = very good partial response.
a The 8 cycles (24 weeks) of initial RVd therapy for the RVd arm in the IFM 2009 study are referred to as "initial treatment."
b In the IFM 2009 study, MRD assessment was performed only for subjects with response ≥ VGPR.
c The last valid response assessment on or before the post-initial treatment visit.
d Percentage is based on the total number of subjects in the treatment arm.
Data cutoff date = 01 Dec 2016.

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

- *Integrated analysis for patients eligible for transplant (TE patients)*

In the absence of a clinical trial directly comparing RVd and VTD in TE NDMM patients, the applicant provided an integrated analysis comparing an initial treatment regimen of RVd versus VTD supporting the claimed indication in this population. This was based on the individual subject data from the 4 identified RCTs:

- **RVd** – PETHEMA GEM2012 and IFM 2009
  - *PETHEMA GEM2012*
  - *IFM 2009*
- **VTD** – PETHEMA GEM2005 and IFM 2013-04
  - *PETHEMA GEM2005*
  - *IFM 2013-04*

The PETHEMA studies were identified as the main studies for the integrated analysis based on the symmetrical design of the induction regimens and the duration of induction cycles (six 4-week cycles) followed by auto-HSCT. The IFM studies were considered supportive studies for the integrated analysis. Both IFM studies included 3-week cycles of induction, the duration of induction therapy varied between the 2 IFM studies.

Table 28: Overview of study design and conduct of studies

	RVd		VTD	
	PETHEMA GEM2012	**IFM 2009**	**PETHEMA GEM2005**	**IFM 2013-04**
Randomization	Randomized (1:1) to compare 2 pretransplant conditioning regimens in subjects who received RVd as induction treatment: RVd Induction and MEL200 conditioning followed by auto-HSCT and consolidation (Arm A) RVd Induction and Bu-Mel conditioning followed by auto-HSCT and consolidation (Arm B)	Randomized (1:1) to: RVd initial treatment[a] followed by len maintenance, without immediate HDM/auto-HSCT (Arm A) RVd Induction + HDM/auto-HSCT followed by RVd consolidation and len maintenance (Arm B)	Double randomization (1:1:1) Randomization for induction: VBMCP-VBAD/Bort (Arm A) TD (Arm B) VTD (Arm C) Randomization for maintenance: IFNα-2b (Group M1) Thal (Group M2) Thal/Bort (Group M3)	Randomized (1:1) to: VTD (Arm A) VCD (Arm B)
Primary Endpoint(s)	PFS after both conditioning regimens	PFS	RR (with a focus on CR) (post-induction) CR (post-transplant) DoR (maintenance)	VGPR rate post-induction
Dose, Route of Administration, and Schedule of RVd or VTD Initial Treatment				
Lenalidomide	25 mg/day PO D 1-21	25 mg/day PO, D 1-14	NA	NA
Bortezomib	1.3 mg/m^2 **Subcutaneous** Days 1, 4, 8, and 11	1.3 mg/m^2 **Intravenous** Days 1, 4, 8, and 11	1.3 mg/m^2 **Intravenous** Days 1, 4, 8, and 11	1.3 mg/m^2 **Subcutaneous** Days 1, 4, 8, and 11
Thalidomide	NA	NA	200 mg/day PO Days 1-28[b]	100 mg/day PO Days 1-21
Dexamethasone	40 mg/day PO Days 1-4 and 9-12	20 mg/day PO[c] Days 1, 2, 4, 5, 8, 9, 11, and 12	40 mg/day PO Days 1-4 and 9-12	40 mg/day PO Days 1-4 and 9-12
Planned Duration of RVd or VTD Initial Treatment				

Cycle Length (weeks)	4	3	4	3
Number of Cycles	6	Arm A: 8[a] Arm B: 3	6	4
Duration (weeks)	**24**	Arm A: **24[a]** Arm B: **9**	**24**	**12**
Enrollment Period	2013 to 2015	2010 to 2012	2006 to 2013	2013 to 2015

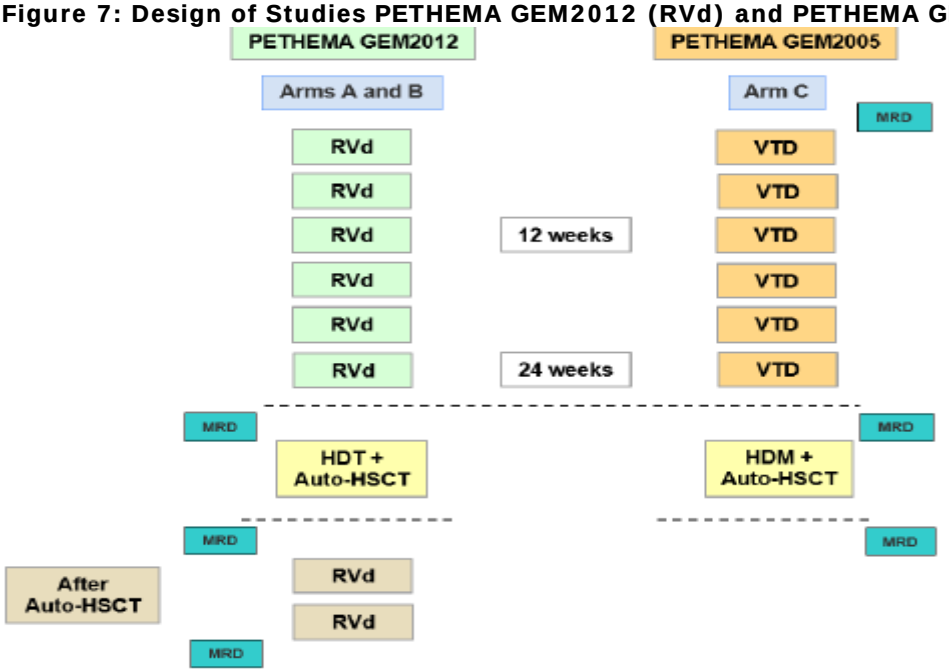
auto-HSCT = autologous hematopoietic stem cell transplantation; bort = bortezomib; Bu-Mel = busulfan with melphalan; CR = complete response; D = day; DoR = duration of response; HDM = high-dose melphalan; IFNα = interferon-α; MEL200 = melphalan 200 mg/m2 (Note: For the PETHEMA GEM2012 study, MEL200 = melphalan 100 mg/m2 on Days -3 and -2, or melphalan 200 mg/m2 on Day -2, relative to infusion of hematopoietic stem cells, according to each site's standard practice.); NA = not applicable; PFS = progression-free survival; PO = oral; RR = response rate; RVd = lenalidomide, bortezomib, and dexamethasone; TD = thalidomide and dexamethasone; thal = thalidomide; VBAD = vincristine, carmustine, doxorubicin, and dexamethasone; VBMCP = vincristine, carmustine, melphalan, cyclophosphamide, and prednisone; VCD = bortezomib, cyclophosphamide, and dexamethasone; VGPR = very good partial response; VTD = bortezomib, thalidomide, and dexamethasone.
a Subjects in Arm A of Study IFM 2009 received 8 cycles of initial therapy with RVd: 3 cycles of RVd "induction therapy" followed by 5 cycles of RVd "consolidation therapy." The same RVd dosing regimen was used for both, except for a reduced dose (10 mg) of dexamethasone during consolidation. For the purpose of comparison to the PETHEMA GEM2012 study, the 8 cycles (24 weeks) of initial RVd therapy for Arm A in the IFM 2009 study are referred to as "initial treatment."
b Escalating doses of thalidomide in Cycle 1 of the IFM 2013-04 study: 50 mg/day on Days 1 to 14 and 100 mg/day on Days 15 to 21.
c Reduced dose of dexamethasone (10 mg) during consolidation.

The efficacy analyses were based on RVd and VTD cohorts stratified based on propensity score (PS-stratified cohorts), except for the covariate-adjusted regression analyses. For propensity score estimation, a logistic regression model was used in which treatment group was regressed based on 11 identified baseline variables: age, sex, height, weight, performance status score, International Staging System (ISS) disease stage, hemoglobin, creatinine clearance (CrCl), albumin, β2-microglobulin, and lactate dehydrogenase (LDH).

- **PETHEMA studies**

The study designs of the 2 PETHEMA studies are provided in the figure below.

Figure 7: Design of Studies PETHEMA GEM2012 (RVd) and PETHEMA GEM2005 (VTD)



auto-HSCT = autologous hematopoietic stem cell transplantation; HDM = high-dose melphalan; HDT = high-dose therapy; MRD = minimal residual disease; RVd = lenalidomide, bortezomib, and dexamethasone; VTD = bortezomib, thalidomide, and dexamethasone.
Notes: 1) Each box represents one 4-week cycle of RVd or VTD.
2) Bortezomib was given subcutaneously in the PETHEMA GEM2012 study and intravenously in the PETHEMA GEM2005 study.
3) In the PETHEMA GEM2012 study, MRD was evaluated in subjects with immunofixation-negative complete response after each phase of treatment (induction, transplant, and consolidation).
4) In the PETHEMA GEM2005 study, bone marrow used for MRD was collected at screening, to confirm a complete response (a minimum of 4 weeks of post-induction chemotherapy and before transplant), and after approximately 3 months post-transplant (which was at pre-randomization for maintenance).

In the PETHEMA GEM2012 study, the PS-stratified cohort included 407 subjects who had received RVd. A total of 51 subjects from the ITT population (N = 458) were excluded from the RVd PS-stratified cohort due to missing data for one or more of the baseline variables used for propensity score calculation.

In the PETHEMA GEM2005 study, the PS-stratified cohort included 129 subjects who had received VTD. One subject from the ITT population (N = 130) was excluded from the VTD PS-stratified cohort due to missing data for the baseline variable of β2-microglobulin, which was used for propensity score calculation.

Table 29: Summary of Propensity Score Population – Studies PETHEMA GEM2012 and PETHEMA GEM2005 (ITT Population)

	RVd[a] (PETHEMA GEM2012) (N = 458) n (%)	VTD (PETHEMA GEM2005) (N = 130) n (%)
Number of Subjects With Baseline Variable Missing[a]	**51 (11.1)**	**1 (0.8)**
Creatinine clearance	18 (3.9)	0
Weight	18 (3.9)	0
Lactate dehydrogenase	17 (3.7)	0
Height	16 (3.5)	0
ISS stage	6 (1.3)	0
Albumin	4 (0.9)	0
β2-Microglobulin	4 (0.9)	1 (0.8)
Performance status (ECOG)	3 (0.7)	0

ECOG = Eastern Cooperative Oncology Group; ITT = intent to treat; RVd = lenalidomide, bortezomib, and dexamethasone; VTD = bortezomib, thalidomide, and dexamethasone.
a A subject may have had multiple missing parameters.
Data cutoff date = 31 Mar 2017 for the PETHEMA GEM2012 study. The database for the PETHEMA GEM2005 study was final in April 2015.

The response rate was defined as the primary efficacy endpoint. The Cochran-Mantel-Haenszel test, stratified on the stratum based on the quintiles of the propensity score, was used to estimate the difference of response rate and 95% CI of achieving a response with RVd versus VTD. For the post-initial treatment response rate of ≥ VGPR, the noninferiority of RVd versus VTD was assessed. The primary analysis for response rate was to be based on IRAC assessment; investigator assessment was used as a sensitivity analysis.

Minimal residual disease negativity defined at a sensitivity level of 10^{-4} in bone marrow was analyzed for RVd in the PETHEMA GEM2012 study versus VTD in the PETHEMA GEM2005 study. The Cochran-Mantel-Haenszel test, stratified on the stratum based on the quintiles of the propensity score, was used to estimate the difference of MRD negativity rate and the 95% CI.

An overview of myeloma response rate and MRD-negative status are presented below.

Table 30: Overview of Myeloma Response Rate (IRAC Review) and MRD-Negative Status (10-4 Sensitivity) Post-initial Treatment and Post-transplant – Studies PETHEMA GEM2012 and PETHEMA GEM2005 (PS-Stratified Cohorts)

	RVd[a] (PETHEMA GEM2012; 4-week cycles × 6 = 24 weeks) (N = 407)	VTD (PETHEMA GEM2005; 4-week cycles × 6 = 24 weeks) (N = 129)
Post-Initial Treatment		
Myeloma Response Post-initial Treatment[b]		
≥ VGPR, n (%)	270 (66.3)	66 (51.2)
PR, SD, PD, or NE[c], n (%)	137 (33.7)	63 (48.8)
Odds ratio (95% CI); p-value[d]	**1.87** (1.23, 2.83); 0.00281	
Response rate difference (%) (95% CI)[e]	**15.0** (5.0, 25.0)	
MRD-Negative Status Post-initial Treatment		
≥ VGPR[b] and MRD-negative rate, n (%)	171 (42.0)	34 (26.4)
Odds ratio (95% CI)	**1.49** (0.81, 2.76)	

Negativity rate difference (%) (95% CI)[e]	**8.6** (-5.5, 22.8)	
Post-Transplant		
Myeloma Response Post-transplant[f]		
≥ VGPR, n (%)	303 (74.4)	69 (53.5)
PR, SD, PD, or NE[c], n (%)	104 (25.6)	60 (46.5)
Odds ratio (95% CI)	**2.52** (1.64, 3.87)	
Response rate difference (%) (95% CI)[e]	**20.8** (11.0, 30.5)	
MRD-Negative Status Post-transplant		
≥ VGPR[f] and MRD-negative rate, n (%)	240 (59.0)	46 (35.7)
Odds ratio (95% CI)	**1.98** (0.93, 4.20)	
Negativity rate difference (%) (95% CI)[e]	**7.6** (-3.5, 18.8)	

CI = confidence interval; IRAC = Independent Response Adjudication Committee; MRD = minimal residual disease; NE = not evaluable; PD = progressive disease; PR = partial response; PS = propensity score; RVd = lenalidomide, bortezomib, and dexamethasone; SD = stable disease; VGPR = very good partial response; VTD = bortezomib, thalidomide, and dexamethasone.
a Both RVd arms combined.
b The last valid response assessment on or before the post-initial treatment visit.
c Including subjects who did not have any response assessment data, or whose response was not evaluable.
d Based on the Cochran-Mantel-Haenszel test stratified by the stratum based on the quintiles of the propensity score.
e Based on Cochran-Mantel-Haenszel common risk difference stratified by the stratum based on the quintiles of the propensity score (RVd versus VTD).
f Response at the post-transplant assessment.
Data cutoff date = 31 Mar 2017 for the PETHEMA GEM2012 study. The database for the PETHEMA GEM2005 study was final in April 2015.

For time-to-events endpoints, including PFS and OS, Kaplan-Meier methodology was used to provide descriptive statistics.

As of 31 Mar 2017, the median follow-up of PFS for all subjects in the RVd cohort was short (24.0 months) (IA Table 20). At that time, 87 (21.4%) PD (investigator review, EMA censoring rules) or death events had occurred in the RVd cohort; therefore, PFS events are considered immature. In the VTD cohort, the median follow-up for all subjects was 48.4 months, with 60.5% PFS events (investigator review, EMA censoring rules).

In this situation, the PFS event-free rate at 2 years (instead of median PFS), which mitigates the differences in median follow-up and number of events, is considered a more representative quantification of PFS comparison between the 2 cohorts. An estimated 82% of subjects in the RVd cohort and 69% of subjects in the VTD cohort did not have PD and remained alive at 2 years.

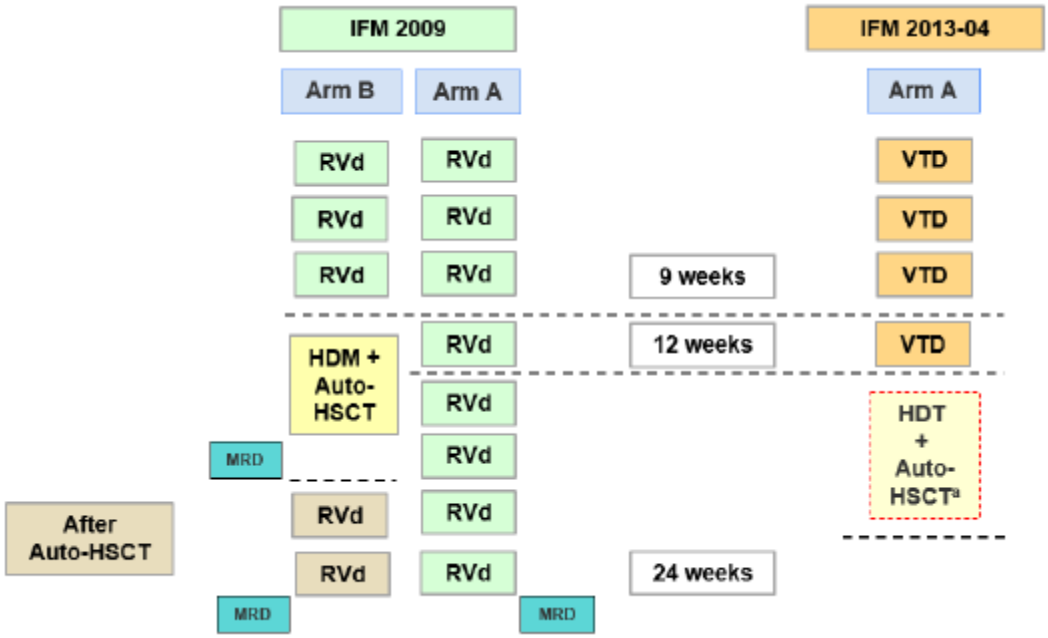
Regarding OS, as of 31 Mar 2017, the median follow-up for all surviving subjects in the RVd cohort was short (26.9 months). At that time, 45 (11.1%) deaths had occurred in the RVd cohort; therefore, OS events are considered immature. In the VTD cohort, the median follow-up for all subjects was 69.1 months, with 34.9% deaths.

An estimated 90% of subjects in the RVd cohort and 87% of subjects in the VTD cohort remained alive in this study at 2 years.

- **IFM studies**

The study designs of the two IFM studies are provided in the figure below.

Figure 8: Design of Studies IFM 2009 (RVd) and IFM 2013-04 (VTD)



auto-HSCT = autologous hematopoietic stem cell transplantation; HDM = high-dose melphalan; HDT = high-dose therapy; MRD = minimal residual disease; RVd = lenalidomide, bortezomib, and dexamethasone; VTD = bortezomib, thalidomide, and dexamethasone.
a Outside of the protocol.
Notes: 1) Each box represents one 3-week cycle of RVd or VTD.
2) Bortezomib was given intravenously in the IFM 2009 study and subcutaneously in the IFM 2013-04 study.
3) In the IFM 2009 study, bone marrow used for MRD was collected before or on Day 1 of RVd Cycle 4 (Arm B only), before or on Day 1 of maintenance, and after maintenance (= end of study treatment) or early discontinuation

In the IFM 2009 study, there were 2 RVd PS-stratified cohorts: the cohort for Arms A + B included 661 subjects. A total of 39 subjects from the ITT population (N = 700) were excluded from the RVd PS-stratified cohort for Arms A + B, and 19 subjects from the ITT population (N = 350) were excluded from the RVd PS-stratified cohort for Arm A.

In the IFM 2013-04 study, the PS-stratified cohort included 154 subjects who had received VTD. A total of 15 subjects from the ITT population (N = 169) were excluded from the PS-stratified cohort.

Table 31: Summary of Propensity Score Population – Studies IFM 2009 and IFM 2013-04 (ITT Population)

	RVd (IFM 2009) Arms A + B (N = 700)	RVd (IFM 2009) Arm A (N = 350)	VTD (IFM 2013-04) (N = 169)
Number of Subjects With Baseline Variable Missing[a]	**39 (5.6)**	**19 (5.4)**	**15 (8.9)**
Lactate dehydrogenase	39 (5.6)	19 (5.4)	11 (6.5)
Height	0	0	2 (1.2)
Performance status (ECOG)	0	0	2 (1.2)

ECOG = Eastern Cooperative Oncology Group; ITT = intent to treat; RVd = lenalidomide, bortezomib, and dexamethasone; VTD = bortezomib, thalidomide, and dexamethasone.
a A subject may have had multiple missing parameters.
Data cutoff date = 01 Dec 2016 for the IFM 2009 study and 01 Mar 2016 for the IFM 2013-04 study.

For the IFM studies, the IRAC was not able to assess response following strict IMWG criteria due to the inconsistent availability of urine protein electrophoresis (UPEP) results. Therefore, central review was used as the primary comparison of RVd versus VTD efficacy data for the IFM studies. The central review of disease

response post-transplant was not conducted for the IFM 2013-04 study, and thus, a comparison of the RVd and VTD PS stratified cohorts was not possible for the IFM studies.

The results of post-initial treatment response rate (based on central review) are presented below.

Table 32: Post-initial Treatment Response Rate (Central Review) of at Least VGPR – Primary Analysis – Studies IFM 2009 and IFM 2013-04 (PS-Stratified Cohorts)

	RVd[a] (IFM 2009)			VTD (IFM 2013-04)
	Arms A + B (3-week cycles × 3 = 9 weeks) (N = 661)	Arm A (3-week cycles × 4 = 12 weeks) (N = 331)	Arm A (3-week cycles × 8 = 24 weeks) (N = 331)	(3-week cycles × 4 = 12 weeks) (N = 154)
Dichotomized Response[b]				
≥ VGPR, n (%)	359 (54.3)	189 (57.1)	224 (67.7)	87 (56.5)
CR	33 (5.0)	25 (7.6)	101 (30.5)	18 (11.7)
VGPR	326 (49.3)	164 (49.5)	123 (37.2)	69 (44.8)
PR, SD, PD, or NE[c], n (%)	302 (45.7)	142 (42.9)	107 (32.3)	67 (43.5)
Comparison:	**Odds Ratio (2-Sided 95% CI)**		**Response Rate Difference (%) (2-Sided 95% CI)**	
RVd (9 weeks) vs VTD	**0.96** (0.66, 1.38)		**-1.3** (-10.2, 7.7)	
RVd (12 weeks) vs VTD	**1.06** (0.71, 1.59)		**1.4** (-8.5, 11.2)	
RVd (24 weeks) vs VTD	**1.65** (1.09, 2.49)		**11.7** (2.1, 21.4)	

CI = confidence interval; CR = complete response; NE = not evaluable; PD = progressive disease; PR = partial response; PS = propensity score; RVd = lenalidomide, bortezomib, and dexamethasone; SD = stable disease; VGPR = very good partial response; vs = versus; VTD = bortezomib, thalidomide, and dexamethasone.
a Initial treatment (induction) for the IFM 2009 study can be considered as the protocol-specified induction of 3 cycles OR the 8 cycles (3 cycles of induction + 5 cycles of consolidation) for Arm A. The 4 cycles (12 weeks) for Arm A are included for comparison to the VTD arm in the IFM 2013-04 study.
b The last valid response assessment on or before the post-initial treatment visit.
c Including subjects who did not have any response assessment data, or whose response was not evaluable.
Data cutoff date = 01 Dec 2016 for the IFM 2009 study and 01 Mar 2016 for the IFM 2013-04 study.

The post-initial treatment and post-transplant MRD were not assessed by the applicant in the IFM 2013-04 study, and thus a comparison of the RVd and VTD PS-stratified cohorts was not possible for the IFM studies.

Regarding the exploratory endpoints:

- Progression-free Survival

As of 1 Dec 2016, the median follow-up for all subjects in the RVd cohort (IFM 2009 Arm B) was 43.9 months, with 59.4% PFS events (investigator review, EMA censoring rules). As of 01 Mar 2016, the median follow-up for all subjects in the VTD cohort (IFM 2013-04) was short (16.6 months). At that time, 26 (16.9%) PFS events (investigator review, EMA censoring rules) had occurred in the VTD cohort; therefore, PFS events are considered immature. An estimated 78% of subjects in the RVd cohort (IFM 2009 Arm B) and 71% of subjects in the VTD cohort did not have PD and remained alive in this study at 2 years.

- Overall Survival

As of 1 Dec 2016, the median follow-up for all surviving subjects in the RVd cohort (IFM 2009 Arm B) was 56.9 months, with 23.3% deaths. As of 01 Mar 2016, the median follow-up for all surviving subjects in the VTD cohort (IFM 2013-04) was short (17.6 months). At that time, 8 (5.2%) deaths had occurred in the VTD cohort; therefore, OS events are considered immature. An estimated 90% of subjects in the RVd cohort (IFM 2009 Arm B) and 93% of subjects in the VTD cohort remained alive in this study at 2 years.

2.4.3. Discussion on clinical efficacy

Design and conduct of clinical studies

Three studies were submitted to support the claimed indication in patients with newly diagnosed multiple myeloma (NDMM).

The SWOG S0777 study evaluated RVd (lenalidomide, bortezomib and dexamethasone) versus Rd (lenalidomide and dexamethasone) for initial treatment in subjects with previously untreated MM not intended to undergo immediate auto-HSCT. Data from 2 other studies conducted in Europe (PETHEMA GEM2012, and IFM 2009) and an integrated analysis comparing an initial treatment regimen of RVd (PETHEMA GEM2012 and IFM 2009) versus bortezomib, thalidomide and dexamethasone (i.e. VTD) (PETHEMA GEM2005 and IFM 2013-04) were submitted to support the treatment of TE patients with NDMM. The data provided come from published investigational studies with different designs, populations, methods for assessment, censoring rules and statistical analysis plans.

Main study - SWOG S0777

The SWOG S0777 was a Phase 3, randomized, active-controlled, open-label, multicentre study that was conducted in the US in 523 subjects (age ≥ 18 years) with NDMM. The study compared the new proposed regimen RVd triplet (eight 3-week cycles) versus the approved regimen Rd doublet (six 4-week cycles) as initial treatment (24 weeks) of subjects not intended to undergo immediate auto-HSCT.

The study was performed in NDMM patients TNE, i.e. aged over 65 years or aged under 65 and with no possibility to undergo auto-HSCT, with a stratification by ISS stage and intent to transplant at progression. The study was open-label, which is considered acceptable given the known safety profile of IV route of administration for bortezomib. The inclusion criteria were in accordance with the IMWG criterion to define active MM, which have remained similar since the beginning of the study. The baseline characteristics were well-balanced between the treatment groups, except for the cytogenetic risk, the frailty and the age: patients in RVd arm seemed to be in a better condition at screening than patients in the Rd arm. However, the slight numeric differences in cytogenetic risk, frailty, and age between the two treatment arms were not considered clinically meaningful.

One of the proposed regimen scheme for RVd for this new indication consists in 21-day cycles with lenalidomide at 25mg on day 1-14, bortezomib at 1,3mg/m² on day 1, 4, 8 and 11 and dexamethasone at 20mg on day 1, 2, 4, 5, 8, 9, 11 and 12. The 21-day cycles schedule has already been used in previous phase II clinical trials (Richardson, 2010; Roussel, 2010), but 28-day cycles schedule is the current approved posology for Revlimid. Exposure for lenalidomide on initial treatment (24 weeks) was comparable for both schedules (2800mg for 21-day cycles / 3150mg for 28-day cycles). During RVd 21-day cycles of induction, patients received 41,6mg/m² of bortezomib, which is consistent with the approved bortezomib posology in MM described in the relevant SmPC.

The primary objective of the SWOG S0777 study was to compare the PFS in subjects with NDMM who received initial treatment with RVd versus Rd. The choice of PFS as primary endpoint was considered acceptable according to EMA guidelines (EMA/CHMP/205/95) and recommendations for the evaluation of efficacy of therapeutic strategies in multiple myeloma. The secondary objectives of the study focused on the overall survival and the response rate of the disease to treatment, which were also considered relevant.

Supportive study - PETHEMA GEM2012

The PETHEMA GEM2012 was a Phase 3, randomized, controlled, open-label, multicenter, national study conducted in Spain in 458 subjects (aged 18 to 65 years) with TE NDMM. Inclusion criteria and baseline characteristics of the subjects included in the study reflected the aimed population of TE patients, who should be young (< 65 years old) and not frail to undergo auto-HSCT.

The second proposed regimen scheme for RVd for this new indication consists in 28-day cycles with lenalidomide at 25mg on day 1-21, bortezomib at 1,3mg/m² on day 1, 4, 8 and 11 and dexamethasone at 40mg on day 1-4 and 8-11. All subjects in the study received RVd as induction treatment followed by 1 of 2 pretransplant conditioning regimens (busulfan with melphalan [Bu-Mel] or MEL20012), then underwent auto-HSCT. After auto-HSCT, subjects were to receive two more 28-day cycles of RVd as consolidation.

The primary objective of the study was to compare PFS after auto-HSCT with the 2 pre transplant conditioning regimens in subjects who had received prior RVd induction treatment. As the study was not designed to compare RVd regimen with the approved standard of care for induction in transplant-eligible patients (VD or VTD), but to compare two pre transplant conditioning regimen after a similar induction by RVd, the results presented would not allow to conclude on the efficacy of Revlimid in the claimed indication for TE NDMM patients.

Supportive study - IFM 2009

The IFM 2009 was a Phase 3, randomized, controlled, open-label, multicenter study conducted in France, Belgium, and Switzerland in 700 subjects (aged 18 to 65 years) with TE NDMM. The study compared the RVd regimen as initial treatment with or without auto-HSCT in the management of TE NDMM.

The primary objective of the study was to compare PFS in subjects who received initial RVd treatment with and without auto-HSCT. Similarly to PETHEMA GEM2012, the study was not designed to compare RVd regimen with the approved standard of care for induction in transplant-eligible patients (VD or VTD), but to compare two therapeutic strategies using RVd as initial regimen treatment. The results presented didn't allow to conclude on the efficacy of Revlimid in the claimed indication for TE NDMM patients.

Integrated analysis

The integrated analysis was based on the individual subject data from 4 identified randomized controlled trials (RCTs).

The objective of the integrated analysis was to compare the efficacy and safety of RVd versus the regulatory-authorized standard of care, VTD. Efficacy was to be based on the assessment of myeloma response by IRAC. The primary objective was to demonstrate noninferiority of the primary endpoint: post-initial treatment response rate (as measured by ≥ VGPR based on IMWG criteria) in TE NDMM subjects receiving RVd or VTD induction regimens.

To support the indication for RVd in TE NDMM patients, the absence of a prospective comparative randomized clinical trial of RVd against one of the standard of care (VD or VTD) remains an issue.

The 2 studies conducted by the PETHEMA Foundation, PETHEMA GEM2012 (RVd) and PETHEMA GEM2005 (VTD), were identified as the main studies for the integrated efficacy and safety analyses based on their symmetrical design of the induction regimens, including number, length, and duration of induction cycles (six 4-week cycles of induction), for a total of 24 weeks of induction (initial) therapy followed by auto-HSCT. The 2 studies conducted by the IFM, IFM 2009 (RVd) and IFM 2013-04 (VTD), are considered supportive studies for the integrated efficacy and safety analyses because the differences in the number of cycles for the RVd and VTD induction regimens used limit the potential to make a direct and easy comparison.

Cohorts with patients from study PETHEMA GEM2012 (Arm A + B) and study PETHEMA GEM2005 (Arm C) were stratified based on propensity score. This process cannot totally mimic the randomization process to re-create two comparable treatment arms. Potential treatment effects that can be observed in this integrated analysis may be related to unselected baseline variables or hidden variables that the propensity score could not account for.

The designs of both PETHEMA studies were similar for induction and auto-HSCT. In the PETHEMA GEM2012 there were 2 cycles of RVd as consolidation after transplant.

Efficacy data and additional analyses

Main study - SWOG S0777

The study reached its primary objective to demonstrate superiority of RVd on Rd. At the time of the 1 December 2016 data cut-off date, the median PFS was 41.7 months in the RVd arm compared to 29.7 months in the Rd arm (HR=0.76; 95% CI: 0.62 to 0.94; P=0.010) as determined by IRAC review and applying EMA censoring rules.

Overall, results from sensitivity analysis (different data cut-offs, investigator, IRAC or Central review assessment, EMA/FDA/SWOG censoring rules) were consistent with those observed in the primary analysis.

The secondary objectives were reached as OS was superior in RVd arm versus Rd, with an improvement of 21.9 months (89,1 vs 67,2), which is statistically and clinically relevant. These results could be considered as sufficiently mature (>50% events in control arm). A negative effect of RVd on OS could reasonably be ruled out. At post-initial treatment, for RVd, 58, 2% subjects obtained ≥ VGPR and for Rd, 31,9% subjects obtained ≥ VGPR. These results are consistent with the primary endpoints results.

For subgroups analyses PFS was better in RVd arms vs Rd arms, whether patients were at intention to undergo transplant or not at randomization. Overall, it appears that respectively 79 subjects in the RVd arm and 91 subjects in the Rd arm effectively underwent stem cell transplantation. Among patients who were categorized as TNE, only 19% (48/261) receiving ASCT. Patients appear to have been well categorized. Among transplanted patients (prior or after progression disease), difference in OS are not statistically significant between RVd and RD treatment (HR= 0.75; IC (0.47; 1.22). This is similar (HR= 0.65 IC: 0.31; 1.33) when analysed only for patients who undergo transplant before PD.

Supportive study - PETHEMA GEM2012

The study failed to demonstrate its primary objective as data were not mature with the chosen cut-off date (31 Mar 2017) to get enough events to reach PFS median. A total of 102 (22.3%) events of PD or death (both arms combined) had occurred, which is approximately one third of the 294 total events needed for the final analysis of PFS.

Regarding the secondary endpoints the OS results weren't mature. A 36 months 83% OS in RVd arm was found in SWOG S0777 study which is consistent with the results presented in PETHEMA GEM2012 study: 84,2 % and 80,2 % for each arm. Post-induction, 24 weeks of RVd (both arms combined) leads to 66, 6% of ≥ VGPR (33, 4% CR). To compare, in SWOG S0777 study, 58, 2% subjects obtained ≥VGPR (5,3% CR).

Supportive study - IFM 2009

The study reached its primary objective as the median PFS was estimated at 35.0 months in the RVd arm and 45.8 months in the RVd + auto-HSCT arm. These results are not informative for the current application but a focus was made on the results of the RVd arm. The PFS was found 42, 5 months in SWOG S0777 study with a slightly older and frailer population. Posology for lenalidomide maintenance differs between the studies as for SWOG S0777 they chose a 25mg/d 21d/28 schedule with 40mg/d 1d/week dexamethasone whereas for IFM it was a 10 or 15mg/d continuous monotherapy of lenalidomide. Also, IFM 2009 integrated an European population of subjects and seemed to get lower results than those obtained in the SWOG S0777 study with an American population.

For secondary objectives, median OS time at the time of the 01 Dec 2016 data cut off was not reached in either treatment arms. By IRAC assessment, after 24 weeks of RVd, 68,3% subjects obtained ≥ VGPR (18,6% CR).

Integrated analysis

The applicant advanced in this integrated analysis the non-inferiority of RVd regimen upon VTD regimen, based on the myeloma response rate: 66,3% ≥ VGPR post-induction against 51,2%.

The respectively 74,4% vs 53,5% rates post-transplant are supportive, but the strategies were different at this point (2 cycles of RVd after auto HSCT vs no treatment) and no conclusions can be drawn from these results. The MRD negativity rate post induction difference was 8,6% which supports the non-inferiority of RVd on VTD.

In conclusion, for the transplant-eligible population, the design of the supportive studies and the interpretation of the results of the integrated analysis did not allow to conclude on the superiority or non-inferiority in clinical efficacy of the RVd regimen compared to the approved standard of care. Since no new data and no detailed outcomes of transplantation were provided with RVd compared to the standard of care, the cross-study comparison as presented by the MAH was insufficient to convincingly establish efficacy. Therefore the CHMP concluded that the indication should be restricted to adult patients with previously untreated multiple myeloma who are not eligible for transplant. Since the indication for adult patients with previously untreated multiple myeloma who are not eligible for transplant was already approved for Revlimid in combination treatment based on the data using the combinations dexamethasone or melphalan with prednisone the CHMP considered that the final indication should be read as follows:

Revlimid as combination therapy with dexamethasone, or bortezomib and dexamethasone, or melphalan and prednisone (see section 4.2) is indicated for the treatment of adult patients with previously untreated multiple myeloma who are not eligible for transplant. This indication covers the previously approved combinations (dexamethasone and melphalan with prednisone) and the new applied combination (with bortezomib and dexamethasone).

2.4.4. Conclusions on the clinical efficacy

The clinical efficacy of the triplet regimen lenalidomide + bortezomib + dexamethasone in newly diagnosed multiple myeloma patients has been demonstrated in transplant non-eligible patients with NDMM as indicated by the improvement of PFS in study SWOG S0777.

2.5. Clinical safety

Introduction

The safety analysis provided by the applicant focused on 24 weeks of RVd initial treatment for the safety populations of the following studies: SWOG S0777 (RVd and Rd arms), PETHEMA GEM2012 (both RVd arms combined), and IFM 2009 Arm A (RVd no transplant). A total of 1076 subjects were included in the safety population to assess the safety profile of RVd as initial treatment: SWOG S0777 (262 subjects), PETHEMA GEM2012 (458 subjects), and IFM 2009 (356 subjects). RVd dosing regimens in these studies were either six 28-day cycles or eight 21-day cycles. The data cut-off dates are 31 March 2017 for the PETHEMA GEM2012 study and 1 December 2016 for the IFM 2009 and SWOG S0777 studies.

The safety population includes all subjects who were randomized and received at least one dose of study drug. If a subject received study drug other than the subject's randomized treatment assignment, then the subject was assigned to the treatment arm reflecting the treatment that the subject actually received during the study. The integrated analysis using data from 2 PETHEMA and 2 IFM studies was provided to support the safety of RVd in comparison to VTD.

Patient exposure

The duration of initial treatment is summarized by study in the table below.

Table 33: Duration of Initial Treatment – Studies PETHEMA GEM2012, IFM 2009 Arm A), and SWOG S0777 (Safety Population)

	PETHEMA GEM2012	IFM 2009	SWOG S0777	
	RVd[a] (4-week cycles × 6 = 24 weeks) (N = 458) n (%)	RVd[b] (3-week cycles × 8 = 24 weeks) (N = 356) n (%)	RVd (3-week cycles × 8 = 24 weeks) (N = 262) n (%)	Rd (4-week cycles × 6 = 24 weeks) (N = 256) n (%)
Treatment Duration (weeks)				
Median	27.0	24.1	24.0	24.1
Minimum, maximum	0.6, 60.0	3.0, 36.0	0.4, 36.6	1.3, 35.1

Rd = lenalidomide and dexamethasone; RVd = lenalidomide, bortezomib, and dexamethasone.
a Both RVd arms combined. For the PETHEMA GEM2012 study.
b For the purpose of comparison to the PETHEMA GEM2012 and SWOG S0777 studies, the 8 cycles (24 weeks) of initial RVd therapy for Arm A in the IFM 2009 study are referred to as "initial treatment."
Data cutoff date = 31 Mar 2017 for the PETHEMA GEM2012 study and 01 Dec 2016 for the IFM 2009 and SWOG S0777 studies.

Adverse events

Table 34: Collection of Safety Information and Protocol-specified AE Reporting – RVd Studies PETHEMA GEM2012, IFM 2009 and SWOG S0777

	PETHEMA GEM2012	IFM 2009	SWOG S0777
Frequency of Collection of AEs	Upon occurrence	Upon occurrence	Every 3 months
AE Start Date	Yes; starting cycle also collected: 3. Cycles 1 to 6 4. Transplant 5. Consolidation	Yes	No. Imputed from start date of 3-month reporting period
AE Stop Date	Yes	Yes	No
AE Reporting Period	From signing of ICF to 30 days after the final study procedure; AEs will continue to be recorded until the AE resolves or medical opinion considers the AE to be clinically stable.	From signing of ICF to 30 days after the last study treatment administration (60 days for patients who withdraw from treatment during RVd cycles)	From signing ICF to 14 days after completion of initial treatment and completion of continued Rd therapy.
SAE Reporting Period	From signing of ICF to 30 days after the final study procedure	From signing of ICF to 30 days following the last study treatment administration (60 days for patients who withdraw from treatment during RVd cycles); SPM reported until 3 years after last patient randomized under Protocol Version 4 (will be extended to 4 more years with next protocol amendment)	From signing of ICF to 30 days after the last dose of treatment

AE Terms Recorded	CRF has 17 preprinted terms; site to complete only if related to study medication (non-serious AEs only): 3. Peripheral Neuropathy 4. Neuropathic Pain 5. Hypotension 6. DVT 7. PE 8. Other Thrombosis 9. Asthenia 10. Diarrhea 11. Constipation 12. Cutaneous 13. Infection 14. Arrhythmia 15. Other Affected Organ (site to complete additional information in the comments section of CRF) 16. Anemia 17. Leukopenia 18. Neutropenia 19. Thrombocytopenia	CRF has drop-down list of terms available (including "other," which is used to report SPMs).[a]	CRF has 80 preprinted CTCAE terms as well a free text field to record any other AEs
Severity Grades of AEs Collected	CTCAE Version 4.0, Grades 1 to 5	CTCAE Version 4.0, Grades 1 to 5 (> Grade 2 for haematologic toxicity or if action taken with study drug)	CTCAE Version 4.0, Grades 1 to 5
Relationship of AE to Study Treatment	Sites instructed to only report non-serious AEs which were related to study treatment; must assume all reported non-serious AEs are related.	Yes	Yes
Action(s) Taken Due to AEs Recorded	Yes	Yes	No
Comments	Yes	No	Yes

AE = adverse event; CRF = case report form; CTCAE = Common Terminology Criteria for Adverse Events; DVT = deep vein thrombosis; ICF = informed consent form; MedDRA = Medical Dictionary for Regulatory Activities; PE = pulmonary embolism; SAE = serious adverse event; RVd = lenalidomide, bortezomib, and dexamethasone; SPM = second primary malignancy; VTD = bortezomib, thalidomide, and dexamethasone.

a Verbatim terms are recorded in French, and then coded to French MedDRA preferred terms; the French MedDRA preferred terms are then converted to English MedDRA preferred terms.

b The NCI CTCAE Version 3.0 criteria are used in 2 AE datasets (source = nonhaematologic toxicity CRF), but no CTCAE version was provided for the other 2 AE datasets (AE, infections).

Notes: For all 3 studies, treatment-emergent adverse events in each treatment phase were defined as any AEs that began on or after the start of study drug in that phase through the day before the start date of the next phase, or through 30 days after the last dose of study drug if the phase was the last phase in the study. A subject with multiple occurrences of a TEAE was counted only once in that TEAE category.

An overview of the treatment-emergent adverse events (TEAEs) during initial treatment for the 3 studies is presented below.

Table 35 : Overview of TEAEs – Initial Treatment – Studies PETHEMA GEM2012, IFM 2009 (Arm A), and SWOG S0777 (Safety Population)

Subjects With ≥ 1:	**PETHEMA GEM2012**	**IFM 2009**	**SWOG S0777**	
	RVd[a] (4-week cycles × 6 = 24 weeks) (N = 458) n (%)	**RVd[b] (3-week cycles × 8 = 24 weeks) (N = 356) n (%)**	**RVd (3-week cycles × 8 = 24 weeks) (N = 262) n (%)**	**Rd (4-week cycles × 6 = 24 weeks) (N = 256) n (%)**
TEAE	402 (87.8)	354 (99.4)	255 (97.3)	245 (95.7)
Grade 3 or 4 TEAE[c]	183 (40.0)	306 (86.0)	200 (76.3)	176 (68.8)
Grade 5 TEAE[c]	9 (2.0)	1 (0.3)	6 (2.3)	3 (1.2)
Treatment-emergent SAE	147 (32.1)	108 (30.3)	105 (40.1)	73 (28.5)
Treatment Discontinuation Due to TEAE[d]	14 (3.1)	30 (8.4)	60 (22.9)	24 (9.4)

CTCAE = Common Terminology Criteria for Adverse Events; Rd = lenalidomide and dexamethasone; RVd = lenalidomide, bortezomib, and dexamethasone; SAE = serious adverse event; TEAE = treatment-emergent adverse event.
a Both RVd arms combined. For the PETHEMA GEM2012 study, TEAEs include all SAEs plus non-SAEs that the investigator considered related to study treatment.
b For the purpose of comparison to the PETHEMA GEM2012 and SWOG S0777 studies, the 8 cycles (24 weeks) of initial RVd therapy for Arm A in the IFM 2009 study are referred to as "initial treatment."
c Graded using CTCAE Version 4.03 for the PETHEMA GEM2012 study and Version 4.0 for the IFM 2009 and SWOG S0777 studies.
d "Discontinuation" refers to study discontinuation for the PETHEMA GEM2012 study and treatment discontinuation for the IFM 2009 and SWOG S0777 studies. The TEAEs leading to treatment discontinuation were recorded on the Off Treatment Notice Form for the SWOG S0777 study.
Notes: Treatment-emergent adverse events in each treatment phase were defined as any AEs that began on or after the start of study drug in that phase through the day before the start date of the next phase, or through 30 days after the last dose of study drug if the phase was the last phase in the study. A subject with multiple occurrences of a TEAE was counted only once in that TEAE category.

The summaries of TEAEs over entire treatment period are presented below for the 3 studies.

Table 36: Overview of Treatment-emergent Adverse Events During Initial Treatment + Continued Rd by Treatment Arm as of 01 Dec 2016 (Study SWOG S0777, Safety Population)

Subjects With at Least One:	RVd (N = 262) n (%)	Rd (N = 256) n (%)
TEAE	255 (97.3)	250 (97.7)
TEAE related to study drug[a]	251 (95.8)	245 (95.7)
Treatment-emergent SAE	133 (50.8)	111 (43.4)
Grade 3 or 4[b] TEAE	222 (84.7)	212 (82.8)
Grade 3 or 4[b] TEAE related to study drug [a]	210 (80.2)	190 (74.2)
Grade 5[b] TEAE	10 (3.8)	7 (2.7)
Treatment discontinuation due to TEAEs[c]	97 (37.0)	64 (25.0)

CTCAE = Common Terminology Criteria for Adverse Events; Rd = lenalidomide and dexamethasone;
RVd = lenalidomide, bortezomib, and dexamethasone; SAE = serious adverse event; TEAE = treatment-emergent adverse event.
a Definition of related: possibly, probably, or definitely related to study drug as deemed by the investigator.
b Graded using CTCAE Version 4.0.
c The AEs leading to treatment discontinuation were recorded on the Off Treatment Form.
Note: Treatment-emergent adverse events include adverse events that started between the date of the first dose and 30 days after the date of the last dose. A subject with multiple occurrences of a TEAE was counted only once in that TEAE category.

The overviews of TEAEs for initial treatment from the integrated analysis (RVd vs VTD) are presented below for PETHEMA studies and IFM studies.

Table 37: Overview of TEAEs – Initial Treatment – Studies PETHEMA GEM2012 and PETHEMA GEM2005 (Safety Population)

Subjects With ≥ 1:	RVd[a] (PETHEMA GEM2012; 4-week cycles × 6 = 24 weeks) (N = 458) n (%)	VTD (PETHEMA GEM2005; 4-week cycles × 6 = 24 weeks) (N = 130) n (%)
TEAE	402 (87.8)	115 (88.5)
Grade 3 or 4 TEAE[b]	183 (40.0)	56 (43.1)
Grade 5 TEAE[b]	9 (2.0)	Not collected
Treatment-emergent SAE	147 (32.1)	37 (28.5)
TEAE Leading to Dose Reduction[c]	99 (21.6)	46 (35.4)
TEAE Leading to Study or Treatment Discontinuation[d]	14 (3.1)	12 (9.2)

CTCAE = Common Terminology Criteria for Adverse Events; RVd = lenalidomide, bortezomib, and dexamethasone; SAE = serious adverse event; TEAE = treatment-emergent adverse event; VTD = bortezomib, thalidomide, and dexamethasone.
a Both RVd arms combined. For the PETHEMA GEM2012 study, TEAEs include all SAEs plus non-SAEs that the investigator considered related to study treatment.
b Graded using CTCAE Version 4.03 for the PETHEMA GEM2012 study and Version 3.0 for the PETHEMA GEM2005 study.
c Dose reduction is referred to as dose adjustment in the PETHEMA GEM2005 study.
d Study discontinuation for PETHEMA GEM2012 and treatment discontinuation for PETHEMA GEM2005.
Notes: Treatment-emergent adverse events in each treatment phase were defined as any adverse events that that began on or after the start of study drug in that phase through the day before the start date of the next phase, or through 30 days after the last dose of study drug if the phase was the last phase in the study. A subject with multiple occurrences of a TEAE was counted only once in that TEAE category.

The frequencies of subjects with TEAEs (any grade) reported in ≥ 20% of subjects in any treatment arm by study and by System Organ Class (SOC) for the studies SWOG S0777, PETHEMA GEM 2012 and IFM2009 are presented in the tables below.

Table 38: TEAEs (Any Grade) Reported in at Least 20% of Subjects in Any Treatment Arm – Initial Treatment – Studies PETHEMA GEM2012, IFM 2009 (Arm A), and SWOG S0777 (Safety Population)

System Organ Class Preferred Term[a]	PETHEMA GEM2012	IFM 2009	SWOG S0777	
	RVd[b] (4-week cycles × 6 = 24 weeks) (N = 458) n (%)	RVd[c] (3-week cycles × 8 = 24 weeks) (N = 356) n (%)	RVd (3-week cycles × 8 = 24 weeks) (N = 262) n (%)	Rd (4-week cycles × 6 = 24 weeks) (N = 256) n (%)
Subjects With ≥ 1 TEAE	402 (87.8)	354 (99.4)	255 (97.3)	245 (95.7)
Blood and Lymphatic System Disorders	**229 (50.0)**	**276 (77.5)**	**208 (79.4)**	**203 (79.3)**
Neutropenia	146 (31.9)	163 (45.8)	77 (29.4)	99 (38.7)
Thrombocytopenia	116 (25.3)	71 (19.9)	151 (57.6)	117 (45.7)
Anemia	69 (15.1)	62 (17.4)	179 (68.3)	175 (68.4)
Leukopenia	41 (9.0)	128 (36.0)	109 (41.6)	126 (49.2)
Lymphopenia	21 (4.6)	186 (52.2)	67 (25.6)	62 (24.2)
Nervous System Disorders	**192 (41.9)**	**290 (81.5)**	**219 (83.6)**	**145 (56.6)**
Neuropathy peripheral	160 (34.9)	16 (4.5)	2 (0.8)	0
Dizziness	7 (1.5)	18 (5.1)	76 (29.0)	41 (16.0)
Paresthesia	5 (1.1)	80 (22.5)	3 (1.1)	2 (0.8)
Dysgeusia	0	13 (3.7)	79 (30.2)	48 (18.8)
Peripheral sensory neuropathy	0	186 (52.2)	184 (70.2)	85 (33.2)
Infections and Infestations	**129 (28.2)**	**188 (52.8)**	**92 (35.1)**	**74 (28.9)**
Infection	129 (28.2)	5 (1.4)	3 (1.1)	1 (0.4)
Gastrointestinal Disorders	**125 (27.3)**	**273 (76.7)**	**211 (80.5)**	**166 (64.8)**
Diarrhea	59 (12.9)	120 (33.7)	104 (39.7)	79 (30.9)
Constipation	55 (12.0)	136 (38.2)	147 (56.1)	115 (44.9)
Nausea	13 (2.8)	109 (30.6)	98 (37.4)	69 (27.0)
General Disorders and Administration Site Conditions	**102 (22.3)**	**258 (72.5)**	**221 (84.4)**	**191 (74.6)**
Pyrexia	21 (4.6)	72 (20.2)	37 (14.1)	22 (8.6)
Edema peripheral	15 (3.3)	90 (25.3)	122 (46.6)	65 (25.4)
Edema	2 (0.4)	4 (1.1)	0	0
Fatigue	0	154 (43.3)	193 (73.7)	167 (65.2)
Respiratory, Thoracic, and Mediastinal Disorders	**68 (14.8)**	**115 (32.3)**	**150 (57.3)**	**117 (45.7)**
Cough	3 (0.7)	43 (12.1)	77 (29.4)	51 (19.9)
Dyspnea	1 (0.2)	34 (9.6)	80 (30.5)	65 (25.4)
Musculoskeletal and Connective Tissue Disorders	**23 (5.0)**	**195 (54.8)**	**185 (70.6)**	**166 (64.8)**
Back pain	4 (0.9)	68 (19.1)	87 (33.2)	71 (27.7)
Muscular weakness	1 (0.2)	4 (1.1)	64 (24.4)	45 (17.6)
Skin and Subcutaneous Tissue Disorders	**21 (4.6)**	**172 (48.3)**	**113 (43.1)**	**104 (40.6)**
Rash	4 (0.9)	78 (21.9)	49 (18.7)	52 (20.3)
Psychiatric Disorders	**18 (3.9)**	**126 (35.4)**	**113 (43.1)**	**110 (43.0)**
Insomnia	0	86 (24.2)	86 (32.8)	74 (28.9)
Metabolism and Nutrition Disorders	**19 (4.1)**	**61 (17.1)**	**201 (76.7)**	**202 (78.9)**
Hyperglycemia	11 (2.4)	8 (2.2)	127 (48.5)	142 (55.5)
Decreased appetite	2 (0.4)	16 (4.5)	90 (34.4)	59 (23.0)
Hyponatremia	2 (0.4)	4 (1.1)	80 (30.5)	65 (25.4)
Hypokalemia	1 (0.2)	14 (3.9)	76 (29.0)	53 (20.7)
Hypoalbuminemia	0	1 (0.3)	78 (29.8)	67 (26.2)
Hypocalcemia	0	9 (2.5)	131 (50.0)	111 (43.4)
Investigations	**28 (6.1)**	**37 (10.4)**	**163 (62.2)**	**144 (56.3)**
ALT increased	7 (1.5)	7 (2.0)	67 (25.6)	49 (19.1)

Blood creatinine increased	2 (0.4)	2 (0.6)	48 (18.3)	64 (25.0)
Blood alkaline phosphatase increased	1 (0.2)	2 (0.6)	66 (25.2)	48 (18.8)
AST increased	1 (0.2)	4 (1.1)	56 (21.4)	38 (14.8)
Weight decreased	1 (0.2)	12 (3.4)	53 (20.2)	54 (21.1)

AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; MedDRA = Medical Dictionary for Regulatory Activities; Rd = lenalidomide and dexamethasone; RVd = lenalidomide, bortezomib, and dexamethasone; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

a System organ classes and preferred terms were coded using MedDRA Version 15.1. A subject with multiple events was counted only once in each preferred term and system organ class. System organ classes and preferred terms are listed in decreasing order of frequency for the RVd column in the PETHEMA GEM2012 study.

b Both RVd arms combined. For the PETHEMA GEM2012 study, TEAEs include all SAEs plus non-SAEs that the investigator considered related to study treatment.

c For the purpose of comparison to the PETHEMA GEM2012 and SWOG S0777 studies, the 8 cycles (24 weeks) of initial RVd therapy for Arm A in the IFM 2009 study are referred to as "initial treatment."

Note: Treatment-emergent adverse events in each treatment phase were defined as any AEs that began on or after the start of study drug in that phase through the day before the start date of the next phase, or through 30 days after the last dose of study drug if the phase was the last phase in the study.

Data cutoff date = 31 Mar 2017 for the PETHEMA GEM2012 study and 01 Dec 2016 for the IFM 2009 and SWOG S0777 studies.

The frequencies of subjects with TEAEs (any grade) during initial treatment are summarized for ≥ 10% of subjects in the PETHEMA studies and IFM studies used for the integrated analysis.

Table 39: TEAEs Reported in at Least 10 Percent of Subjects in Any Cohort – Initial Treatment – Studies PETHEMA GEM2012 and PETHEMA GEM2005 (Safety Population)

System Organ Class Preferred Term[a]	RVd[b] (PETHEMA GEM2012; 4-week cycles × 6 = 24 weeks) (N = 458) n (%)	VTD (PETHEMA GEM2005; 4-week cycles × 6 = 24 weeks) (N = 130) n (%)
Subjects With ≥ 1 TEAE	402 (87.8)	115 (88.5)
Blood and Lymphatic System Disorders	**229 (50.0)**	**13 (10.0)**
Neutropenia	146 (31.9)	6 (4.6)
Thrombocytopenia	116 (25.3)	5 (3.8)
Anemia	69 (15.1)	5 (3.8)
Nervous System Disorders	**192 (41.9)**	**84 (64.6)**
Neuropathy peripheral	160 (34.9)	49 (37.7)
Neuralgia	25 (5.5)	13 (10.0)
Dizziness	7 (1.5)	17 (13.1)
Paresthesia	5 (1.1)	18 (13.8)
Peripheral sensory neuropathy	0	21 (16.2)
Infections and Infestations	**129 (28.2)**	**19 (14.6)**
Infection	129 (28.2)	6 (4.6)
Gastrointestinal Disorders	**125 (27.3)**	**78 (60.0)**
Diarrhea	59 (12.9)	17 (13.1)
Constipation	55 (12.0)	61 (46.9)
General Disorders and Administration Site Conditions	**102 (22.3)**	**69 (53.1)**
Asthenia	56 (12.2)	41 (31.5)
Pyrexia	21 (4.6)	23 (17.7)
Edema peripheral	15 (3.3)	18 (13.8)
Edema	2 (0.4)	20 (15.4)
Injury, Poisoning, and Procedural Complications	**93 (20.3)**	**0**
Skin toxicity	91 (19.9)	0
Respiratory, Thoracic, and Mediastinal Disorders	**68 (14.8)**	**56 (43.1)**
Pneumonia	24 (5.2)	13 (10.0)
Nasopharyngitis	4 (0.9)	16 (12.3)

MedDRA = Medical Dictionary for Regulatory Activities; RVd= lenalidomide, bortezomib, and dexamethasone; SAE = serious adverse event; TEAE = treatment-emergent adverse event; VTD = bortezomib, thalidomide, and dexamethasone.

a System organ classes and preferred terms were coded using MedDRA Version 15.1. A subject with multiple events was counted only once in each preferred term and system organ class. System organ classes and preferred terms are listed in decreasing order of frequency for the RVd column.

b Both RVd arms combined. For the PETHEMA GEM2012 study, TEAEs include all SAEs plus non-SAEs that the investigator considered related to study treatment.

Notes: Treatment-emergent adverse events in each treatment phase were defined as any adverse events that that began on or after the start of study drug in that phase through the day before the start date of the next phase, or through 30 days after the last dose of study drug if the phase was the last phase in the study.

Data cutoff date = 31 Mar 2017 for the PETHEMA GEM2012 study. The database for the PETHEMA GEM2005 study was final in April 2015.

Table 40 : TEAEs Reported in at Least 10 Percent of Subjects in Any Cohort – Initial Treatment – Studies IFM 2009 (Arm A) and IFM 2013-04 (Safety Population)

System Organ Class Preferred Term[a]	RVd[b] (IFM 2009 Arm A; 3-week cycles × 4 = 12 weeks) (N = 356) n (%)	VTD (IFM 2013-04; 3-week cycles × 4 = 12 weeks) (N = 169) n (%)
Subjects With ≥ 1 TEAE	354 (99.4)	164 (97.0)
Blood and Lymphatic System Disorders	**269 (75.6)**	**63 (37.3)**
Lymphopenia	178 (50.0)	41 (24.3)
Neutropenia	158 (44.4)	21 (12.4)
Leukopenia	125 (35.1)	6 (3.6)
Thrombocytopenia	70 (19.7)	11 (6.5)
Anemia	60 (16.9)	16 (9.5)
Nervous System Disorders	**267 (75.0)**	**104 (61.5)**
Peripheral sensory neuropathy	157 (44.1)	13 (7.7)
Paresthesia	67 (18.8)	26 (15.4)
Headache	50 (14.0)	9 (5.3)
Neuropathy peripheral	13 (3.7)	51 (30.2)
Gastrointestinal Disorders	**257 (72.2)**	**91 (53.8)**
Constipation	126 (35.4)	55 (32.5)
Nausea	106 (29.8)	38 (22.5)
Diarrhea	101 (28.4)	8 (4.7)
Vomiting	54 (15.2)	12 (7.1)
General Disorders and Administration Site Conditions	**236 (66.3)**	**86 (50.9)**
Fatigue	129 (36.2)	3 (1.8)
Edema peripheral	81 (22.8)	31 (18.3)
Pyrexia	65 (18.3)	11 (6.5)
Asthenia	3 (0.8)	36 (21.3)
Musculoskeletal and Connective Tissue Disorders	**159 (44.7)**	**41 (24.3)**
Back pain	59 (16.6)	17 (10.1)
Muscle spasms	38 (10.7)	3 (1.8)
Skin and Subcutaneous Tissue Disorders	**155 (43.5)**	**41 (24.3)**
Rash	69 (19.4)	14 (8.3)
Psychiatric Disorders	**115 (32.3)**	**29 (17.2)**
Insomnia	81 (22.8)	7 (4.1)

MedDRA = Medical Dictionary for Regulatory Activities; RVd = lenalidomide, bortezomib, and dexamethasone; TEAE = treatment-emergent adverse event; VTD = bortezomib, thalidomide, and dexamethasone.
a System organ classes and preferred terms were coded using MedDRA Version 15.1. A subject with multiple events was counted only once in each preferred term and system organ class. System organ classes and preferred terms are listed in decreasing order of frequency for the RVd column.
b For the purpose of comparison to the IFM 2013-04 study, the 4 cycles (12 weeks) of initial RVd therapy for Arm A in the IFM 2009 study are referred to as "initial treatment."
Note: Treatment-emergent adverse events in each treatment phase were defined as any adverse events that began on or after the start of study drug in that phase through the day before the start date of the next phase, or through 30 days (IFM 2009) or 28 days (IFM 2013-04) after the last dose of study drug if the phase was the last phase in the study.
Data cutoff date = 01 Dec 2016 for IFM 2009 and 01 Mar 2016 for IFM 2013-04.

All Grade 3 or 4 TEAEs reported during initial treatment in ≥ 5% of subjects in any treatment arm are summarized in one table for PETHEMA GEM2012, IFM 2009 (Arm A), and SWOG S0777 studies. Grade 3 or 4 TEAEs reported during initial treatment in ≥ 2% of subjects are summarized in two tables for the integrated analysis for PETHEMA studies and IFM studies.

Table 41 : Grade 3 or 4 TEAEs Reported in at Least 5% of Subjects in Any Treatment Arm – Initial Treatment – Studies PETHEMA GEM2012, IFM 2009 (Arm A), and SWOG S0777 (Safety Population)

System Organ Class Preferred Term[a]	PETHEMA GEM2012	IFM 2009	SWOG S0777	
	RVd[b] (4-week cycles × 6 = 24 weeks) (N = 458) n (%)	RVd[c] (3-week cycles × 8 = 24 weeks) (N = 356) n (%)	RVd (3-week cycles × 8 = 24 weeks) (N = 262) n (%)	Rd (4-week cycles × 6 = 24 weeks) (N = 256) n (%)
Subjects With ≥ 1 Grade 3 or 4 TEAE[d]	183 (40.0)	306 (86.0)	200 (76.3)	176 (68.8)
Blood and Lymphatic System Disorders	**89 (19.4)**	**262 (73.6)**	**104 (39.7)**	**106 (41.4)**
Neutropenia	59 (12.9)	159 (44.7)	26 (9.9)	42 (16.4)
Thrombocytopenia	29 (6.3)	66 (18.5)	45 (17.2)	24 (9.4)
Anemia	9 (2.0)	27 (7.6)	32 (12.2)	41 (16.0)
Lymphopenia	7 (1.5)	185 (52.0)	49 (18.7)	39 (15.2)
Leukopenia	5 (1.1)	127 (35.7)	23 (8.8)	29 (11.3)
Infections and Infestations	**45 (9.8)**	**28 (7.9)**	**36 (13.7)**	**24 (9.4)**
Infection	45 (9.8)	1 (0.3)	1 (0.4)	0
Lung infection	0	3 (0.8)	19 (7.3)	14 (5.5)
Nervous System Disorders	**22 (4.8)**	**30 (8.4)**	**89 (34.0)**	**24 (9.4)**
Syncope	1 (0.2)	1 (0.3)	23 (8.8)	7 (2.7)
Peripheral sensory neuropathy	0	18 (5.1)	54 (20.6)	4 (1.6)
Peripheral motor neuropathy	0	1 (0.3)	17 (6.5)	3 (1.2)
Respiratory, Thoracic, and Mediastinal Disorders	**21 (4.6)**	**10 (2.8)**	**26 (9.9)**	**9 (3.5)**
Dyspnea	0	2 (0.6)	16 (6.1)	3 (1.2)
Vascular Disorders	**15 (3.3)**	**9 (2.5)**	**41 (15.6)**	**18 (7.0)**
Hypotension	3 (0.7)	1 (0.3)	20 (7.6)	0
Embolism	0	0	18 (6.9)	16 (6.3)
Gastrointestinal Disorders	**12 (2.6)**	**21 (5.9)**	**46 (17.6)**	**18 (7.0)**
Diarrhea	4 (0.9)	7 (2.0)	24 (9.2)	4 (1.6)
General Disorders and Administration Site Conditions	**10 (2.2)**	**21 (5.9)**	**49 (18.7)**	**29 (11.3)**
Fatigue	0	9 (2.5)	38 (14.5)	26 (10.2)
Investigations	**9 (2.0)**	**8 (2.2)**	**29 (11.1)**	**22 (8.6)**
Alanine aminotransferase increased	3 (0.7)	3 (0.8)	13 (5.0)	4 (1.6)
Renal and Urinary Disorders	**8 (1.7)**	**2 (0.6)**	**8 (3.1)**	**17 (6.6)**
Renal failure acute	3 (0.7)	0	7 (2.7)	14 (5.5)
Musculoskeletal and Connective Tissue Disorders	**6 (1.3)**	**22 (6.2)**	**45 (17.2)**	**30 (11.7)**
Muscular weakness	0	0	22 (8.4)	11 (4.3)
Metabolism and Nutrition Disorders	**4 (0.9)**	**18 (5.1)**	**85 (32.4)**	**70 (27.3)**
Hyperglycemia	2 (0.4)	4 (1.1)	19 (7.3)	24 (9.4)
Hyponatremia	1 (0.2)	3 (0.8)	17 (6.5)	16 (6.3)
Hypokalemia	0	3 (0.8)	30 (11.5)	12 (4.7)
Hypocalcemia	0	2 (0.6)	17 (6.5)	21 (8.2)
Dehydration	0	0	22 (8.4)	6 (2.3)

CTCAE = Common Terminology Criteria for Adverse Events; MedDRA = Medical Dictionary for Regulatory Activities; Rd = lenalidomide and dexamethasone; RVd = lenalidomide, bortezomib, and dexamethasone; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

a System organ classes and preferred terms were coded using MedDRA Version 15.1. A subject with multiple events was counted only once in each preferred term and system organ class. System organ classes and preferred terms are listed in decreasing order of frequency for the RVd column in the PETHEMA GEM2012 study.

b Both RVd arms combined. For the PETHEMA GEM2012 study, TEAEs include all SAEs plus non-SAEs that the investigator considered related to study treatment.

c For the purpose of comparison to the PETHEMA GEM2012 and SWOG S0777 studies, the 8 cycles (24 weeks) of initial RVd therapy for Arm A in the IFM 2009 study are referred to as "initial treatment."

d Graded using CTCAE Version 4.03 for the PETHEMA GEM2012 study and Version 4.0 for the IFM 2009 and SWOG S0777 studies.

Note: Treatment-emergent adverse events in each treatment phase were defined as any AEs that began on or after the start of study drug in that phase through the day before the start date of the next phase, or through 30 days after the last dose of study drug if the phase was the last phase in the study.

Data cutoff date = 31 Mar 2017 for the PETHEMA GEM2012 study and 01 Dec 2016 for the IFM 2009 and SWOG S0777 studies.

Table 42 : Grade 3 or 4 TEAEs Reported in at Least 2 Percent of Subjects in Any Cohort – Initial Treatment –Integrated analysis, PETHEMA GEM2012 and PETHEMA GEM2005 (Safety Population)

System Organ Class Preferred Term[a]	RVd[b] (PETHEMA GEM2012; 4-week cycles × 6 = 24 weeks) (N = 458) n (%)	VTD (PETHEMA GEM2005; 4-week cycles × 6 = 24 weeks) (N = 130) n (%)
Subjects With ≥ 1 Grade 3 or 4[c] TEAE	183 (40.0)	56 (43.1)
Blood and Lymphatic System Disorders	**89 (19.4)**	**6 (4.6)**
Neutropenia	59 (12.9)	3 (2.3)
Thrombocytopenia	29 (6.3)	0
Anemia	9 (2.0)	1 (0.8)
Infections and Infestations	**45 (9.8)**	**3 (2.3)**
Infection	45 (9.8)	0
Nervous System Disorders	**22 (4.8)**	**16 (12.3)**
Neuropathy peripheral	15 (3.3)	9 (6.9)
Neuralgia	3 (0.7)	4 (3.1)
Peripheral sensory neuropathy	0	3 (2.3)
Respiratory, Thoracic, and Mediastinal Disorders	**21 (4.6)**	**18 (13.8)**
Pneumonia	10 (2.2)	9 (6.9)
Respiratory tract infection	7 (1.5)	4 (3.1)
Injury, Poisoning, and Procedural Complications	**16 (3.5)**	**0**
Skin toxicity	14 (3.1)	0
Gastrointestinal Disorders	**12 (2.6)**	**10 (7.7)**
Constipation	1 (0.2)	4 (3.1)
General Disorders and Administration Site Conditions	**10 (2.2)**	**15 (11.5)**
Asthenia	3 (0.7)	6 (4.6)
Pyrexia	1 (0.2)	5 (3.8)

CTCAE = Common Terminology Criteria for Adverse Events; MedDRA = Medical Dictionary for Regulatory Activities; RVd= lenalidomide, bortezomib, and dexamethasone; SAE = serious adverse event; TEAE = treatment-emergent adverse event; VTD = bortezomib, thalidomide, and dexamethasone.

a System organ classes and preferred terms were coded using MedDRA Version 15.1. A subject with multiple events was counted only once in each preferred term and system organ class. System organ classes and preferred terms are listed in decreasing order of frequency for the RVd column.

b Both RVd arms combined. For the PETHEMA GEM2012 study, TEAEs include all SAEs plus non-SAEs that the investigator considered related to study treatment.

c Graded using CTCAE Version 4.03 for PETHEMA GEM2012 and Version 3.0 for PETHEMA GEM2005.

Notes: Treatment-emergent adverse events in each treatment phase were defined as any adverse events that that began on or after the start of study drug in that phase through the day before the start date of the next phase, or through 30 days after the last dose of study drug if the phase was the last phase in the study.

A summary of adverse events of special interest (AESIs) for lenalidomide as well as overlapping AESIs of bortezomib that occurred during initial treatment is provided below.

Table 43 : Lenalidomide, Bortezomib, and Overlapping adverse event of special interest (AESIs)

Overlapping AESI for Lenalidomide / Bortezomib	AESI for Lenalidomide Only	AESI for Bortezomib Only
Peripheral neuropathy	Constipation and Diarrhea	Peripheral neuropathy (Autonomic neuropathy – custom)
Thrombocytopenia and bleeding / Thrombocytopenia with associated bleeding	Cutaneous reactions	Optic neuropathy and different degrees of visual impairment (up to blindness)
Hepatic disorders / Hepatotoxicity	Renal failure	Pulmonary hypertension
Neutropenia and infection / Neutropenia with associated infection	Venous thromboembolism	Guillain-Barré syndrome
	Cataract	Pericardial disease
Cardiac arrhythmias / Ventricular rhythm abnormalities	Arterial thromboembolism	Posterior reversible encephalopathy syndrome
--	Myocardial infarction / Ischemic heart disease	Progressive multifocal leukoencephalopathy
Hypersensitivity / Acute hypersensitivity reaction	Teratogenicity	Herpes zoster virus infection
Interstitial lung disease / Acute diffuse infiltrative pulmonary disease	--	--
Cardiac failure / Heart failure	--	--
Tumour lysis syndrome	--	--

Table 44 : Treatment-emergent Adverse Events of Special Interest (AESIs) for Lenalidomide and Overlapping AESIs of Bortezomib by AESI Category – Initial Treatment – Studies PETHEMA GEM2012, IFM 2009 (Arm A), and SWOG S0777 (Safety Population)

	PETHEMA GEM2012			IFM 2009			SWOG S0777					
	RVd[b] (4-week cycles × 6 = 24 weeks) (N = 458)			RVd[c] (3-week cycles × 8 = 24 weeks) (N = 356)			RVd (3-week cycles × 8 = 24 weeks) (N = 262)			Rd (4-week cycles × 6 = 24 weeks) (N = 256)		
AESI Category[a]	All TEAEs n (%)	Grade 3/4[d] n (%)	SAEs n (%)	All TEAEs n (%)	Grade 3/4[d] n (%)	SAEs n (%)	All TEAEs n (%)	Grade 3/4[d] n (%)	SAEs n (%)	All TEAEs n (%)	Grade 3/4[d] n (%)	SAEs n (%)
Peripheral Neuropathy[e,f]	174 (38.0)	18 (3.9)	0	201 (56.5)	22 (6.2)	5 (1.4)	188 (71.8)	62 (23.7)	4 (1.5)	90 (35.2)	7 (2.7)	1 (0.4)
Neutropenia	146 (31.9)	59 (12.9)	2 (0.4)	167 (46.9)	162 (45.5)	6 (1.7)	78 (29.8)	27 (10.3)	3 (1.1)	101 (39.5)	45 (17.6)	6 (2.3)
Infections[e]	143 (31.2)	48 (10.5)	81 (17.7)	188 (52.8)	28 (7.9)	24 (6.7)	92 (35.1)	36 (13.7)	28 (10.7)	74 (28.9)	24 (9.4)	17 (6.6)
Thrombocytopenia[e]	116 (25.3)	29 (6.3)	0	71 (19.9)	66 (18.5)	0	151 (57.6)	45 (17.2)	10 (3.8)	117 (45.7)	24 (9.4)	3 (1.2)
Diarrhea	59 (12.9)	4 (0.9)	4 (0.9)	120 (33.7)	7 (2.0)	4 (1.1)	104 (39.7)	24 (9.2)	10 (3.8)	79 (30.9)	4 (1.6)	3 (1.2)
Constipation	55 (12.0)	1 (0.2)	1 (0.2)	136 (38.2)	2 (0.6)	1 (0.3)	147 (56.1)	5 (1.9)	2 (0.8)	115 (44.9)	2 (0.8)	0
Hepatic Disorders[e]	37 (8.1)	15 (3.3)	3 (0.7)	47 (13.2)	18 (5.1)	4 (1.1)	148 (56.5)	24 (9.2)	8 (3.1)	120 (46.9)	16 (6.3)	4 (1.6)
Cutaneous Reactions	15 (3.3)	9 (2.0)	10 (2.2)	114 (32.0)	5 (1.4)	3 (0.8)	77 (29.4)	9 (3.4)	3 (1.1)	77 (30.1)	7 (2.7)	2 (0.8)
Renal Failure	13 (2.8)	5 (1.1)	6 (1.3)	8 (2.2)	1 (0.3)	2 (0.6)	55 (21.0)	8 (3.1)	6 (2.3)	71 (27.7)	17 (6.6)	15 (5.9)
Venous Thromboembolism	12 (2.6)	6 (1.3)	5 (1.1)	17 (4.8)	6 (1.7)	9 (2.5)	9 (3.4)	4 (1.5)	3 (1.1)	3 (1.2)	2 (0.8)	2 (0.8)
Cardiac Arrhythmias[e]	10 (2.2)	1 (0.2)	5 (1.1)	21 (5.9)	1 (0.3)	0	43 (16.4)	27 (10.3)	16 (6.1)	21 (8.2)	9 (3.5)	4 (1.6)
Bleeding[e]	9 (2.0)	3 (0.7)	6 (1.3)	25 (7.0)	0	0	35 (13.4)	8 (3.1)	8 (3.1)	32 (12.5)	3 (1.2)	3 (1.2)
Cardiac Failure[e]	8 (1.7)	4 (0.9)	6 (1.3)	0	0	0	6 (2.3)	4 (1.5)	2 (0.8)	3 (1.2)	3 (1.2)	3 (1.2)
Hypersensitivity and Angioedema[e]	5 (1.1)	1 (0.2)	1 (0.2)	17 (4.8)	2 (0.6)	1 (0.3)	17 (6.5)	2 (0.8)	1 (0.4)	14 (5.5)	2 (0.8)	1 (0.4)
Myocardial Infarction/IHD	5 (1.1)	3 (0.7)	5 (1.1)	2 (0.6)	2 (0.6)	1 (0.3)	1 (0.4)	1 (0.4)	1 (0.4)	3 (1.2)	2 (0.8)	2 (0.8)
Arterial Thromboembolism	4 (0.9)	2 (0.4)	4 (0.9)	1 (0.3)	1 (0.3)	1 (0.3)	1 (0.4)	1 (0.4)	1 (0.4)	1 (0.4)	1 (0.4)	1 (0.4)
Interstitial Lung Disease[e]	1 (0.2)	1 (0.2)	1 (0.2)	2 (0.6)	0	0	7 (2.7)	5 (1.9)	4 (1.5)	4 (1.6)	4 (1.6)	4 (1.6)
Cataracts	0	0	0	1 (0.3)	0	0	3 (1.1)	0	0	0	0	0
Tumor Lysis Syndrome[e]	0	0	0	0	0	0	2 (0.8)	2 (0.8)	2 (0.8)	2 (0.8)	2 (0.8)	2 (0.8)

AESI = adverse event of special interest; CTCAE = Common Terminology Criteria for Adverse Events; IHD = ischemic heart disease; MedDRA = Medical Dictionary for Regulatory Activities; Rd = lenalidomide and dexamethasone; RVd = lenalidomide, bortezomib, and dexamethasone; SAE = serious adverse event; SMQ = Standardized MedDRA Query; TEAE = treatment-emergent adverse event.
a The AESI categories are listed in decreasing order of frequency for the first RVd column. A subject with multiple events was counted only once in each AESI category.
b Both RVd arms combined. For the PETHEMA GEM2012 study, TEAEs include all SAEs plus non-SAEs that the investigator considered related to study treatment.
c For the purpose of comparison to the PETHEMA GEM2012 and SWOG S0777 studies, the 8 cycles (24 weeks) of initial RVd therapy for Arm A in the IFM 2009 study are referred to as "initial treatment."
d Treatment-emergent adverse events were graded using CTCAE Version 4.03 for the PETHEMA GEM2012 study and Version 4.0 for the IFM 2009 and SWOG S0777 studies.
e Overlapping toxicities of lenalidomide and bortezomib.
f Narrow Scope SMQ search using MedDRA Version 15.1 to identify events of peripheral neuropathy associated with lenalidomide. This approach is consistent with the lenalidomide Risk Management Plan.
Data cutoff date = 31 Mar 2017 for the PETHEMA GEM2012 study and 01 Dec 2016 for the IFM 2009 and SWOG S0777 studies.

Serious adverse event / deaths / other significant events

- ***Serious adverse events (SAEs)***

All treatment-emergent SAEs reported during initial treatment in ≥ 2% of subjects in any treatment arm are summarized by study in the table below.

Table 45 : Treatment-emergent SAEs Reported in at Least 2% of Subjects in Any Treatment Arm – Initial Treatment – Studies PETHEMA GEM2012, IFM 2009 (Arm A), and SWOG S0777 (Safety Population)

System Organ Class Preferred Term[a]	PETHEMA GEM2012	IFM 2009	SWOG S0777	
	RVd[b] (4-week cycles × 6 = 24 weeks) (N = 458) n (%)	RVd[c] (3-week cycles × 8 = 24 weeks) (N = 356) n (%)	RVd (3-week cycles × 8 = 24 weeks) (N = 262) n (%)	Rd (4-week cycles × 6 = 24 weeks) (N = 256) n (%)
Subjects With ≥ 1 Treatment-emergent SAE	147 (32.1)	108 (30.3)	105 (40.1)	73 (28.5)
Infections and Infestations	**74 (16.2)**	**24 (6.7)**	**28 (10.7)**	**17 (6.6)**
Infection	74 (16.2)	1 (0.3)	0	0
Lung infection	0	4 (1.1)	15 (5.7)	12 (4.7)
Urinary tract infection	0	0	6 (2.3)	2 (0.8)
Respiratory, Thoracic, and Mediastinal Disorders	**56 (12.2)**	**11 (3.1)**	**17 (6.5)**	**8 (3.1)**
Pneumonia	24 (5.2)	0	0	0
Respiratory tract infection	20 (4.4)	0	0	0

Dyspnea	0	1 (0.3)	9 (3.4)	1 (0.4)
General Disorders and Administration Site Conditions	**26 (5.7)**	**16 (4.5)**	**16 (6.1)**	**7 (2.7)**
Pyrexia	12 (2.6)	9 (2.5)	0	1 (0.4)
Fatigue	0	0	8 (3.1)	4 (1.6)
Vascular Disorders	**13 (2.8)**	**5 (1.4)**	**22 (8.4)**	**9 (3.5)**
Hypotension	2 (0.4)	0	17 (6.5)	1 (0.4)
Embolism	0	0	4 (1.5)	5 (2.0)
Gastrointestinal Disorders	**12 (2.6)**	**15 (4.2)**	**31 (11.8)**	**11 (4.3)**
Diarrhea	4 (0.9)	4 (1.1)	10 (3.8)	3 (1.2)
Abdominal pain	0	0	6 (2.3)	1 (0.4)
Renal and Urinary Disorders	**12 (2.6)**	**3 (0.8)**	**6 (2.3)**	**15 (5.9)**
Renal failure acute	3 (0.7)	0	4 (1.5)	13 (5.1)
Musculoskeletal and Connective Tissue Disorders	**10 (2.2)**	**17 (4.8)**	**16 (6.1)**	**13 (5.1)**
Back pain	3 (0.7)	11 (3.1)	5 (1.9)	4 (1.6)
Muscular weakness	0	0	10 (3.8)	4 (1.6)
Nervous System Disorders	**6 (1.3)**	**9 (2.5)**	**22 (8.4)**	**8 (3.1)**
Syncope	1 (0.2)	0	11 (4.2)	3 (1.2)
Metabolism and Nutrition Disorders	**5 (1.1)**	**0**	**32 (12.2)**	**22 (8.6)**
Hyperglycemia	2 (0.4)	0	4 (1.5)	6 (2.3)
Dehydration	0	0	13 (5.0)	4 (1.6)
Hypocalcemia	0	0	7 (2.7)	6 (2.3)
Hypokalemia	0	0	8 (3.1)	2 (0.8)
Blood and Lymphatic System Disorders	**4 (0.9)**	**10 (2.8)**	**21 (8.0)**	**22 (8.6)**
Anemia	1 (0.2)	2 (0.6)	10 (3.8)	20 (7.8)
Thrombocytopenia	0	0	10 (3.8)	3 (1.2)

AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; Rd = lenalidomide and dexamethasone; RVd = lenalidomide, bortezomib, and dexamethasone; SAE = serious adverse event; TEAE = treatment-emergent adverse event.
a System organ classes and preferred terms were coded using MedDRA Version 15.1. A subject with multiple events was counted only once in each preferred term and system organ class. System organ classes and preferred terms are listed in decreasing order of frequency for the RVd column in the PETHEMA GEM2012 study.
b Both RVd arms combined. For the PETHEMA GEM2012 study, TEAEs include all SAEs plus non-SAEs that the investigator considered related to study treatment.
c For the purpose of comparison to the PETHEMA GEM2012 and SWOG S0777 studies, the 8 cycles (24 weeks) of initial RVd therapy for Arm A in the IFM 2009 study are referred to as "initial treatment."
Note: Treatment-emergent adverse events in each treatment phase were defined as any AEs that began on or after the start of study drug in that phase through the day before the start date of the next phase, or through 30 days after the last dose of study drug if the phase was the last phase in the study.
Data cutoff date = 31 Mar 2017 for the PETHEMA GEM2012 study and 01 Dec 2016 for the IFM 2009 and SWOG S0777 studies.

Regarding the integrated analysis, treatment-emergent SAEs reported during initial treatment in ≥ 1% of subjects in any treatment arm are summarized for PETHEMA studies and IFM studies in the tables below.

Table 46 : Treatment-emergent SAEs Reported in at Least 1 Percent of Subjects in Any Cohort – Initial Treatment – Integrated analysis, Studies PETHEMA GEM2012 and PETHEMA GEM2005 (Safety Population)

System Organ Class Preferred Term[a]	RVd[b] (PETHEMA GEM2012; 4-week cycles × 6 = 24 weeks) (N = 458) n (%)	VTD (PETHEMA GEM2005; 4-week cycles × 6 = 24 weeks) (N = 130) n (%)
Subjects With ≥ 1 Treatment-emergent SAE	147 (32.1)	37 (28.5)
Infections and Infestations	**74 (16.2)**	**3 (2.3)**
Infection	74 (16.2)	0
Septic shock	6 (1.3)	2 (1.5)
Respiratory, Thoracic, and Mediastinal Disorders	**56 (12.2)**	**20 (15.4)**
Pneumonia	24 (5.2)	11 (8.5)
Respiratory tract infection	20 (4.4)	2 (1.5)
Respiratory failure	4 (0.9)	2 (1.5)
General Disorders and Administration Site Conditions	**26 (5.7)**	**7 (5.4)**
Pyrexia	12 (2.6)	5 (3.8)
Device related infection	7 (1.5)	0
Vascular Disorders	**13 (2.8)**	**4 (3.1)**

Orthostatic hypotension	1 (0.2)	2 (1.5)
Renal and Urinary Disorders	**12 (2.6)**	**1 (0.8)**
Urinary tract infection	6 (1.3)	0
Injury, Poisoning, and Procedural Complications	**8 (1.7)**	**0**
Skin toxicity	5 (1.1)	0
Nervous System Disorders	**6 (1.3)**	**5 (3.8)**
Neuropathy peripheral	0	3 (2.3)
Hepatobiliary Disorders	**4 (0.9)**	**2 (1.5)**
Hepatitis	0	2 (1.5)

MedDRA = Medical Dictionary for Regulatory Activities; RVd= lenalidomide, bortezomib, and dexamethasone; SAE = serious adverse event; VTD = bortezomib, thalidomide, and dexamethasone.
a System organ classes and preferred terms were coded using MedDRA Version 15.1. A subject with multiple events was counted only once in each preferred term and system organ class. System organ classes and preferred terms are listed in decreasing order of frequency for the RVd column.
b Both RVd arms combined.
Notes: Treatment-emergent adverse events in each treatment phase were defined as any adverse events that that began on or after the start of study drug in that phase through the day before the start date of the next phase, or through 30 days after the last dose of study drug if the phase was the last phase in the study.
Data cutoff date = 31 Mar 2017 for the PETHEMA GEM2012 study. The database for the PETHEMA GEM2005 study was final in April 2015.

Table 47 : Treatment-emergent SAEs Reported in at Least 1 Percent of Subjects in Any Cohort – Initial Treatment – Integrated analysis, Studies IFM 2009 (Arm A) and IFM 2013-04 (Safety Population)

System Organ Class Preferred Term[a]	RVd[b] (IFM 2009 Arm A; 3-week cycles × 4 = 12 weeks) (N = 356) n (%)	VTD (IFM 2013-04; 3-week cycles × 4 = 12 weeks) (N = 169) n (%)
Subjects With ≥ 1 Treatment-emergent SAE	98 (27.5)	54 (32.0)
Infections and Infestations	**20 (5.6)**	**15 (8.9)**
Lung infection	4 (1.1)	2 (1.2)
Pneumonia	4 (1.1)	2 (1.2)
Septic shock	1 (0.3)	2 (1.2)
Musculoskeletal and Connective Tissue Disorders	**17 (4.8)**	**2 (1.2)**
Back pain	11 (3.1)	2 (1.2)
Gastrointestinal Disorders	**15 (4.2)**	**3 (1.8)**
Diarrhea	4 (1.1)	0
General Disorders and Administration Site Conditions	**12 (3.4)**	**6 (3.6)**
Pyrexia	7 (2.0)	2 (1.2)
Blood and Lymphatic System Disorders	**10 (2.8)**	**4 (2.4)**
Febrile neutropenia	4 (1.1)	1 (0.6)
Nervous System Disorders	**9 (2.5)**	**8 (4.7)**
Neuropathy peripheral	4 (1.1)	1 (0.6)
Respiratory, Thoracic, and Mediastinal Disorders	**7 (2.0)**	**5 (3.0)**
Pulmonary embolism	2 (0.6)	4 (2.4)
Vascular Disorders	**5 (1.4)**	**2 (1.2)**
Deep vein thrombosis	3 (0.8)	2 (1.2)
Renal and Urinary Disorders	**3 (0.8)**	**4 (2.4)**
Renal failure acute	0	3 (1.8)
Hepatobiliary Disorders	**3 (0.8)**	**2 (1.2)**
Hepatocellular injury	2 (0.6)	2 (1.2)
Metabolism and Nutrition Disorders	**0**	**5 (3.0)**
Diabetes mellitus inadequate control	0	2 (1.2)

MedDRA = Medical Dictionary for Regulatory Activities; RVd = lenalidomide, bortezomib, and dexamethasone; SAE = serious adverse event; VTD = bortezomib, thalidomide, and dexamethasone.
a System organ classes and preferred terms were coded using MedDRA Version 15.1. A subject with multiple events was counted only once in each preferred term and system organ class. System organ classes and preferred terms are listed in decreasing order of frequency for the RVd column.
b For the purpose of comparison to the IFM 2013-04 study, the 4 cycles (12 weeks) of initial RVd therapy for Arm A in the IFM 2009 study are referred to as "initial treatment."
Notes: Treatment-emergent adverse events in each treatment phase were defined as any adverse events that began on or after the start of study drug in that phase through the day before the start date of the next phase, or through 30 days (IFM 2009) or 28 days (IFM 2013-04) after the last dose of study drug if the phase was the last phase in the study.
Data cutoff date = 01 Dec 2016 for IFM 2009 and 01 Mar 2016 for IFM 2013-04.

- ***Deaths***

A summary of primary causes of death during initial treatment is provided by study in the table below.

Table 48 : Summary of Primary Causes of Death – Initial Treatment – Studies PETHEMA GEM2012, IFM 2009 (Arm A), and SWOG S0777 (Safety Population)

Primary Cause	PETHEMA GEM2012	IFM 2009	SWOG S0777	
	RVd[a] (4-week cycles × 6 = 24 weeks) (N = 458) n (%)	RVd[b] (3-week cycles × 8 = 24 weeks) (N = 356) n (%)	RVd (3-week cycles × 8 = 24 weeks) (N = 262) n (%)	Rd (4-week cycles × 6 = 24 weeks) (N = 256) n (%)
Deaths During Initial Treatment	**7 (1.5)**	**1 (0.3)**	**7 (2.7)**	**6 (2.3)**
TEAE	6 (1.3)	1 (0.3)	5 (1.9)	3 (1.2)
MM (or MM-Treatment Related)	0	0	2 (0.8)	3 (1.2)
Other[c]	1 (0.2)	0	0	0

AE = adverse event; MM = multiple myeloma; Rd = lenalidomide and dexamethasone; RVd = lenalidomide, bortezomib, and dexamethasone;
SAE = serious adverse event; TEAE = treatment-emergent adverse event.
a Both RVd arms combined. For the PETHEMA GEM2012 study, TEAEs include all SAEs plus non-SAEs that the investigator considered related to study treatment.
b For the purpose of comparison to the PETHEMA GEM2012 and SWOG S0777 studies, the 8 cycles (24 weeks) of initial RVd therapy for Arm A in the IFM 2009 study are referred to as "initial treatment."
c Cause of death was unknown or missing.
Note: Treatment-emergent adverse events in each treatment phase were defined as any AEs that began on or after the start of study drug in that phase through the day before the start date of the next phase, or through 30 days after the last dose of study drug if the phase was the last phase in the study.
Data cutoff date = 31 Mar 2017 for the PETHEMA GEM2012 study and 01 Dec 2016 for the IFM 2009 and SWOG S0777 studies.

Table 49 : Summary of Causes of Death by Treatment Arm as of 01 Dec 2016 (Safety Population) – Study SWOG S0777

	RVd (N = 262) n (%)	Rd (N = 256) n (%)	Total (N = 518) n (%)
All Deaths (during the study)	103 (39.3)	129 (50.4)	232 (44.8)
MM (or MM-treatment related)	67 (25.6)	88 (34.4)	155 (29.9)
Post-treatment toxicity (> 30 days from last dose)	22 (8.4)	24 (9.4)	46 (8.9)
TEAE	9 (3.4)	7 (2.7)	16 (3.1)
SPM	1 (0.4)	3 (1.2)	4 (0.8)
Other[a]	4 (1.5)	7 (2.7)	11 (2.1)

MM = multiple myeloma; Rd = lenalidomide and dexamethasone; RVd = lenalidomide, bortezomib, and dexamethasone; SPM = second primary malignancy; TEAE = treatment-emergent adverse event.
a Cause of death was unknown or missing.
Data cutoff date = 01 Dec 2016

- ***Secondary Primary Malignancies (SPMs)***

Second primary malignancies (SPMs) following lenalidomide-containing treatment were first noted in 2010 when an increased frequency of haematologic SPMs was reported in subjects with newly diagnosed multiple myeloma (NDMM) receiving lenalidomide in combination with oral melphalan and prednisone (Palumbo, 2012) or as long-term maintenance treatment after high-dose melphalan (HDM) conditioning therapy supported by autologous hematopoietic stem cell transplantation (auto-HSCT) (Attal, 2012; McCarthy, 2012). Following these findings, lenalidomide protocols were amended to report all SPMs as serious adverse events (SAEs) and to continue to follow study subjects for the occurrence of SPMs after discontinuation of study treatment during follow-up for survival. An overview of SPM data following initial (induction) therapy with lenalidomide, bortezomib, and dexamethasone (RVd) in subjects with NDMM from trials was conducted by independent cooperative research groups.

The observed incidence rates for haematologic (range: 0 to 0.16 per 100 person-years) and solid tumour (range: 0.21 to 1.04 per 100 person-years) SPMs observed in the RVd arms of the 3 NDMM studies (SWOG S0777, PETHEMA GEM2012, and IFM 2009) are consistent with those for the Rd arm in the SWOG S0777 study (incidence rates: 0.27 per 100 person-years [haematologic SPMs] and 0.90 per 100 person-years [solid tumour SPMs]). Furthermore, the observed incidence rates are comparable with those observed in the MM-020 study that forms the basis of the current language for lenalidomide in combination with dexamethasone in the approved EU SmPC (incidence rates: 0.16 per 100 person-years [haematologic SPMs] and 1.58 per 100 person-years [solid tumour SPMs]).

Safety in special populations

- ***Transplant eligibility***

Transplant eligibility was assessed in the SWOG S0777 study using an age cutoff of ≤ 65 years and an assessment on the fitness/frailty level of subjects based on age, Charlson comorbidity index score, and Eastern Cooperative Oncology Group (ECOG) performance status. The frequencies of subjects with TEAEs (any grade) by transplant eligibility reported in ≥ 20% of subjects in any treatment arm are summarized below.

Table 50 : TEAEs (Any Grade) Reported in at Least 20% of Subjects in Any Treatment Arm by Transplant Eligibility – Initial Treatment – Study SWOG S0777 (Safety Population)

System Organ Class Preferred Term[a]	TNE		TE	
	RVd (3-week cycles × 8 = 24 weeks) (N = 120) n (%)	Rd (4-week cycles × 6 = 24 weeks) (N = 137) n (%)	RVd (3-week cycles × 8 = 24 weeks) (N = 142) n (%)	Rd (4-week cycles × 6 = 24 weeks) (N = 119) n (%)
Subjects With ≥ 1 TEAE	115 (95.8)	133 (97.1)	140 (98.6)	112 (94.1)
Nervous System Disorders	**100 (83.3)**	**82 (59.9)**	**119 (83.8)**	**63 (52.9)**
Peripheral sensory neuropathy	80 (66.7)	47 (34.3)	104 (73.2)	38 (31.9)
Dizziness	36 (30.0)	23 (16.8)	40 (28.2)	18 (15.1)
Dysgeusia	35 (29.2)	29 (21.2)	44 (31.0)	19 (16.0)
Gastrointestinal Disorders	**99 (82.5)**	**93 (67.9)**	**112 (78.9)**	**73 (61.3)**
Constipation	63 (52.5)	69 (50.4)	84 (59.2)	46 (38.7)
Diarrhea	52 (43.3)	45 (32.8)	52 (36.6)	34 (28.6)
Nausea	40 (33.3)	36 (26.3)	58 (40.8)	33 (27.7)
Dyspepsia	19 (15.8)	17 (12.4)	31 (21.8)	16 (13.4)
General Disorders and Administration Site Conditions	**99 (82.5)**	**103 (75.2)**	**122 (85.9)**	**88 (73.9)**
Fatigue	84 (70.0)	90 (65.7)	109 (76.8)	77 (64.7)
Edema peripheral	57 (47.5)	41 (29.9)	65 (45.8)	24 (20.2)
Blood and Lymphatic System Disorders	**96 (80.0)**	**118 (86.1)**	**112 (78.9)**	**85 (71.4)**
Anemia	82 (68.3)	101 (73.7)	97 (68.3)	74 (62.2)
Thrombocytopenia	77 (64.2)	77 (56.2)	74 (52.1)	40 (33.6)
Leukopenia	46 (38.3)	76 (55.5)	63 (44.4)	50 (42.0)
Neutropenia	35 (29.2)	58 (42.3)	42 (29.6)	41 (34.5)
Lymphopenia	34 (28.3)	37 (27.0)	33 (23.2)	25 (21.0)
Metabolism and Nutrition Disorders	**93 (77.5)**	**111 (81.0)**	**108 (76.1)**	**91 (76.5)**
Hypocalcemia	66 (55.0)	63 (46.0)	65 (45.8)	48 (40.3)
Hyperglycemia	58 (48.3)	81 (59.1)	69 (48.6)	61 (51.3)
Decreased appetite	43 (35.8)	35 (25.5)	47 (33.1)	24 (20.2)
Hypoalbuminemia	43 (35.8)	40 (29.2)	35 (24.6)	27 (22.7)
Hyponatremia	41 (34.2)	42 (30.7)	39 (27.5)	23 (19.3)
Hypokalemia	36 (30.0)	31 (22.6)	40 (28.2)	22 (18.5)
Dehydration	25 (20.8)	13 (9.5)	18 (12.7)	4 (3.4)
Musculoskeletal and Connective Tissue Disorders	**87 (72.5)**	**96 (70.1)**	**98 (69.0)**	**70 (58.8)**

Muscular weakness	36 (30.0)	29 (21.2)	28 (19.7)	16 (13.4)
Back pain	35 (29.2)	37 (27.0)	52 (36.6)	34 (28.6)
Investigations	**73 (60.8)**	**83 (60.6)**	**90 (63.4)**	**61 (51.3)**
Blood AP increased	31 (25.8)	29 (21.2)	35 (24.6)	19 (16.0)
Blood creatinine increased	30 (25.0)	38 (27.7)	18 (12.7)	26 (21.8)
Weight decreased	26 (21.7)	41 (29.9)	27 (19.0)	13 (10.9)
ALT increased	24 (20.0)	21 (15.3)	43 (30.3)	28 (23.5)
AST increased	18 (15.0)	21 (15.3)	38 (26.8)	17 (14.3)
Respiratory, Thoracic, and Mediastinal Disorders	**69 (57.5)**	**74 (54.0)**	**81 (57.0)**	**43 (36.1)**
Dyspnea	43 (35.8)	38 (27.7)	37 (26.1)	27 (22.7)
Cough	36 (30.0)	30 (21.9)	41 (28.9)	21 (17.6)
Skin and Subcutaneous Tissue Disorders	**47 (39.2)**	**55 (40.1)**	**66 (46.5)**	**49 (41.2)**
Rash	20 (16.7)	25 (18.2)	29 (20.4)	27 (22.7)
Vascular Disorders	**47 (39.2)**	**44 (32.1)**	**54 (38.0)**	**29 (24.4)**
Hypotension	24 (20.0)	11 (8.0)	19 (13.4)	2 (1.7)
Psychiatric Disorders	**45 (37.5)**	**64 (46.7)**	**68 (47.9)**	**46 (38.7)**
Insomnia	35 (29.2)	40 (29.2)	51 (35.9)	34 (28.6)

AE = adverse event; ALT = alanine aminotransferase; AP = alkaline phosphatase; AST = aspartate aminotransferase; MedDRA = Medical Dictionary for Regulatory Activities; Rd = lenalidomide and dexamethasone; RVd = lenalidomide, bortezomib, and dexamethasone; TE = transplant eligible; TEAE = treatment-emergent adverse event; TNE = transplant non-eligible.
a System organ classes and preferred terms were coded using MedDRA Version 15.1. A subject with multiple events was counted only once in each preferred term and system organ class. System organ classes and preferred terms are listed in decreasing order of frequency by the TNE RVd column.

- ***Intent to transplant at progression***

Overall, in the SWOG S0777 study, 358 subjects were stratified at randomization as with intent for immediate transplant at progression (yes) (181 in the RVd arm and 177 in the Rd arm) and 160 subjects were stratified at randomization as without intent for immediate transplant at progression (No) (81 in the RVd arm and 79 in the Rd arm). A summary of safety in subjects by intent to transplant at progression (yes or no) is presented below.

Table 51 : Overview of Treatment-emergent Adverse Events During Initial Treatment by Intent to Transplant at Progression (Safety Population)

Subjects with at Least One:	Yes		No	
	RVd (N = 181) n (%)	Rd (N = 177) n (%)	RVd (N = 81) n (%)	Rd (N = 79) n (%)
TEAE	177 (97.8)	167 (94.4)	78 (96.3)	78 (98.7)
TEAE related[a] to study drug	173 (95.6)	162 (91.5)	78 (96.3)	78 (98.7)
Serious TEAE	68 (37.6)	41 (23.2)	37 (45.7)	32 (40.5)
Grade 3 or 4[b] TEAE	133 (73.5)	111 (62.7)	67 (82.7)	65 (82.3)
Grade 3 or 4[b] TEAE related[a] to study drug	123 (68.0)	90 (50.8)	62 (76.5)	57 (72.2)
Grade 5[b] TEAE	5 (2.8)	2 (1.1)	1 (1.2)	1 (1.3)
Treatment discontinuations due to TEAE[c]	34 (18.8)	15 (8.5)	26 (32.1)	9 (11.4)

Rd = lenalidomide and dexamethasone; RVd = lenalidomide, bortezomib, and dexamethasone; TEAE = treatment-emergent adverse event.
a Definition of related: possible, probable, or definitely related to study drug as deemed by investigator.
b Graded using Common Terminology Criteria for Adverse Events, Version 4.0
c The adverse events leading to treatment discontinuation were recorded on the Off Treatment Notice Form.

This parameter was not evaluated in the PETHEMA GEM 2012 and IFM 2009 studies.

- ***Age***

The PETHEMA GEM2012 and IFM 2009 studies enrolled subjects ≤ 65 years, only SWOG S0777 study enrolled subjects > 65 years of age. The summary of safety in subjects by age group (≤ 65 years versus > 65 years, and ≤75 years versus > 75 years) for the SWOG S0777 study is presented below.

Table 52 : Overview of Treatment-emergent Adverse Events During Initial Treatment by Age Group – Study SWOG S0777 (Safety Population)

	SWOG S0777			
	RVd (3-week cycles × 8 = 24 weeks)	**Rd (4-week cycles × 6 = 24 weeks)**	**RVd (3-week cycles × 8 = 24 weeks)**	**Rd (4-week cycles × 6 = 24 weeks)**
Subjects with at least 1:	**≤ 65 years**		**≤ 75 years**	
	N = 167 n (%)	**N = 149 n (%)**	**N = 234 n (%)**	**N = 232 n (%)**
TEAE	164 (98.2)	141 (94.6)	228 (97.4)	226 (97.4)
Grade 3 or 4 TEAE [a]	120 (71.9)	89 (59.7)	178 (76.1)	157 (67.7)
Grade 5 TEAE [a]	5 (3.0)	1 (0.7)	10 (4.3)	6 (2.6)
Treatment-emergent SAE	57 (34.1)	35 (23.5)	90 (38.5)	63 (27.2)
Treatment Discontinuation Due to TEAE[b]	32 (19.2)	11 (7.4)	51 (21.8)	19 (8.2)
Subjects with at least 1:	**> 65 years**		**> 75 years**	
	N = 95 n (%)	**N = 107 n (%)**	**N = 28 n (%)**	**N = 24 n (%)**
TEAE	91 (95.8)	104 (97.2)	27 (96.4)	24 (100.0)
Grade 3 or 4 TEAE [a]	80 (84.2)	87 (81.3)	22 (78.6)	19 (79.2)
Grade 5 TEAE [a]	1 (1.1)	2 (1.9)	0 (0.0)	1 (4.2)
Treatment-emergent SAE	48 (50.5)	38 (35.5)	15 (53.6)	10 (41.7)
Treatment Discontinuation Due to TEAE[b]	28 (29.5)	13 (12.1)	9 (32.1)	5 (20.8)

Rd = lenalidomide and dexamethasone; RVd = lenalidomide, bortezomib, and dexamethasone; SAE = serious adverse event; TEAE = treatment-emergent adverse event.
a Graded using Common Terminology Criteria for Adverse Events, Version 4.0
b The adverse events leading to treatment discontinuation were recorded on the Off Treatment Notice Form.
Note: Treatment-emergent adverse events include adverse events that started between the date of first dose and 30 days after the date of last dose.
Data cutoff date = 01 Dec 2016.

- ***ISS stage***

A summary of safety in subjects by baseline ISS stage during initial treatment for studies SWOG S0777, PETHEMA GEM2012 and IFM 2009 is presented below.

Table 53 : Overview of Treatment-emergent Adverse Events During Initial Treatment by ISS Stage (I or II Versus III) – Studies SWOG S0777, PETHEMA GEM2012 and IFM 2009 (Arm A) (Safety Population)

	PETHEMA GEM2012	IFM 2009	SWOG S0777	
	RVd[a] (4-week cycles × 6 = 24 weeks)	**RVd[b] (3-week cycles × 8 = 24 weeks)**	**RVd (3-week cycles × 8 = 24 weeks)**	**Rd (4-week cycles × 6 = 24 weeks)**
ISS Stage I or II				
Subjects with at least 1:	**N = 345 n (%)**	**N = 290 n (%)**	**N = 176 n (%)**	**N = 171 n (%)**
TEAE	302 (87.5)	288 (99.3)	171 (97.2)	165 (96.5)
Grade 3 or 4 TEAE [c]	132 (38.3)	220 (75.9)	130 (73.9)	111 (64.9)
Grade 5 TEAE [c]	4 (1.2)	1 (0.3)	2 (1.1)	2 (1.2)
Treatment-emergent SAE	101 (29.3)	70 (24.1)	65 (36.9)	35 (20.5)
Treatment Discontinuation Due to TEAE[d]	8 (2.3)	2 (0.7)	48 (27.3)	9 (5.3)
ISS Stage III				

Subjects with at least 1:	N = 107 n (%)	N = 66 n (%)	N = 86 n (%)	N = 85 n (%)
TEAE	95 (88.8)	66 (100.0)	84 (97.7)	80 (94.1)
Grade 3 or 4 TEAE [c]	50 (46.7)	57 (86.4)	70 (81.4)	65 (76.5)
Grade 5 TEAE [c]	5 (4.7)	0	4 (4.7)	1 (1.2)
Treatment-emergent SAE	44 (41.1)	22 (33.3)	40 (46.5)	38 (44.7)
Treatment Discontinuation Due to TEAE[d]	6 (5.6)	2 (3.0)	12 (14.0)	15 (17.6)

ISS = International Staging System; Rd = lenalidomide and dexamethasone; RVd = lenalidomide, bortezomib, and dexamethasone; SAE = serious adverse event; TEAE = treatment-emergent adverse event.
a Both RVd arms combined. For the PETHEMA GEM2012 study, TEAEs include all SAEs plus non-SAEs that the investigator considered related to study treatment.
b For the purpose of comparison to the PETHEMA GEM2012 and SWOG S0777 studies, the 8 cycles (24 weeks) of initial RVd therapy for Arm A in the IFM 2009 study are referred to as "initial treatment."
c Graded using Common Terminology Criteria for Adverse Events, Version 4.03 for the PETHEMA GEM2012 study and Version 4.0 for the IFM 2009 and SWOG S0777 studies.
d "Discontinuation" refers to study discontinuation for the PETHEMA GEM2012 study and treatment discontinuation for the IFM 2009 and SWOG S0777 studies.

- ***Baseline Creatinin clearance (CrCl)***

The summary of safety in subjects by baseline CrCl subgroup (< 60 mL/min or ≥ 60 mL/min) during initial treatment in presented below.

Table 54 : Overview of Treatment-emergent Adverse Events During Initial Treatment by Baseline Creatinine Clearance Group (< 60 mL/min and ≥ 60 mL/min) –Studies SWOG S0777, PETHEMA GEM2012 and IFM 2009 (Arm A) (Safety Population)

	PETHEMA GEM2012	IFM 2009	SWOG S0777	
	RVd[a] (4-week cycles × 6 = 24 weeks)	RVd[b] (3-week cycles × 8 = 24 weeks)	RVd (3-week cycles × 8 = 24 weeks)	Rd (4-week cycles × 6 = 24 weeks)
< 60 mL/min				
Subjects with at least 1:	**N = 70 n (%)**	**N = 33 n (%)**	**N = 78 n (%)**	**N = 76 n (%)**
TEAE	63 (90.0)	33 (100.0)	75 (96.2)	73 (96.1)
Grade 3 or 4 TEAE [c]	38 (54.3)	28 (84.8)	63 (80.8)	58 (76.3)
Grade 5 TEAE [c]	3 (4.3)	0	3 (3.8)	2 (2.6)
Treatment-emergent SAE	32 (45.7)	11 (33.3)	40 (51.3)	34 (44.7)
Treatment Discontinuation Due to TEAE[d]	6 (8.6)	1 (3.0)	18 (23.1)	14 (18.4)
≥ 60 mL/min				
Subjects with at least 1:	**N = 370 n (%)**	**N = 323 n (%)**	**N = 184 n (%)**	**N = 179 n (%)**
TEAE	322 (87.0)	321 (99.4)	180 (97.8)	171 (95.5)
Grade 3 or 4 TEAE [c]	137 (37.0)	249 (77.1)	137 (74.5)	117 (65.4)
Grade 5 TEAE [c]	4 (1.1)	1 (0.3)	3 (1.6)	1 (0.6)
Treatment-emergent SAE	106 (28.6)	81 (25.1)	65 (35.3)	38 (21.2)
Treatment Discontinuation Due to TEAE[d]	8 (2.2)	3 (0.9)	42 (22.8)	10 (5.6)

CrCl = creatinine clearance; Rd = lenalidomide and dexamethasone; RVd = lenalidomide, bortezomib, and dexamethasone; SAE = serious adverse event; TEAE = treatment-emergent adverse event.
a Both RVd arms combined. For the PETHEMA GEM2012 study, TEAEs include all SAEs plus non-SAEs that the investigator considered related to study treatment.
b For the purpose of comparison to the PETHEMA GEM2012 and SWOG S0777 studies, the 8 cycles (24 weeks) of initial RVd therapy for Arm A in the IFM 2009 study are referred to as "initial treatment."
c Graded using Common Terminology Criteria for Adverse Events, Version 4.03 for the PETHEMA GEM2012 study and Version 4.0 for the IFM 2009 and SWOG S0777 studies.
d "Discontinuation" refers to study discontinuation for the PETHEMA GEM2012 study and treatment discontinuation for the IFM 2009 and SWOG S0777 studies.

- ***ECOG performance status***

A summary of safety in subjects by baseline ECOG PS status (0 or 1 versus ≥ 2) is presented below.

Table 55 : Overview of Treatment-emergent Adverse Events During Initial Treatment by Baseline ECOG Performance Status (0 or 1 Versus ≥ 2) – Studies SWOG S0777 and PETHEMA GEM2012 (Safety Population)

	PETHEMA GEM2012	SWOG S0777	
	RVd[a] (4-week cycles × 6 = 24 weeks)	RVd (3-week cycles × 8 = 24 weeks)	Rd (4-week cycles × 6 = 24 weeks)
ECOG PS 0 or 1			
Subjects with at least 1:	**N = 377 n (%)**	**N = 233 n (%)**	**N = 217 n (%)**
TEAE	330 (87.5)	228 (97.9)	207 (95.4)
Grade 3 or 4 TEAE[b]	144 (38.2)	178 (76.4)	146 (67.3)
Grade 5 TEAE [b]	4 (1.1)	3 (1.3)	3 (1.4)
Treatment-emergent SAE	107 (28.4)	90 (38.6)	59 (27.2)
Treatment Discontinuation Due to TEAE[d]	10 (2.7)	54 (23.2)	17 (7.8)
ECOG PS ≥ 2			
Subjects with at least 1:	**N = 78 n (%)**	**N = 29 n (%)**	**N = 39 n (%)**
TEAE	69 (88.5)	27 (93.1)	38 (97.4)
Grade 3 or 4 TEAE [b]	37 (47.4)	22 (75.9)	30 (76.9)
Grade 5 TEAE [b]	5 (6.4)	3 (10.3)	0 (0.0)
Treatment-emergent SAE	38 (48.7)	15 (51.7)	14 (35.9)
Treatment Discontinuation Due to TEAE[c]	4 (5.1)	6 (20.7)	7 (17.9)

ECOG = Eastern Cooperative Oncology Group; PS = Performance Status; Rd = lenalidomide and dexamethasone; RVd = lenalidomide, bortezomib, and dexamethasone; SAE = serious adverse events; TEAE = treatment-emergent adverse event.
a Both RVd arms combined. For the PETHEMA GEM2012 study, TEAEs include all SAEs plus non-SAEs that the investigator considered related to study treatment.
b Graded using Common Terminology Criteria for Adverse Events, Version 4.03 for the PETHEMA GEM2012 study and Version 4.0 for the SWOG S0777 study.
c "Discontinuation" refers to study discontinuation for the PETHEMA GEM2012 study and treatment discontinuation for the SWOG S0777 study.

Discontinuation due to adverse events

Discontinuations due to TEAEs reported for ≥ 2 subjects in either treatment arm during initial treatment are summarized in the table below.

Table 56 : Discontinuation Due to TEAEs Reported in at Least 2 Subjects in Any Treatment Arm – Initial Treatment – Studies PETHEMA GEM2012, IFM 2009 (Arm A), and SWOG S0777 (Safety Population)

System Organ Class Preferred Term[a]	PETHEMA GEM2012	IFM 2009	SWOG S0777	
	RVd[b] (4-week cycles × 6 = 24 weeks) (N = 458) n (%)	RVd[c] (3-week cycles × 8 = 24 weeks) (N = 356) n (%)	RVd (3-week cycles × 8 = 24 weeks) (N = 262) n (%)	Rd (4-week cycles × 6 = 24 weeks) (N = 256) n (%)
Subjects With ≥ 1 TEAE Leading to Discontinuation[d]	14 (3.1)	30 (8.4)	60 (22.9)	24 (9.4)
Infections and Infestations	**4 (0.9)**	**1 (0.3)**	**4 (1.5)**	**1 (0.4)**
Infection	4 (0.9)	0	0	0
Septic shock	2 (0.4)	0	0	0
Pneumonia	0	0	2 (0.8)	1 (0.4)
General Disorders and Administration Site Conditions	**2 (0.4)**	**2 (0.6)**	**12 (4.6)**	**4 (1.6)**
Disease progression	2 (0.4)	0	0	0
Edema peripheral	0	0	2 (0.8)	0
Asthenia	0	0	3 (1.1)	0
Fatigue	0	1 (0.3)	5 (1.9)	1 (0.4)
Respiratory, Thoracic, and Mediastinal Disorders	**2 (0.4)**	**1 (0.3)**	**4 (1.5)**	**1 (0.4)**
Dyspnea	0	0	2 (0.8)	0
Gastrointestinal Disorders	**1 (0.2)**	**3 (0.8)**	**5 (1.9)**	**0**
Diarrhea	1 (0.2)	1 (0.3)	4 (1.5)	0
Skin and Subcutaneous Tissue Disorders	**1 (0.2)**	**2 (0.6)**	**2 (0.8)**	**4 (1.6)**
Rash	0	1 (0.3)	2 (0.8)	2 (0.8)
Nervous System Disorders	**0**	**12 (3.4)**	**39 (14.9)**	**3 (1.2)**
Peripheral sensory neuropathy	0	6 (1.7)	12 (4.6)	0
Neuropathy peripheral[e]	0	4 (1.1)	21 (8.0)	1 (0.4)
Peripheral motor neuropathy	0	0	3 (1.1)	0
Dizziness	0	0	2 (0.8)	0
Neurotoxicity	0	0	2 (0.8)	0
Vascular Disorders	**0**	**4 (1.1)**	**5 (1.9)**	**0**
Deep vein thrombosis	0	2 (0.6)	1 (0.4)	0
Hypotension	0	1 (0.3)	2 (0.8)	0
Musculoskeletal and Connective Tissue Disorders	**0**	**2 (0.6)**	**3 (1.1)**	**0**
Muscular weakness	0	0	2 (0.8)	0
Blood and Lymphatic System Disorders	**0**	**1 (0.3)**	**0**	**8 (3.1)**
Thrombocytopenia	0	1 (0.3)	0	4 (1.6)
Pancytopenia	0	0	0	2 (0.8)
Metabolism and Nutrition Disorders	**0**	**0**	**3 (1.1)**	**0**
Decreased appetite	0	0	2 (0.8)	0
Investigations	**0**	**0**	**2 (0.8)**	**1 (0.4)**
Liver function test abnormal	0	0	2 (0.8)	0

AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; Rd = lenalidomide and dexamethasone; RVd = lenalidomide, bortezomib, and dexamethasone; TEAE = treatment-emergent adverse event.
a System organ classes and preferred terms were coded using MedDRA Version 15.1. A subject with multiple events was counted only once in each preferred term and system organ class. System organ classes and preferred terms are listed in decreasing order of frequency for the RVd column in the PETHEMA GEM2012 study.
b Both RVd arms combined.
c For the purpose of comparison to the PETHEMA GEM2012 and SWOG S0777 studies, the 8 cycles (24 weeks) of initial RVd therapy for Arm A in the IFM 2009 study are referred to as "initial treatment."
d "Discontinuation" refers to study discontinuation for the PETHEMA GEM2012 study and treatment discontinuation for the IFM 2009 and SWOG S0777 studies. The TEAEs leading to treatment discontinuation were recorded on the Off Treatment Notice Form for the SWOG S0777 study.
e In the Off Treatment Notice form, neuropathy peripheral reported as a reason for discontinuation was not specified as sensory or motor.

Discontinuations due to TEAEs reported for ≥2 subjects during the initial treatment for the integrated analysis are presented below.

Table 57 : TEAEs Leading to Discontinuation in 2 or More Subjects – Initial Treatment – Studies PETHEMA GEM2012 and PETHEMA GEM2005 (Safety Population)

System Organ Class Preferred Term[a]	RVd[b] (PETHEMA GEM2012; 4-week cycles × 6 = 24 weeks) (N = 458) n (%)	VTD (PETHEMA GEM2005; 4-week cycles × 6 = 24 weeks) (N = 130) n (%)
Subjects With ≥ 1 TEAE Leading to Discontinuation[c]	14 (3.1)	12 (9.2)
Infections and Infestations	**4 (0.9)**	**0**
Infection	4 (0.9)	0
Septic shock	2 (0.4)	0
General Disorders and Administration Site Conditions	**2 (0.4)**	**1 (0.8)**
Disease progression	2 (0.4)	0
Nervous System Disorders	**0**	**8 (6.2)**
Neuropathy peripheral	0	4 (3.1)
Peripheral sensory neuropathy	0	4 (3.1)

MedDRA = Medical Dictionary for Regulatory Activities; RVd= lenalidomide, bortezomib, and dexamethasone; SAE = serious adverse event; TEAE = treatment-emergent adverse event; VTD = bortezomib, thalidomide, and dexamethasone.
a System organ classes and preferred terms were coded using MedDRA Version 15.1. A subject with multiple events was counted only once in each preferred term and system organ class. System organ classes and preferred terms are listed in decreasing order of frequency for the RVd column.
b Both RVd arms combined. For the PETHEMA GEM2012 study, TEAEs include all SAEs plus non-SAEs that the investigator considered related to study treatment.
c Study discontinuation for PETHEMA GEM2012 and treatment discontinuation for PETHEMA GEM2005.

Table 58 : TEAEs Leading to Discontinuation in 2 or More Subjects – Initial Treatment – Studies IFM 2009 and IFM 2013-04 (Safety Population)

System Organ Class Preferred Term[a]	RVd[a] (IFM 2009 Arm A; 3-week cycles × 4 = 12 weeks) (N = 356) n (%)	VTD (IFM 2013-04; 3-week cycles × 4 = 12 weeks) (N = 169) n (%)
Subjects With ≥ 1 TEAE Leading to Discontinuation[c]	23 (6.5)	19 (11.2)
Nervous System Disorders	**10 (2.8)**	**11 (6.5)**
Neuropathy peripheral	4 (1.1)	6 (3.6)
Peripheral sensory neuropathy	4 (1.1)	1 (0.6)
Vascular Disorders	**3 (0.8)**	**2 (1.2)**
Deep vein thrombosis	2 (0.6)	1 (0.6)
Respiratory, Thoracic, and Mediastinal Disorders	**1 (0.3)**	**3 (1.8)**
Pulmonary embolism	0	3 (1.8)

MedDRA = Medical Dictionary for Regulatory Activities; RVd= lenalidomide, bortezomib, and dexamethasone; TEAE = treatment-emergent adverse event; VTD = bortezomib, thalidomide, and dexamethasone.
a For the purpose of comparison to the IFM 2013-04 study, the 4 cycles (12 weeks) of initial RVd therapy for Arm A in the IFM 2009 study are referred to as "initial treatment."

Post marketing experience

Lenalidomide was first approved for marketing by the US Food and Drug Administration (FDA) on 27 Dec 2005. The most recent Periodic Safety Update Report (PSUR 14) covered the reporting period 27 Dec 2016 through 26 Dec 2017. As of the cut-off date for this PSUR, lenalidomide is approved in 83 countries worldwide, including the US, 28 countries in the European Union (EU), 3 countries in the European Free Trade Association (EFTA), as well as in 52 countries outside of the US and EU/European Economic Area (EEA).

As of the cut-off date for the most recent PSUR, approximately 686,537 patients have been exposed cumulatively to lenalidomide from all sources and all geographic areas. During the most recent PSUR interval, 183,357 patients have been exposed to lenalidomide from all sources and all geographic areas.

During the reporting period, nine new safety signals were evaluated: solid organ transplant (SOT) rejection and immune thrombocytopenia (ITP) were identified from the literature; leukocytoclastic vasculitis (LCV) was identified following a review of vasculitis for thalidomide; B-cell acute lymphoblastic leukemia (B-ALL) was identified in a German investigator-initiated trial; and the remaining five signals were identified by Pharmacovigilance Risk Assessment Committee (PRAC). Glaucoma, retinal disorders, acute generalized exanthematous pustulosis (AGEP) and increased human chorionic gonadotropin (hCG) were identified by PRAC in its assessment of the PSUR covering the period from 27 Dec 2015 to 26 Dec 2016. The signal of progressive multifocal leukoencephalopathy (PML) was identified by PRAC through the dedicated European Pharmacovigilance Issues Tracking Tool (EPITT) procedure.

2.5.1. Discussion on clinical safety

Overview of TEAE

With regard to the frailer and older population for the subjects of SWOG S0777, although the proportion of treatment discontinuation due to TEAE was higher than in other studies, especially in the RVd arm, this can be partly attributed to study conduct including management of discontinuations during the initial treatment period, the receipt of subsequent AMT, and the management of toxicities, which was consistent with standard clinical practice.

In SWOG S07777 study, RVd is associated with more Grade 3 or 4 TEAE related to study drug and greater treatment discontinuation due to TEAEs during the entire treatment period compared to Rd.

The RVd regimen was associated with comparable rates of TEAEs, for all grades as well as grades 3 and 4, with the VTD regimen. Fewer treatment discontinuations or dose reductions due to TEAE were reported in PETHEMA GEM2012.

TEAEs (any grade) frequencies by SOC reported in SWOG S0777 for the Rd arm were consistent with the well-known lenalidomide + dexamethasone association safety profile. No new risk has been identified.

TEAEs frequencies with RvD were variable throughout the studies but addition of bortezomib to lenalidomide and dexamethasone led to an overall similar safety profile, notably with particular increased risk for peripheral sensory neuropathy. This adverse effect, which occurs at a very common frequency as described in Velcade SmPC, may be reduced with a subcutaneous administration (SC) instead of intraveinous infusion of the product. Due to differences in reporting of adverse effects, it seems that the preferred term “peripheral neuropathy” for PETHEMA GEM2012 actually might contain both peripheral sensory neuropathy and peripheral neuropathy and was not clearly reported. PETHEMA GEM2012 was the only study where subjects received SC bortezomib.

In study SWOG S0777, subjects showed an increase in some TEAEs frequencies compared to the other studies, such as metabolism and nutrition disorders, investigations, musculoskeletal and connective tissue disorders and respiratory, thoracic, and mediastinal disorders, for both arms.

Safety data from the integrated analysis comparing TEAE between RVd and VTD should be assessed with caution as bortezomib route of administration, and so subsequent toxicity profile, was different for PETHEMA GEM2012 and IFM 2009 studies. Furthermore, some of TEAE rates in the VTD cohorts (for example “Blood and Lymphatic System Disorders”), are not consistent between studies. For IFM studies, the comparison was made on a 12 weeks duration of therapy which is quite short. The safety data are mostly supportive. However, no new safety concerns seem to emerge from these data.

The Grade 3 or 4 TEAEs frequencies were allocated similarly to the All grades frequencies. RVd was associated with higher adverse events frequencies than Rd, although these frequencies have to be considered taking into account the frailty and age of the population of the studies. Same grade 3 or 4 TEAEs were reported but at a lower frequency in studies PETHEMA GEM2012 and IFM 2009.

Both PETHEMA GEM2012 and IFM 2009 studies in the integrated analysis showed an increase in grades 3 or 4 TEAEs for Blood and Lymphatic System Disorders for the RVd regimen compared to the VTD regimen.

AESIs

In SWOG S07777 study, for overlapping toxicities of lenalidomide and bortezomib, higher frequencies in the RVd arm compared with the Rd arm were reported during initial treatment for TEAEs in the AESI categories of peripheral neuropathy (a difference of 36.6%), thrombocytopenia (difference of 11.9%), hepatic disorders (difference of 9.6%), cardiac arrhythmias (difference of 8.2%), and infections (difference of 6.2%).

In PETHEMA GEM2012 study, the frequencies of treatment-emergent AEs in the following categories were reported in ≥ 5% of subjects (both RVd arms combined) during the initial treatment phase: peripheral neuropathy (38.0%), neutropenia (31.9%), infections (31.2%), thrombocytopenia (25.3%), and hepatic disorders (8.1%) were reported.

In IFM 2009 study, the frequencies of TEAEs in the following categories were reported in ≥ 5% of subjects in Arm A (RVd; no transplant) during the initial treatment phase: peripheral neuropathy (56.5%), infections (52.8%), neutropenia (46.9%), thrombocytopenia (19.9%), hepatic disorders (13.2%), bleeding (7.0%), and cardiac arrhythmias (5.9%).

No new safety concerns were observed with RVd initial treatment in the NDMM setting when administered for up to 24 weeks, and no changes are proposed to the classification of these selected TEAEs as identified of potential risks in the Revlimid EU RMP.

SAEs

Overall, 40,1% of the subjects experienced SAEs in the RVd arm of SWOG S0777 study, versus 28,5% in the Rd arm. The results were consistent between the studies, unless for “Infections and Infestations” and “Respiratory, Thoracic, and Mediastinal Disorders” in PETHEMA study where reported at a higher frequency.

It should be noted that SAEs of neuropathies were not reported in ≥ 2% of the subjects despite the known effects of the association of bortezomib and lenalidomide and the reported frequency of grades 3 or 4 TEAEs.

Deaths

The rate of deaths is low during the initial treatment period, which is consistent with the non-aggressive type of the Multiple Myeloma.

For SWOG S0777 study, in the RVd arm, 5 subjects died of pneumonia, myocardial ischemia, coronary artery disease, diabetic hyperglycemic coma, and “death” (1 subject each), and 2 subjects died of their Myeloma. In the Rd arm, 3 subjects died of sepsis, coronary artery disease, and acute renal failure (1 subject each) and 3 subjects died of their Myeloma.

In PETHEMA GEM2012 (both arms combined), 6 subjects died of infection (4 subjects), cardiovascular disease (1 subject) and the last subject died from multiple causes (acute pulmonary edema, cardiac arrest, hypocalcemia, renal failure, and its Myeloma). 1 subject also died of unknown cause.

In IFM 2009 (arm A : RVd only), 1 subject died of respiratory distress.

Overall there were 103 deaths in SWOG S07777 RVd arm and 129 deaths in Rd arm. In the RVd arm, 9 of 11 deaths that occurred on treatment were due to a TEAE. These included coronary artery disease, myocardial infarction, myocardial ischemia, convulsion, diabetic hyperglycemic coma, influenza, pneumonia, death, and pulmonary embolism for 1 subject each. In the Rd arm, 7 of 12 deaths that occurred on treatment were due to a TEAE. Treatment-emergent AEs resulting in death included cardiac arrest, coronary artery disease, cerebrovascular accident, anemia, multiple organ failure, sepsis, encephalopathy, and acute renal failure for 1 subject each.

Second Primary Malignancies

There were no findings of an increase in secondary primary malignancies associated with adding bortezomib to the lenalidomide-dexamethasone combination.

Subgroup analysis

Age

The great age of subjects was associated with more TEAEs of any grade and also more TEAEs of grades 3 or 4, in RVd arm as well as in Rd arm. The safety profile of both combinations seems to converge with advanced age, probably more related to the associated comorbidities rather than with the regimen of treatment itself.

Score ISS

A more advanced disease, as characterized by the ISS Stage III, was associated with more grades 3 or 4 TEAE, treatment-emergent SAE or treatment discontinuation due to TEAE for all groups (RVd or Rd)

Clearance of creatinine

Lower baseline creatinine clearance was associated with more grades 3 or 4 TEAE, treatment-emergent SAE or treatment discontinuation due to TEAE for all groups (RVd or Rd), which is consistent with the safety profile of lenalidomide.

ECOG status

Frailer subjects (with an ECOG status $\geq$ 2) seem to be at higher risk for TEAEs of grades 3, 4, or 5 and treatment emergent SAEs. The small number of patients, precluding a robust assessment, should however be highlighted.

Discontinuations due to adverse events

The frequencies of discontinuations were quite variables between studies, taking into account that the assessment of toxicities could have been underestimated in PETHEMA GEM2012 compared to IFM 2009 and SWOG S07777.

Furthermore, the frailty and the advanced age of patients in SWOG S0777 led to more discontinuations.

Overall, despite the differences of frequencies of discontinuations among the studies, they were consistent with the known safety profile of lenalidomide and bortezomib.

Safety data from the integrated analysis showed that RVd regimen (with SC bortezomib) seems to be associated with less peripheral neuropathy toxicities leading to discontinuation than VTD regimen (with IV bortezomib), which is consistent with lenalidomide and thalidomide well-known safety profiles.

2.5.2. Conclusions on clinical safety

No new risks were identified for the combination of lenalidomide and bortezomib but there was an overlapping in some toxicities, which remained manageable. Overall the safety profile is acceptable.

2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.6. Risk management plan

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

The PRAC considered that the risk management plan version 36.4 is acceptable.

The CHMP endorsed the Risk Management Plan version 36.4 with the following content:

Safety concerns

Table 59 Summary of the safety concerns

Important Identified Risks	– Teratogenicity – Serious infection due to neutropenia – SPM Important Identified Risk Related to Indication/Target Population – For MCL: TFR
Important Potential Risks	– Cardiac failure – Cardiac arrhythmias – Ischaemic heart disease (including myocardial infarction) – Off-label use
Missing Information	None

Pharmacovigilance plan

Table 60 Ongoing and Planned Additional Pharmacovigilance Activities

Study/Activity Type, Title and Category (1 to 3)	Objectives	Safety Concerns Addressed	Status (planned, started)	Date for Submission of Interim or Final Reports (planned or actual)
MDS PASSes *Non-interventional: observational Category 1*	To gather safety data on the use of lenalidomide in MDS patients and monitor off-label use (prospective disease registry in transfusion-dependent low- and INT-1-risk MDS with an isolated del 5q [MDS-010] and a retrospective drug utilisation study of Revlimid in MDS [MDS-012]).	AML and survival. Safety profile in a 'real world' setting.	Ongoing	Safety updates will be submitted with future PSURs. The final study report for MDS-010 is expected Q1 2023. The final study report for MDS-012 is expected Q3 2023.
Revlimid TNE NDMM Registry *Non-interventional: Category 1*	The primary objectives are to compare the incidence of cardiovascular events between TNE NDMM patients treated with a first-line lenalidomide-containing regimen and those treated with a first-line non lenalidomide-containing regimen; and to identify, quantify, and characterise risk factors for cardiovascular events in this population of TNE NDMM patients.	Cardiac events (cardiac failure, cardiac arrhythmias, IHD [including MI]).	Ongoing.	An interim study report is expected 30 Jun 2024. The final study report is expected 01 Dec 2025. Safety updates will be submitted with future PSURs.
Monitoring of off-label use and Pregnancy Prevention Programme implementation *Category 3*	Monitoring of off-label use and implementation of PPP.	Monitoring of off-label use and pregnancy prevention.	Ongoing	Safety updates will be submitted with future PSURs.

Study/Activity Type, Title and Category (1 to 3)	Objectives	Safety Concerns Addressed	Status (planned, started)	Date for Submission of Interim or Final Reports (planned or actual)
Connect® MM Registry. *Category 3*	The primary objectives of the registry are to describe practice patterns of common first-line and subsequent treatment regimens (including lenalidomide based) in patients with previously untreated MM, whether or not eligible for transplant, as well as diagnostic patterns and occurrence of SPM in a 'real world' population.	SPM (AML and B-cell malignancies, NMSC and other SPM), cardiac events (cardiac failure, cardiac arrhythmias, IHD [including MI]), Serious Infection due to Neutropenia.	Ongoing	Safety updates will be submitted with future PSURs.

Connect® MDS/AML Disease Registry *Non-interventional: observational Category 3*	The objectives of the registry are: to describe patterns for diagnosis, prognosis, treatment, clinical monitoring and outcome measures in patients with MDS, ICUS and AML; to compare routine clinical practice patterns with existing management guidelines (eg, National Comprehensive Cancer Network); to describe treatment patterns and outcomes in del(5q) patients with or without additional cytogenetic abnormalities; and in non-del(5q) patients; and to summarise patient-reported outcomes (eg, HRQoL) and economic outcomes, and their association with patient characteristics, treatment regimens, and clinical outcomes. Exploratory objectives are: to evaluate molecular and/or cellular markers in the blood/bone marrow tissues and oral epithelial cells that may provide further prognostic classification of MDS and AML subtypes and/or may provide information on drug mechanism of action and on-therapy markers predictive of clinical outcomes and potentially impact clinical outcomes with therapy; to summarise the clinical status (eg, OS, PFS, response rate) of patients with or without mutations by treatment regimen, and to analyse the correlation between mutation detection/allele burden in bone marrow and peripheral blood samples. Data regarding SPM are also being collected.	SPM	Ongoing	Safety updates will be submitted with future PSURs.

Study/Activity Type, Title and Category (1 to 3)	**Objectives**	**Safety Concerns Addressed**	**Status (planned, started)**	**Date for Submission of Interim or Final Reports (planned or actual)**
RRMCL PASS *Category 3*	The study is designed as a retrospective non-interventional study of patients with RRMCL with the objective to quantify and characterise the event of TFR by tumour burden and the proportion of early deaths by tumour burden in patients treated with lenalidomide in a 'real world' setting.	TFR/high tumour burden and early deaths	Ongoing	Version 3 of the protocol was submitted on 14 Aug 2017, approved by PRAC on 26 Oct 2017 and endorsed by CHMP on 09 Nov 2017. The final study report could be available in Q4 2027. Safety updates will be submitted with future PSURs.

Risk minimisation measures

Table 61 Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Off-label Use	**Routine risk minimisation activities:** – Collection of off-label use data detailed in Section 4.4 of SmPC. **Additional risk minimisation measures:** None.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Collection of detailed data relating to indication as part of the national controlled distribution system, where possible per national regulation. **Additional pharmacovigilance activities:** o MDS PASSes. o PPP for off-label use tracking.
Safety Concern	**Risk Minimisation Measures**	**Pharmacovigilance Activities**
Important Identified Risks		
Teratogenicity	**Routine risk minimisation activities:** Section 4.3 of SmPC: contraindicated in pregnant women and in FCBP unless all the conditions of the Celgene PPP are met. Section 4.4 of SmPC: warnings and precautions for use – Criteria for women of non-childbearing potential – Counselling – Contraception – Pregnancy testing – Precautions for men – Additional precautions – Reference to educational materials, prescribing and dispensing restrictions. Section 4.6 of SmPC: fertility, pregnancy and lactation. Sections 4.8 and 5.3 of SmPC: the potential teratogenic effects of lenalidomide are highlighted. Pack size: The pack is based on a maximum 4-week supply of capsules to ensure that FCBP are required to obtain a new monthly prescription with a medically supervised pregnancy test. Legal status: Lenalidomide is subject to restricted medical prescription. **Additional risk minimisation measures** – Celgene PPP – Educational Programme o Direct HCP communication prior to launch o Direct HCP communication with findings from CC-501-TOX-004 o HCP kit to include booklet o Treatment algorithm, pregnancy reporting form, patient card, patient guide and checklists. – Therapy management	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** o Expedited reporting of all pregnancies as a serious event. o Optimise data collection and reporting of pregnancies by use of specific pregnancy reporting forms for collection of the pregnancy exposure and follow-up in HCP Kits. o Follow-up of all pregnancies until one year after delivery. o Root cause analysis of failed Celgene PPP as part of standard follow-up. o Review of PSURs (periodic and cumulative). **Additional pharmacovigilance activities:** o MDS PASSes. o Additional monitoring of implementation of Celgene PPP on a country specific basis in accordance with local legal framework and with agreement of the relevant NCA (ie, monitoring of patient card completion, monitoring by external agency and surveys).

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Teratogenicity (Continued)	○ Criteria for determining FCBP, Contraceptive measures and pregnancy testing for FCBP ○ Advice in SmPC, Dear HCP letter and educational materials – System to ensure appropriate measures have been completed. – Patient card to document childbearing status, counselling and pregnancy testing.	
Serious Infection due to Neutropenia	**Routine risk minimisation activities:** – Section 4.2 of SmPC: dose reduction advice for neutropenia. – Section 4.4 of SmPC: warning of neutropenia, and infection with or without neutropenia, and advice for monitoring patients, including blood testing for neutropenia. Advice that patients should report febrile episodes promptly. Advice regarding establishing HBV status before treatment, use in patients previously infected with HBV and monitoring for signs and symptoms of active HBV infection throughout therapy. – Listed as ADRs in Section 4.8 of SmPC. – Advice to patients in PL, including that the doctor is advised to check if the patient has ever had hepatitis B infection prior to starting lenalidomide treatment. **Additional risk minimisation measures:** None.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Event specific questionnaire for the collection of the AE and follow-up. **Additional pharmacovigilance activities:** ○ Connect® MM Registry ○ MDS PASSes.
SPM	**Routine risk minimisation activities:** – Section 4.4 of SmPC warning of SPM and advice for cancer screening. – Listed as ADRs in Section 4.8 of SmPC. – Advice to patients provided in PL. **Additional risk minimisation measures:** – Dear HCP letter. – HCP Kit: HCP Guide.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Event specific questionnaire for the collection of the AE and follow-up. **Additional pharmacovigilance activities:** ○ Connect® MM Registry ○ MDS PASSes ○ Connect® MDS/AML Disease Registry.

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
SPM (Continued)		○ Long-term follow-up (at least 5 years from the date of the randomisation of the last patient in the study) for SPM in all Celgene-sponsored clinical trials; 3 years for MDS PASSes. ○ Solicited reporting of SPM in all Celgene-sponsored clinical trials (status of trials will be updated with each PSUR and DSUR cycle).
Tumour Flare Reaction (MCL Indication)	**Routine risk minimisation activities:** – Section 4.2 of SmPC: dose interruption advice for TFR. – Section 4.4 of SmPC warning. – Listed as an ADR in Section 4.8 of SmPC. **Additional risk minimisation measures:** – HCP Kit: HCP Guide.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Event specific questionnaire for the collection of the AE and follow-up. **Additional pharmacovigilance activities:** ○ RRMCL PASS.
Important Potential Risks		
Cardiac Failure and Cardiac Arrhythmias	**Routine risk minimisation activities:** – Listed as ADRs in Section 4.8 of SmPC. – Listed in PL. **Additional risk minimisation measures:** None.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Event specific questionnaire for the collection of the AE and follow-up. **Additional pharmacovigilance activities:** ○ Connect® MM Registry ○ Revlimid TNE NDMM Registry ○ MDS PASSes.
Ischaemic Heart Disease (including myocardial infarction)	**Routine risk minimisation activities:** The association between ischaemic heart disease and lenalidomide is unknown. Close monitoring will continue. – Myocardial infarction is included in Sections 4.4 and 4.8 of the SmPC. **Additional risk minimisation measures:** None.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Event specific questionnaire for the collection of the AE and follow-up. **Additional pharmacovigilance activities:** ○ Connect® MM Registry. ○ Revlimid TNE NDMM Registry. ○ MDS PASSes.

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Off-label Use	**Routine risk minimisation activities:** – Collection of off-label use data detailed in Section 4.4 of SmPC. **Additional risk minimisation measures:** None.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Collection of detailed data relating to indication as part of the national controlled distribution system, where possible per national regulation. **Additional pharmacovigilance activities:** ○ MDS PASSes. ○ PPP for off-label use tracking.

Safety Concern	Routine Risk Minimisation Activities
Off-label Use (Continued)	**PL** This document details the indications for which lenalidomide is approved. **Routine risk minimisation activities recommending specific clinical measures to address the risk:** None. **Other routine risk minimisation measures beyond the Product Information:** Legal status: Lenalidomide is subject to restricted medical prescription.

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.8, 5.1, 6.5 and 8 of the SmPC are updated. The Package Leaflet has been updated accordingly.

As a consequence, the MAH submitted a request to add 7-capsule pack sizes for the 7.5 mg, 20 mg and 25 mg strengths of Revlimid (lenalidomide) to support the proposed posology and lenalidomide dose modification which was accepted by the CHMP.

Additionally, minor editorial changes have been introduced throughout the PI and annex II key elements of the RMM have been updated to include information on timing of blood and semen donation in line with the SmPC section 4.4.

2.7.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the MAH show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

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

3.1.2. Available therapies and unmet medical need

A number of drugs are authorized as initial treatment for adult patients with previously untreated multiple myeloma who are not eligible for transplant such as: lenalidomide in combination with dexamethasone (Rd) or lenalidomide in combination with melphalan and prednisone followed by lenalidomide for maintenance (MPR+R),; bortezomib in combination with melphalan and prednisone is indicated for the treatment of adult patients with previously untreated multiple myeloma who are not eligible for high dose chemotherapy with haematopoietic stem cell transplantation and thalidomide in combination with melphalan and prednisone is indicated as first line treatment of patients with untreated multiple myeloma, aged $\geqslant$ 65 years or ineligible for high dose chemotherapy.

Despite the introduction of therapeutic options with new mechanisms of action and a better understanding of the disease biology, MM is not curable with current therapies. Most patients still experience disease

relapse and require several lines of therapy (Agarwal, 2017; Larocca, 2017; van de Velde, 2017; Yong, 2016). The course of MM is characterized by subsequently shorter periods of remission and relapse following sequential lines of treatment (Agarwal, 2017; Larocca, 2017; Moreau, 2017). Thus, first-line therapy is generally accepted to be of primary importance in providing long-term benefits for MM patients (Mateos, 2015). Furthermore, many patients only receive 1 or at most 2 lines of treatment (Raab, 2016; Willenbacher, 2018; Yong, 2016). Thus, all patients with newly diagnosed multiple myeloma (NDMM) should receive the most effective therapy available upfront.

3.1.3. Main clinical studies

The clinical package of Lenalidomide for the proposed indication was supported by:

SWOG S0777 study a randomized, multicenter, Phase III clinical study studying lenalidomide and low dose dexamethasone (LLD) versus bortezomib, lenalidomide and low dose dexamethasone (BLLD) for induction, in patients with previously untreated multiple myeloma without an intent for immediate autologous stem cell transplant.

PETHEMA GEM2012 an open-label, randomized, multicenter, national trial studying induction therapy with bortezomib/lenalidomide/dexamethasone followed by high dose chemotherapy with melphalan-200 (MEL-200) versus busulfan-melphalan and consolidation with VRD-GEM in patients under 65 years old with newly diagnosed symptomatic multiple myeloma.

IFM 2009 study, a Phase 3, randomized, study comparing conventional dose treatment using a combination of lenalidomide, bortezomib and dexamethasone to high-dose treatment with peripheral stem transplant in the initial management of myeloma in patients up to 65 years of age.

An integrated analysis comparing the efficacy and safety of an initial treatment regimen of RVd (PETHEMA GEM2012 and IFM 2009) or VTD (PETHEMA GEM2005 and IFM 2013-04) in support of the treatment of TE patients with NDMM.

3.2. Favourable effects

Based on the results (1 December 2016 data cut-off date) from SWOG S0777 study in the ITT population, 170 of 263 subjects (64.6%) in the RVd arm and 196 of 260 subjects (75.4%) in the Rd arm had progressed or died, based on events as determined by IRAC review and applying EMA censoring rules. The median PFS was 41.7 months in the RVd arm compared to 29.7 months in the Rd arm (HR=0.76; 95% CI: 0.62 to 0.94; P=0.010). The results from the sensitivity analysis of the PFS were consistent with those observed in the primary analysis.

In addition, results in secondary endpoints such as overall survival (a statistically and clinically relevant difference of 21.9 months) or response rate (58,2% subjects in RVd arm versus 31,9% subjects obtained VGPR or CR at post-initial treatment) were consistent with the primary endpoints results. These results could be considered as sufficiently mature (>50% events in control arm). A negative effect of RVd on OS could reasonably be ruled out. Overall survival results for the updated cut-off 15 May 2018 are consistent with those in the primary analysis where a wide separation of the Kaplan-Meier curves is maintained through this latest follow-up. As of 15 May 2018, there was a 27% reduction in the risk of death for subjects in the RVd arm compared with those in the Rd arm (HR = 0.73; 95% CI = 0.57 to 0.94).

3.3. Uncertainties and limitations about favourable effects

There are no uncertainties and limitations about favourable effects.

3.4. Unfavourable effects

The most commonly reported grades 3 or 4 ADRs in the study SWOG S0777 for the arm RVd were peripheral sensory neuropathy (20.6% vs 1.6% for Rd), thrombocytopenia (17.2% vs 9.4% for Rd) and lymphopenia (18.7% vs 15.2% for Rd).

The most commonly reported grades 3 or 4 ADRs in the integrated analysis for RVd were neutropenia (12.9% vs 2.3% for VTD), thrombocytopenia (6.3% vs 0% for VTD), infections (9.8% vs 0% for VTD) and neuropathy peripheral (3.3% vs 6.9% for VTD).

Lenalidomide in combination with bortezomib and dexamethasone (RVd) was associated with an increase in treatment-emergent SAEs (40.1% vs 28.5%) compared to lenalidomide in combination with dexamethasone (Rd), during the initial treatment phase of study SWOG S0777. These treatment-emergent SAEs are coherent with the known safety profile of lenalidomide and bortezomib.

3.5. Uncertainties and limitations about unfavourable effects

There are no uncertainties and limitations about unfavourable effects.

3.6. Effects Table

Table 62 : Effects Table for Revlimid in combination with bortezomib and dexamethasone for the treatment of patients with previously untreated multiple myeloma without an intent for immediate autologous stem cell transplant (study SWOG S0777, data cut-of 1 December 2016)

Effect	Short Description	Unit	Treatment (RVd) N=263	Control (Rd) N=260	Uncertainties / Strength of evidence	References
Favourable Effects						
PFS	Median time from randomization to progression disease or death	Months	43.9 (39.4, 52.5)	32.8 (25.3, 39.9)	Results supported by sensitivity analysis	See 'clinical efficacy' section
OS	Median time from randomization to death of any cause	Months	89.1 (76.1, NE)	67.2 (58.4, 90.8)		
Unfavourable Effects						
Thrombocytopenia	Incidence of grade 3 or 4 ADRs	%	17.2	9.4	Safety data from initial treatment (induction) 24 week period	See 'clinical safety' section
Peripheral sensory neuropathy	Incidence of grade 3 or 4 ADRs	%	20.6	1.6		
Syncope	Incidence of grade 3 or 4 ADRs	%	8.8	2.7		
Hypokalaemia	Incidence of grade 3 or 4 ADRs	%	11.5	4.7		
Diarrhoea	Incidence of grade 3 or 4 ADRs	%	9.2	1.6		
Lung infection	Incidence of grade 3 or 4 ADRs	%	7.3	5.5		
Hypotension	Incidence of grade 3 or 4 ADRs	%	7.6	0		

Abbreviations: NE: not estimable; Rd: lenalidomide and dexamethasone RVd: lenalidomide, bortezomib, and dexamethasone; OS: overall survival; PFS: progression-free survival data

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

In the SWOG S0777 study, RVd as initial treatment for NDMM in TNE patients was associated with a significant better survival benefit, in PFS such as in OS, and a better response rate of the disease than Rd. No new risks were identified for the combination of lenalidomide and bortezomib but there was an overlapping in some toxicities, which remained manageable.

3.7.2. Balance of benefits and risks

In the TNE NDMM population, the efficacy of the RVd regimen is considered clinically relevant and the safety of such a combination manageable, the benefits are thus considered to outweight the combined risks. The overall B/R for Revlimid in combination with bortezomib and dexamethasone is indicated for the treatment of adult patients with previously untreated multiple myeloma who are not eligible for transplant is positive.

3.7.3. Additional considerations on the benefit-risk balance

The PETHEMA GEM2012 study was not designed to compare RVd regimen with the approved standard of care for induction in transplant-eligible patients (VD or VTD), but to compare two pre-transplant conditioning regimen after a similar induction by RVd. In addition, the study failed to demonstrate its primary objective as data were not mature with the chosen cut-off date to get enough events to reach PFS median. Similarly, the IFM 2009 study was not designed to compare RVd regimen with the approved standard of care for induction in transplant-eligible patients (VD or VTD), but to compare two therapeutic strategies using RVd as initial regimen treatment. The integrated analysis was based on the individual subject data from 4 identified randomized controlled trials (RCTs). Overall, for the transplant-eligible population, the design of the studies and the interpretation of the results of the integrated analysis do not allow to conclude on the superiority or non-inferiority in clinical efficacy of the RVd regimen compared to the standard of care. Therefore, the indication was restricted to patient with previously untreated multiple myeloma who are not eligible for transplant.

3.8. Conclusions

The overall B/R of Revlimid in combination with bortezomib and dexamethasone of adult patients with previously untreated multiple myeloma who are not eligible for transplant is positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following group of variations acceptable and therefore recommends by consensus the variations to the terms of the Marketing Authorisation, concerning the following changes:

Variations accepted		**Type**	**Annexes affected**
B.II.e.5.a.2	B.II.e.5.a.2 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change outside the range of the currently approved pack sizes	Type IB	I, IIIA, IIIB and A
B.II.e.5.a.2	B.II.e.5.a.2 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change outside the range of the currently approved pack sizes	Type IB	I, IIIA, IIIB and A
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, II, IIIB and A

Extension of indication to include treatment with Revlimid in combination with bortezomib and dexamethasone of adult patients with previously untreated multiple myeloma who are not eligible for transplant. As a consequence, the MAH submitted a request to add 7-capsule pack sizes for the 7.5 mg, 20 mg and 25 mg strengths of Revlimid (lenalidomide) to support the proposed posology and lenalidomide dose modification. Sections 4.1, 4.2, 4.4, 4.8, 5.1, 6.5 and 8 of the SmPC are updated; the Package Leaflet is updated in accordance. Additionally, minor editorial changes have been introduced throughout the PI and annex II key elements of the RMM have been updated to include information on timing of blood and semen donation in line with the SmPC section 4.4. The RMP (version 36.4) has also been updated.

The group of variations leads to amendments to the Summary of Product Characteristics, Annex II, Package Leaflet, Annex A and Labelling and to the Risk Management Plan (RMP).

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Revlimid is not similar to Ninlaro, Darzalex, Kyprolis, Farydak and Imnovid within the meaning of Article 3 of Commission Regulation (EC) No. 847/200. See appendix 1.

5. EPAR changes

The EPAR will be updated following Commission Decision for this group of variations. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Extension of indication to include treatment with Revlimid in combination with bortezomib and dexamethasone of adult patients with previously untreated multiple myeloma who are not eligible for transplant. As a consequence, the MAH submitted a request to add 7-capsule pack sizes for the 7.5 mg, 20 mg and 25 mg strengths of Revlimid (lenalidomide) to support the proposed posology and lenalidomide dose modification. Sections 4.1, 4.2, 4.4, 4.8, 5.1, 6.5 and 8 of the SmPC are updated; the Package Leaflet is

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Summary

Please refer to the Scientific Discussion Revlimid-II-102/G.