28 March 2019
EMA/CHMP/674052/2018
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Imnovid

International non-proprietary name: pomalidomide

Procedure No. EMEA/H/C/002682/II/0031/G

Note

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

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

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List of abbreviations

AE	Adverse event
ANC	Absolute neutrophil count
ASA	Acetylsalicylic acid
BTZ	Bortezomib
CI	Confidence interval
CR	Complete response
CRBN	Cereblon
CrCl	Creatinine clearance
CSR	Clinical Study Report
DEX	Dexamethasone
EBMT	European Group for Blood and Marrow Transplantation
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
EOI	Event of interest
EORTC	European Organization for Research and Treatment of Cancer
ESMO	European Society for Medical Oncology
EQ-5D	European Quality of Life-Five Dimensions
FDA	Food and Drug Administration
HR	Hazard ratio
HRQoL	Health-related quality of life
IDMC	Independent Data Monitoring Committee
IMWG	International Myeloma Working Group
IRAC	Independent Response Adjudication Committee
ISS	International Staging System
ITT	Intent-to-treat
IV	Intravenous
LD-DEX	Low-dose dexamethasone
LEN	Lenalidomide
MedDRA	Medical Dictionary for Regulatory Activities
MM	Multiple myeloma
MPD	Maximum planned dose
MTD	Maximum tolerated dose
NCCN	National Comprehensive Cancer Network
NDMM	Newly diagnosed multiple myeloma
OR	Odds ratio
ORR	Overall response rate
OS	Overall survival
PD	Progressive disease
PFS	Progression-free survival
PFS2	Progression-free survival after next-line therapy
PK	Pharmacokinetics
POM	Pomalidomide
PR	Partial response
PT	Preferred term
PVd	Pomalidomide-bortezomib-dexamethasone
QLQ-C30	Quality of Life Core 30
QLQ-MY20	Quality of Life Questionnaire for Patients with Multiple Myeloma
RMP	Risk Management Plan
RRMM	Relapsed or refractory multiple myeloma
SAE	Serious adverse event
sCR	Stringent complete response
SmPC	Summary of Product Characteristics
SMQ	Standardized MedDRA query
SOC	System organ class
SPM	Second primary malignancy
SQ	Subcutaneous
TEAE	Treatment-emergent adverse event
Vd	Bortezomib-dexamethasone
VGPR	Very good partial response
VTE	Venous thromboembolic events

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 Limited submitted to the European Medicines Agency on 29 June 2018 an application for a group of variations.

The following variations were requested in the group:

Variations requested		Type	Annexes affected
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	I
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
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, IIIB and A

Extension of indication to include treatment with Imnovid in combination with bortezomib and dexamethasone of adult patients with multiple myeloma who have received at least one prior treatment regimen including lenalidomide; as a result, sections 4.1, 4.2, 4.3, 4.4, 4.5, 4.8 and 5.1 of the SmPC are updated. As a further consequence, the MAH submitted a request to add 14-capsule pack sizes for the 1 mg, 2 mg, 3 mg and 4 mg Imnovid strengths to support the proposed posology and pomalidomide dose modification. The SmPC, Labelling and Package leaflet are updated in accordance. Finally, section 5.1 of the SmPC is updated in order to update the information on pomalidomide mechanism of action based on literature data. An updated RMP (version 15.0) is also submitted.

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

Imnovid was designated as an orphan medicinal product EU/3/09/672 on 8 October 2009. Imnovid was designated as an orphan medicinal product in the following indication: for the treatment of multiple myeloma (MM).

The new indication, which is the subject of this application, falls within the above mentioned orphan designation.

Information on paediatric requirements

Not applicable

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.

MAH request for additional market protection

The MAH requested consideration of its application in accordance with Article 14(11) of Regulation (EC) 726/2004 - one year of market protection for a new indication.

Protocol assistance

The MAH received Protocol Assistance from the CHMP on 25 January 2018 (EMEA/H/SA/3734/1/2017/PA/II). The Protocol Assistance pertained to clinical aspects of the dossier; in particular, the definition of the target population and confirmation of the unmet medical need in the lenalidomide-refractory subgroup and on significant benefit relating to the maintenance of the orphan designation with the new indication.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Robert James Hemmings Co-Rapporteur: Jorge Camarero Jiménez

Timetable	Actual dates
Submission date	29 June 2018
Start of procedure:	21 July 2018
CHMP Co-Rapporteur Assessment Report	26 September 2018
CHMP Rapporteur Assessment Report	14 September 2018
PRAC Rapporteur Assessment Report	14 September 2018
PRAC members comments	26 September 2018
Updated PRAC Rapporteur Assessment Report	n/a
PRAC Outcome	4 October 2018
CHMP members comments	8 October 2018
Updated CHMP Rapporteur's Joint Assessment Report	11 October 2018
Request for supplementary information and extension of timetable adopted by the CHMP on:	18 October 2018

Timetable	Actual dates
MAH's responses submitted to the CHMP on:	18 January 2019
Joint Rapporteur's updated assessment report on the MAH's responses circulated on:	13 February 2019
CHMP members comments	18 February 2019
Joint updated Rapporteur's updated assessment report on the MAH's responses circulated on:	25 February 2019
Request for supplementary information and extension of timetable adopted by the CHMP on:	28 February 2019
MAH's responses submitted to the CHMP on:	5 March 2019
Joint updated Rapporteur's updated assessment report on the MAH's responses circulated on:	14 March 2019
CHMP members comments	18 March 2019
CHMP opinion:	28 March 2019
The CHMP adopted a report on similarity of Imnovid with name of the authorised orphan medicinal products	28 March 2019
The CHMP adopted a report on the novelty of the indication/significant clinical benefit in comparison with existing therapies	28 March 2019

2. Scientific discussion

2.1. Introduction

Multiple myeloma (MM) is a malignant disorder of plasma cells, characterized by uncontrolled and progressive proliferation of a plasma cell clone. The proliferation of myeloma cells causes displacement of the normal bone marrow leading to dysfunction in normal hematopoietic tissue and destruction of the normal bone marrow architecture, resulting in progressive morbidity and eventual mortality.

MM is a heterogeneous disease in terms of response to treatment and survival. Prognostic features that contribute to this heterogeneity can be related to disease biology, patient characteristics (eg, age, frailty, and comorbidities), and prior treatment. The disease remains incurable using current therapies. Therefore, most patients experience disease relapse and will require multiple effective lines of therapy.

Lenalidomide-based therapy is a major current standard of care in MM, and it is expected that the vast majority of patients will receive lenalidomide for the treatment of newly diagnosed MM (NDMM) and/or early relapsed refractory MM (RRMM). Consequently, the treatment where lenalidomide is no longer an option, including refractory patients, represent a clinically relevant population. Currently, there are no treatments that were developed specifically to address this patient population but there are still available treatment options for patients who are lenalidomide refractory (e.g. daratumumab or carfilzomib based regimens).

Pomalidomide (POM) is an immunomodulatory agent whose mechanism of action is primarily mediated through direct antimyeloma tumoricidal and immunomodulatory activities.

Pomalidomide has direct anti-myeloma tumoricidal activity, immunomodulatory activities and inhibits stromal cell support for multiple myeloma tumour cell growth. Specifically, pomalidomide inhibits proliferation and induces apoptosis of haematopoietic tumour cells. Additionally, pomalidomide inhibits the proliferation of lenalidomide resistant multiple myeloma cell lines and synergises with dexamethasone in both lenalidomide sensitive and lenalidomide resistant cell lines to induce tumour cell apoptosis. Pomalidomide enhances T cell- and natural killer (NK) cell-mediated immunity and inhibits production of pro-inflammatory cytokines (e.g., TNF α and IL 6) by monocytes. Pomalidomide also inhibits angiogenesis by blocking the migration and adhesion of endothelial cells.

POM is currently approved in combination with dexamethasone for the treatment of adult patients with relapsed and refractory multiple myeloma who have received at least two prior treatment regimens, including both lenalidomide and bortezomib, and have demonstrated disease progression on the last therapy.

The indication proposed by the MAH and approved by the CHMP is as follows: Imnovid in combination with bortezomib and dexamethasone is indicated in the treatment of adult patients with multiple myeloma who have received at least one prior treatment regimen including Lenalidomide (SmPC, section 4.1).

The recommended starting dose of Imnovid is 4 mg orally once daily on Days 1 to 14 of repeated 21-day cycles.

Pomalidomide is administered in combination with bortezomib and dexamethasone, as shown in Table 1.

The recommended starting dose of bortezomib is 1.3 mg/m^2 intravenous or subcutaneous once daily, on the days shown in Table 1. The recommended dose of dexamethasone is 20 mg orally once daily, on the days shown in Table 1. Treatment with pomalidomide combined with bortezomib and dexamethasone should be given until disease progression or until unacceptable toxicity occurs.

Table 1. Recommended dosing scheme for Imnovid in combination with bortezomib and dexamethasone

Cycle 1-8	Day (of 21-day cycle)																				
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
Pomalidomide (4 mg)	•	•	•	•	•	•	•	•	•	•	•	•	•	•							
Bortezomib (1.3 mg/m^2)	•			•				•			•										
Dexamethasone (20 mg) *	•	•		•	•			•	•		•	•									
Cycle 9 onwards	Day (of 21-day cycle)																				
	1		2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
Pomalidomide (4 mg)	•		•	•	•	•	•	•	•	•	•	•	•	•	•							
Bortezomib (1.3 mg/m^2)	•								•													
Dexamethasone (20 mg) *	•		•						•	•												

* For patients > 75 years of age, see Special populations.

2.2. Non-clinical aspects

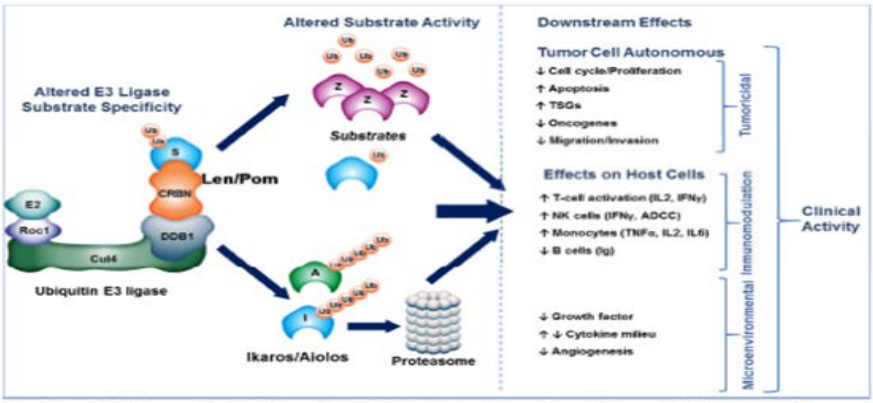
2.2.1. Introduction

The applicant has submitted a non-clinical overview addendum to support the inclusion of additional text in section 5.1 of the SmPC.

2.2.2. Pharmacology

- *In vitro pharmacology*

  Molecular Mechanism of action



A = aiolos; CRBN = cereblon; CUL4 = cullin 4; DDB1 = deoxyribonucleic acid damage-binding protein 1; I = ikaros; IFNγ = interferon gamma; Ig = immunoglobulin; IL = interleukin; IRF4 = interferon regulatory factor 4; IL-2 = interleukin-2; Len = lenalidomide; NK = natural killer; Pom = pomalidomide; Roc1 = regulator of cullins 1; S = substrate; TSGs = tumor suppressor genes; Ub = ubiquitin; Z = additional substrates.
Cartoon illustrates how CRBN containing E3 ligase functions in tumor cell in the presence of lenalidomide or pomalidomide. Engagement of lenalidomide or pomalidomide is proposed to alter substrate specificity of CRBN leading to alteration of the balance of protein homeostasis resulting in ultimate biological effects. Pomalidomide binding to CRBN causes ubiquitination of substrate proteins and subsequent downstream effects (Gandhi 2014; Kronke 2014; Lopez-Girona, 2011; Lopez-Girona, 2012; Lu, 2014).

Figure 1 Proposed mechanism of action of pomalidomide in multiple myeloma

Pomalidomide has a dual mechanism of action, it is directly tumoricidal for MM cells, and it also has immunomodulatory activity with direct effects on T and NK-mediated immunity.

Pomalidomide's pleiotropic activities in a range of cell types including MM cells and immune effector cells suggests the existence of multiple molecular target molecules and downstream modulation of multiple molecular pathways.

The molecular mechanism of action of pomalidomide has been investigated in MM cell lines and in primary tumor cells and human mononuclear cells. Pomalidomide inhibits proliferation and induces apoptosis in a range of MM cell lines and this has been linked to its ability to induce tumor suppressor gene expression, caspase activation, and cell cycle arrest.

In vitro activities of pomalidomide across multiple MM cell lines include effects on the cell cycle such as G0/G1 arrest associated with up-regulation of the cyclin- dependent kinase (CDK) inhibitor p21WAF-1 (Escoubet-Lozach, 2009), downregulation of translational checkpoint protein eIF4E and concomitant decrease in the protein level of C/EBPβ isoforms and downregulation of IRF4 (Li, 2011). Interferon regulatory factor 4 is a critical factor for MM cell survival and IRF4 inhibition is toxic to myeloma cell lines. Consistent with a key role of IRF4 in MM cell survival, IRF4 expression has been found to correlate with poor clinical outcomes in several hematological malignancies (Iida, 1997; Shaffer, 2009). In primary human monocytes and T cells, pomalidomide regulates activity of Rho GTPases and the formation of

F-actin through activating Rho guanosine-5'-triphosphate binding and hydrolyzing enzymes (GTPases) signaling with downstream effects on actin cytoskeleton, immune synapse formation and induction of IL-2 expression (Xu, 2009).

The possibility of a common molecular mediator that is proximal to the downstream modulation of multiple signaling pathways was explored in various cell types. The first suggestion of a common molecular mediator was the finding that thalidomide was shown to bind cereblon a protein responsible for the teratogenic effects of thalidomide in zebrafish and chicken embryos (Ito, 2010). Cereblon forms a ubiquitin E3 ligase complex with DDB1, CUL4 and protein Roc1 and thalidomide treatment has been shown to inhibit the ubiquitin ligase activity of the complex (Ito, 2010). E3 ubiquitin ligases are responsible for the poly-ubiquitination of a variety of substrate proteins. Pomalidomide and lenalidomide are analogs of thalidomide. It was showed that pomalidomide and lenalidomide bind human cereblon, and can modulate ubiquitination of substrates within the complex and that the expression of cereblon in myeloma cells is linked to both the efficacy of pomalidomide and lenalidomide and to the acquisition of resistance to lenalidomide (Report DM2528; Lopez-Girona, 2012).

The affinities of pomalidomide and lenalidomide for binding to cereblon were similar (Report DM2528). In U266 myeloma cell extracts, pomalidomide was shown to bind to the cereblon-DDB1 complexes (Report DM2528; Lopez-Girona, 2012). Both pomalidomide and lenalidomide competed for thalidomide analog bead binding with potencies of ~2 μM, a concentration achieved clinically at peak exposure of effective lenalidomide concentrations (Chen, 2007).

When cereblon levels were decreased transiently in myeloma cells by small interfering (si) ribonucleic acid against human cereblon, pomalidomide and lenalidomide were no longer able to inhibit proliferation and cell cycle progression. Expression of wild-type cereblon in KMS12 myeloma cells enhanced the effects of pomalidomide to decrease expression of oncogenes c-myc and IRF4 and increase p21, effects that are abrogated by overexpression of a pomalidomide/lenalidomide binding defective mutant, FH-cereblonYW/AA. In stable myeloma cell lines selected for 60% and 75% reduction of cereblon, the potency of pomalidomide antiproliferative activity was reduced but at high concentrations; notably, maximal proliferation inhibition, similar to that seen with the parental cell line, could be achieved. In activated human T cells in which cereblon was transiently decreased, IL-2 and TNF-α induction by pomalidomide was markedly reduced.

An important aspect of the clinical use of lenalidomide is that tumours can acquire resistance to lenalidomide efficacy over time (Bjorklund, 2011; Chen, 2007; Zhu, 2011). This phenomenon was replicated with *in vitro* cell culture studies by long-term exposure to increasing concentrations of lenalidomide until the cells were resistant to antiproliferative effects up to 30 μM lenalidomide. These results indicated that cereblon expression decreased concurrently with the decrease of efficacy of lenalidomide (Report DM2528) (Zhu, 2011). However, pomalidomide maintained efficacy, although with somewhat lower potency, in these lenalidomide-resistant cells.

Cereblon-mediated mechanisms at least partially explain the pleiotropic effects of pomalidomide, including inhibition of tumor cell proliferation, induction of tumor cell apoptosis, and activation of immune effector cells (Gandhi, 2014; Lopez-Girona, 2012; Zhu, 2011; Zhu, 2013). The hematopoietic transcription factors, Aiolos and Ikaros, were first identified as cereblon substrate proteins degraded in tumour or immune cells in the presence of lenalidomide. Aiolos and Ikaros were initially discovered as regulators of T cells and are required for proper hematopoiesis, particularly lymphocyte development and plasma cell maturation (John, 2011). The expression of Aiolos and Ikaros is required for the proliferation of some MM cell lines (Krönke, 2014; Lu, 2014). Upon binding to cereblon, lenalidomide and pomalidomide induce ubiquitination and proteasomal degradation of Aiolos and Ikaros in a time- and concentration- dependent manner, leading to both direct cytotoxic and immunomodulatory effects (Bjorklund, 2015; Gandhi, 2014; Krönke, 2014; Lu, 2014). In MM cells, degradation of Aiolos and Ikaros

leads to decreased expression of IRF4 and c-Myc, cell-cycle arrest, decreased proliferation, and increased apoptosis (Bjorklund, 2015; Lopez-Girona, 2011; Lu, 2014). In MM.1S or U266 cells, short hairpin RNA (shRNA)-mediated knockdown of Ikaros and Aiolos was required to be sustained for more than 24 hours, to achieve effective downregulation of c- Myc and IRF4 levels (Bjorklund, 2015).

Pomalidomide- and lenalidomide-induced degradation of these transcription factors in immune cells provides a mechanistic link for increased IL-2 production in T cells and activation of T, NK, and NKT cells (Gandhi, 2014; Hagner, 2015a; Ramsay, 2008; Schafer, 2003; Wu, 2008). In primary human T cells treated with lenalidomide or pomalidomide, time-dependent degradation of Aiolos and Ikaros was observed as early as 1 hour after drug treatment, with stronger effect observed with pomalidomide as compared to lenalidomide. In Lopez-Girona, 2012, culture with lenalidomide or pomalidomide enhanced IL-2 and TNF-α secretion by human T cells pre- cultured with phytohaemagglutinin for 24 hours and these effects were significantly reduced by knockdown of cereblon using shRNA. Furthermore, ability of lenalidomide or pomalidomide to induce Aiolos and Ikaros degradation in T cells was abrogated in the presence of small interfering ribonucleic acid (siRNA) targeting cereblon, confirming that lenalidomide and pomalidomide induce degradation of Aiolos and Ikaros in a cereblon-dependent manner.

Knockdown of Aiolos and Ikaros with siRNAs resulted to 61% and 67% decrease in the IL-2 messenger ribonucleic acid (mRNA) and protein, respectively, providing a mechanistic basis for lenalidomide and pomalidomide pharmacological effect in T cells (Gandhi 2014).

Pomalidomide therapy led to reduction in the levels of Ikaros protein in T cells and NK cells in patients with relapsed lenalidomide-refractory MM, which was detected as early as 2 to 4 hours after dosing and was maximal 1 week after dosing (Sehgal, 2015). Depletion of Ikaros in these patients correlated with changes in immune cell profile and function including an increase in circulating T cells and NK cells, increase in the expression of CD16, CD56, and NKG2D on NK cells, consistent with therapy-induced activation of NK cells, and increase in the production of cytokines by T cells and NK cells. In patients treated with lenalidomide, decreased expression of Aiolos and Ikaros has also been observed in multiple cell types (including T and NK cells) (Gandhi, 2014; Hagner, 2015a). The identification of Aiolos and Ikaros and characterization of their degradation in response to lenalidomide and pomalidomide provide additional insights into the molecular mechanisms of cytotoxicity and immunomodulation.

Aiolos and Ikaros have now been identified as common substrate proteins in a variety of cell types including MM, MDS, MCL, DLBCL, and T cells (Gandhi, 2014; Hagner, 2015; Hagner, 2015a; Krönke, 2014; Lu, 2014). However, additional substrates continue to be identified, which support the differential substrate hypothesis and provide insights into differential effects of lenalidomide and pomalidomide. ZFP91, a zinc finger protein and a putative ubiquitin ligase, was identified as a novel lenalidomide- and pomalidomide-dependent substrate (An, 2017). Lenalidomide and pomalidomide promote binding of ZFP91 to cereblon, followed by ubiquitination and degradation in MM1.S cells in vitro. When MM.1S cells were treated with increasing concentrations of thalidomide, lenalidomide, and pomalidomide promoted ZFP91 degradation to a similar extent while thalidomide had a minimal effect

Another substrate, casein kinase 1alpha (CK1α), was identified as a substrate of lenalidomide but not pomalidomide in del(5q) MDS (Krönke, 2015). Lenalidomide induces significant degradation of CK1α and that may underlie its clinical activity in MDS. In contrast, Ikaros is a shared substrate between lenalidomide, pomalidomide, and thalidomide in MDS cells. Additionally, distinct kinetics of substrate degradation and downregulation of their downstream targets by lenalidomide and pomalidomide may, at least in part, underlie differential activity of these compounds. In the U266 cell line, pomalidomide was more effective than lenalidomide in triggering degradation of Aiolos and Ikaros 6 hours following treatment across a range of concentrations tested. Pomalidomide had a greater effect than lenalidomide on the rate of either Ikaros or Aiolos degradation and this correlated with its greater growth inhibitory effect (Bjorklund, 2015).

Cereblon, Aiolos, and Ikaros Gene Expression Studies

In Heintel, 2013, cereblon expression was measured by reverse transcription polymerase chain reaction (RT-PCR) against cereblon exons 8 and 9 in 49 bone marrow samples of patients with newly diagnosed multiple myeloma (NDMM) treated with lenalidomide plus dexamethasone. In this study, increased median cereblon mRNA expression correlated with treatment response such that the higher expression levels correlated with a better clinical response (i.e., median cereblon expression levels of 3.45, 3.75, 2.01, 0.78 and 0.7 were associated with complete response (CR), very good partial response (VGPR), partial response (PR), stable disease (SD) and progressive disease (PD), respectively). There were overlapping confidence levels within the defined thresholds such that the measurement of cereblon mRNA transcript levels were not clearly separated for the responses (e.g., the range of cereblon expression in the CR population is 0.81 to 7.26, VGPR is 0.6 to 28.74, PR is 0 to 6.7, SD is 0 to 2.37 and PD is 0.31 to 1.09). Finally, the total bone marrow compartment was used to quantify the amounts of cereblon mRNA transcript, instead of purified CD138 positive MM cells. Schuster, 2014 measured cereblon gene expression using an Affymetrix GeneChip (Human Genome U133 + 2.0 array) from 53 MM patients relapsed/refractory to both lenalidomide and bortezomib who were then subsequently treated with pomalidomide plus dexamethasone. To evaluate progression free survival and overall survival with cereblon expression data, this investigation utilized a quartile analysis system where quartile cut-off points for cereblon normalized median expression was defined as cereblon < 0.889 (Q1), cereblon < 1.027 (Q2) and cereblon > 1.027 (Q3 and Q4) was defined. The results indicated lower clinical response for those patients who expressed less than the normalized median cereblon expression in lowest quartile (Q1) than those in the upper three quartiles (Q2-Q4) (~10% vs. 40% respectively; p= not significant). Schuster, 2014 reported that measurement of low cereblon expression significantly correlated with progression free survival (3.0 vs. 8.9 mos) and overall survival (9.1 vs. 27.2 mos). In contrast, Heintel, 2013 found no significant correlation between cereblon expression and progression free survival or overall survival, highlighting the variability in the technical and analytical approaches of these two studies.

Broyl, 2013 measured cereblon gene expression using an Affymetrix GeneChip (Human Genome U133 + 2.0 array) from 95 bone marrow samples from MM patients on thalidomide maintenance. The results indicated that cereblon gene expression significantly correlated with an extended progression free survival; however, there was no association with an upgrade of response. Interestingly, Broyl, 2013 did not use a validated Affymetrix assay test, the quartile cut-off algorithm presented by Schuster, 2012 and later published (Schuster, 2014), although both groups used the same gene expression assay based on the same Affymetrix probes for their analysis.

Neri, 2013 performed quantitative RT-PCR targeting cereblon exons 8-9 and exons 10-11 on 17 MM patients prior and after disease progression on a lenalidomide-based regimen, thereby classifying these patients as having acquired resistance to lenalidomide. The result showed that low cereblon mRNA significantly correlated with shorter progression free survival and a lack of lenalidomide response.

In a study by Huang, 2014, immunohistochemical (IHC) analysis was performed on cereblon protein in paraffin-embedded bone marrow sections from 40 relapsed/refractory (RR) MM patients receiving lenalidomide plus dexamethasone, 45 NDMM patients who received thalidomide plus dexamethasone, and 22 NDMM patients who received melphalan plus bortezomib and prednisolone. The IHC scoring method used diffuseness and the intensity of positively stained malignant plasma cells with a range from 0 to 8, with a defined cut-off of ≥ 4.5 as a determination of a cereblon positive (CRBN+) patient and < 4.5 as a cereblon negative (CRBN-) patient. In both the lenalidomide plus dexamethasone and the thalidomide plus dexamethasone cohorts, the investigators found that the overall response rates were higher in CRBN+ patients versus those determined to be CRBN- (79% vs. 33% and 75% vs. 29% respectively). The particular anti- cereblon antibody utilized in this study is of low specificity. In a study

published by Gandhi, 2014a; the same antibody was examined by Western blot analysis where it was shown to have multiple non-specific bands for cereblon, suggesting that the total staining observed in these slides was not cereblon only, but contaminated with non-specific binding. The antibody was also found to be nonspecific in IHC testing (Ren, 2016). Additionally, even though a cut-off score of ≥ 4.5 showed a higher overall response, it failed to identify all patients who would not respond to lenalidomide. This is highlighted by the observation that the only patient to achieve a CR in the cohort co-administered lenalidomide and dexamethasone had a cut-off score <4.5 and was therefore considered CRBN-. Additionally, another 28% of those considered to be CRBN- achieved at least a PR or better, further highlighting the difficulty in using this particular assay for its predictive value.

A retrospective study by Zhu, 2014 investigated Ikaros and Aiolos gene expression data from 44 patients with refractory MM treated with pomalidomide and dexamethasone. Quartile analysis of Ikaros and Aiolos gene expression data prior to therapy suggested that there was a better overall response in those expressing the highest levels of Ikaros, but that there was no correlation with Aiolos expression (Zhu, 2014).

Development of Analytical Assays and Retrospective Testing

Celgene has developed analytically validated assays for cereblon, Aiolos, and Ikaros and performed retrospective testing. Specifically, Celgene developed a highly sensitive and specific anti-cereblon antibody (CRBN65), and an analytically validated semi-quantitative IHC assay using this antibody for detecting cereblon protein in patient samples (Gandhi, 2014a; Ren, 2016). This assay has been used in the analysis of clinical samples (pre-treatment bone marrow biopsy) from MM patients to investigate the potential role of cereblon level to response to lenalidomide or pomalidomide-based regimen (Kalff, 2015; Sehgal, 2015).

Celgene validated assay for cereblon was utilized in an exploratory biomarker study conducted as a part of the Study CC-4047-MM-010 to evaluate the safety and efficacy of pomalidomide in combination with low dose dexamethasone in a large cohort of subjects with RRMM. Objectives of the exploratory biomarker study included investigation of utility of several potential biomarkers as markers predictive of pomalidomide response or resistance. Five biomarkers were chosen (cereblon, cMYC, IRF4, BLIMP1, and XBP1) and correlative analyses were conducted in 224 subjects. Clinical responses were observed with all cereblon expression levels. There was a trend in progression free survival (PFS; P = 0.038) and a potential trend in overall survival (OS; P = 0.059) in favor of high cereblon expressers; however, there was no notable difference in overall response rate (ORR). Overall response rate (30%), median PFS (17.7 weeks) and median OS (52.3 weeks) in low cereblon expressers were comparable to the intent-to-treat population (ORR, 33%; median PFS, 20.0 weeks; median OS, 51.7 weeks). The results of this biomarker study, conducted with Celgene validated cereblon assay, do not support cereblon as a biomarker for selecting patients for pomalidomide therapy (Exploratory Biomarker Study, Clinical Study Report CC-4047-MM-010)1.

Additionally, Celgene has developed novel, dual stain IHC assays for both Ikaros and Aiolos (with CD138) (Ren, 2016). A small study investigating alternative schedules of pomalidomide and dexamethasone found no correlation between levels of Ikaros or Aiolos as measured by this IHC assay (Sehgal, 2015). In a larger phase II study of lenalidomide maintenance following autologous stem cell transplant, IHC analysis found no correlation with Aiolos protein measurement on PFS or OS (Kalff, 2015). However, in the same study, they found that the highest quartile of Ikaros protein levels significantly correlated with an inferior PFS and OS (Kalff, 2015). Analysis of a public dataset of mRNA expression of either Ikaros or Aiolos showed no significant correlation with disease pathogenesis from healthy donors, to MGUS, smoldering myeloma, NDMM, or relapse and/or refractory MM (RRMM) (Bjorklund, 2015). Yet, dual-stain (CD138/Ikaros or CD138/Aiolos) immunohistochemistry analysis indicated a trending increase of Ikaros and a significant increase in Aiolos when comparing normal versus MM bone marrow.

2.2.3. Pharmacokinetics

No new non-clinical data have been submitted.

2.2.4. Toxicology

No new non-clinical data have been submitted.

2.2.5. Ecotoxicity / environmental risk assessment

The MAH was asked to provide suitable information on an experimentally derived n-octanol/water partition coefficient (log Kow) of pomalidomide in order to assess its PBT potential. The calculated n-octanol/water partition coefficient value of -1.16 was used in the environmental risk assessment (ERA) submitted in the original marketing authorization application (MAA) for pomalidomide submitted on 29 May 2012 (EMEA/H/C/2682/0000). The logKow for POM has also been determined experimentally, using a shake flask method. The derived logKow value was determined to be 0.58, with a standard deviation of 0.02.

2.2.6. Discussion on non-clinical aspects

The pleiotropic activities of pomalidomide on a range of cell types including MM cells and immune effector cells suggested modulation of multiple molecular pathways. Indeed, activity of pomalidomide and lenalidomide are cell type- and context-dependent (Bartlett, 2004; Escoubet-Lozach, 2009; Hayashi, 2005; Lu, 2009; Teo, 2005; Xu, 2009; Zhu, 2008). Activities included effects on the cell cycle such as G0/G1 arrest associated with the upregulation of the cyclin-dependent kinase (CDK) inhibitor p21WAF-1 (Escoubet-Lozach, 2009), downregulation of the expression of IRF4 in both MM cell lines (Li, 2011), and modulation of Rho guanosine-5'- triphosphate binding and hydrolyzing enzymes (GTPases) which are critical for actin hyperpolymerization and immune synapse formation (Xu, 2009).

From a technical perspective, the use of Affymetrix GeneChip microarrays for absolute measurement of a specific mRNA transcript is not considered a robust approach. In practice, microarrays serve more accurately to measure relative levels of mRNA transcripts in comparison to a reference point, rather than background. Also, the well published difficulties of DNA microarray technology, including accuracy, precision, and specificity would suggest that there is too much variability associated in the data output and therefore the weight given to the analysis of that data. In consideration of these technical challenges, the cut-offs retrospectively determined by Schuster, 2014 are narrow and overlapping, making it difficult to assess the predictive value of cereblon in larger prospective trials.

There are multiple limitations of with measuring cereblon, Aiolos, and Ikaros mRNA or protein levels to correlate with clinical outcome. First, cereblon mRNA levels and protein levels do not correlate in cell lines (Gandhi, 2014a). In 12 MM cell lines, both mRNA and protein levels of cereblon was compared to their relative sensitivity to lenalidomide. There is also no correlation between the level of mRNA or protein of cereblon within any cell line or between two cell lines. Both high and low levels of cereblon was seen to correlate with sensitivity to drug treatment. In addition, use of whole bone marrow cells rather than CD 138+ MM cells will also confound the results. Therefore, it is imperative to detect cereblon protein in CD138+ MM cells in any correlation analysis.

Second, Celgene and others have shown that splice variants of cereblon exist in primary MM cells (Gandhi, 2014a; Lode, 2013). Therefore, the commercial quantitative RT-PCR primers used by Heintel, 2013 and Broyl, 2013 only target select cereblon isoforms and may lead to an imprecise measurement of

cereblon expression. Similarly, there are also multiple splice isoforms of Aiolos and Ikaros which make precise measurements of expression challenging (Rebollo, 2003; Matulic, 2010).

Third, antibody quality for IHC further complicates interpretation of this assay for quantitative measurement of cereblon protein (Gandhi, 2014a). Commercially available antibodies for Aiolos and Ikaros are limited, but there are antibodies suitable for Western blot analysis; however, the presence of non-specific bands makes them unsuitable for IHC or flow cytometry (Celgene, unpublished data).

Beyond the technical limitations mentioned above, the diagnostic assessment of cereblon for response or resistance is further complicated by a number of clinical considerations. First, MM treatment regimens are becoming more combination-based with an increasing use of novel agents in addition to IMiDs compounds. Thus, cereblon measurement would have to be examined in the combination setting in randomized control trials to ascertain its true utility.

Second, the disease stage (newly diagnosed vs. relapsed/refractory) presents another complexity, as the natural history of the disease plays a role in response to therapy. And finally, other members of the CRL4 E3 ligase complex, DDB1, Roc1 or Cullin4 and the substrates for the IMiDs compounds may have a significant role in determining response/resistance to IMiDs compound therapy. Proper understanding of the role of cereblon measurement in the clinic will emerge from addressing the technical as well as these clinical considerations in the future.

Any assessment of cereblon expression to predict individual patients' response to lenalidomide and pomalidomide therapy would require standardized reagents and assays. The complexity of cereblon, Aiolos and Ikaros gene expression given the splice variants warrants more than a simple quantitative RT-PCR assay.

The possibility was explored that a common molecular mediator exists that is proximal to the downstream modulation of multiple signaling pathways involved in the inhibition of proliferation, induction of apoptosis in tumour cells, and in the activation of immune effector cells. Human cereblon has been identified as one common molecular mediator and both pomalidomide and lenalidomide bind human cereblon with similar affinities and the expression of cereblon in myeloma cells is linked to both the efficacy of pomalidomide and lenalidomide and to the acquisition of resistance to lenalidomide (Report DM2528). Cereblon directly binds DNA-DDB1 in a DDB1-CUL4 E3 ubiquitin ligase complex and pomalidomide and lenalidomide binding to cereblon alters the function of the cereblon associated E3 ubiquitin ligase (Lopez-Girona, 2012; Zhu, 2011). Cytotoxic and immunomodulatory activities of pomalidomide and lenalidomide are linked to cereblon-dependent ubiquitination and proteasomal degradation of substrate proteins Aiolos and Ikaros and rate of substrate degradation underlies, at least in part, the differential activity of lenalidomide and pomalidomide (Bjorklund, 2015; Gandhi, 2014; Krönke, 2014; Lu, 2014; Krönke, 2015).

The non-clinical results presented support the proposed update of section 5.1 of the SmPC with regard to the mechanism of action: "Pomalidomide binds directly to the protein cereblon (CRBN), which is part of an E3 ligase complex that includes deoxyribonucleic acid (DNA) damage-binding protein 1(DDB1), cullin 4 (CUL4), and regulator of cullins-1 (Roc1), and can inhibit the auto-ubiquitination of CRBN within the complex. E3 ubiquitin ligases are responsible for the poly-ubiquitination of a variety of substrate proteins, and may partially explain the pleiotropic cellular effects observed with pomalidomide treatment.

In the presence of pomalidomide *in vitro*, substrate proteins Aiolos and Ikaros are targeted for ubiquitination and subsequent degradation leading to direct cytotoxic and immunomodulatory effects. *In vivo*, pomalidomide therapy led to reduction in the levels of Ikaros in patients with relapsed lenalidomide-refractory multiple myeloma''.

Since the calculated value of logKow is -1.16 and the experimentally derived value of logKow has been determined to be 0.58 for POM, and both values are far below the action limit of 4.5, a persistent,

bioaccumulative, and toxic (PBT) assessment is not triggered for pomalidomide. Based on currently available data it is concluded that pomalidomide is of no concern for the environment.

2.2.7. Conclusion on the non-clinical aspects

The applicant has submitted a detailed non-clinical overview on the mechanism of action of pomalidomide which examined the pleiotropic activities of pomalidomide and provided evidence to support the proposed additional text in section 5.1 of the SmPC.

2.3. Clinical aspects

2.3.1. Introduction

GCP

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

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

- Tabular overview of clinical studies

Study No. Study Sites (Country) Status	**Study Design Population**	**Treatment Arm Total Daily Dose and Regimen** [a]	**Number of Subjects**	**Efficacy Endpoints**
Dose finding Phase 1 study				
CC-4047-MM-005 US (6 sites) Ongoing for subjects without PD or not discontinued for another reason	Phase 1, multicenter, open label Dose escalation (3 + 3 design) RRMM after 1-4 prior therapies (LEN refractory)	All 21-day cycles **Cohorts 1 to 4**: POM PO Days 1 to 14 1 mg/day (Cohort 1) 2 mg/day (Cohort 2) 3 mg/day (Cohort 3) 4 mg/day (Cohort 4) BTZ 1 mg/m^2 IV: Cycles 1 to 8: Days 1, 4, 8, 11 Cycle 9 and onward: Days 1, 8. LD-DEX PO 20 mg/day (≤ 75 years) 10 mg/day (> 75 years) Cycles 1 to 8: Days 1, 2, 4, 5, 8, 9, 11 and 12; Cycles 9 onwards: Days 1, 2, 8, 9. **Cohorts 5 and 6**: POM (as cohorts 1-4)	**ITT:** 34 **Cohort 1:** 3 **Cohort 2:** 3 **Cohort 3:** 3 **Cohort 4:** 3 **Cohort 5:** 10 **Cohort 6:** 12	Primary MTD for POM + IV BTZ + LD-DEX Secondary/ Exploratory • Safety/efficacy of POM + IV (or SQ) BTZ + LD-DEX • PK (POM)

		BTZ 1.3 mg/m^2 IV (Cohort 5), SQ (Cohort 6): Cycles (as cohorts 1-4) LD-DEX PO (as cohorts 1-4)		
Pivotal Phase 3 Study				
CC-4047-MM-007 US, Europe, Russia, Turkey, Israel, Canada, and Japan Final PFS cutoff date: 26 Oct 2017 Ongoing for subjects without PD or who have not discontinued for another reason	Phase 3, multicenter, randomized, open label Efficacy and safety of POM + BTZ + LD-DEX RRMM subjects After 1-3 prior treatment regimens, including a LEN containing regimen	**Randomization (1:1)** **Arm A**: • POM PO 4 mg on Days 1 to 14 of each 21-day treatment cycle • BTZ SQ or IV 1.3 mg/m^2: Cycles 1 to 8 on Days 1, 4, 8, and 11; Cycle 9 and onwards on Days 1 and 8 • LD-DEX PO 20 mg/day (≤ 75 years) 10 mg/day (> 75 years): Cycles 1 to 8 on Days 1, 2, 4, 5, 8, 9, 11 and 12; Cycle 9 and onwards; Days 1, 2, 8, and 9 **Arm B**: • BTZ SQ or IV (as Arm A) • LD-DEX PO (as Arm A)	N = 559 A (n = 281) B (n = 278) 138 subjects remain on treatment as of data cutoff date, (93 Arm A/ 45 Arm B)	Primary: • PFS Secondary: • OS • ORR (IMWG) • Duration of response Exploratory: • ORR (EBMT) • Time to response • Time to progression • Efficacy subgroups • PFS after next-line therapy (PFS2) • Time to treatment failure • Clinical benefit • QoL questionnaires

2.3.2. Pharmacokinetics

New PK data of POM plasma concentrations when administering the proposed triplet combination (POM+BTZ+DEX) has been submitted as part of the exploratory objective of dose finding study CC-4047-MM-005 a Phase 1, multicenter, open-label, dose-escalation study to determine the maximum tolerated dose (MTD) for the combination of pomalidomide, bortezomib and low-dose dexamethasone in subjects with RRMM. The study is described under section 2.4.1. however the PK results from the study are presented below.

Pharmacokinetic results of the pomalidomide from maximum tolerated dose determination cohorts and the exploratory subcutaneous BTZ cohort

MTD determination cohorts and the exploratory SC BTZ Cohort

The plasma concentration versus time profiles from the MTD determination cohorts and the exploratory SQ BTZ cohort were characterized by an absorption phase with median Tmax ranging from 1.8 to 4.0 hours post-dose. Pomalidomide exposures for both AUC0-t and Cmax appeared to increase in a dose dependent manner over the 1 to 4 mg dose range. Mild to moderate between-subject variability is noted for both AUC0-t and Cmax with values ranging from 16.7% to 54.21%.

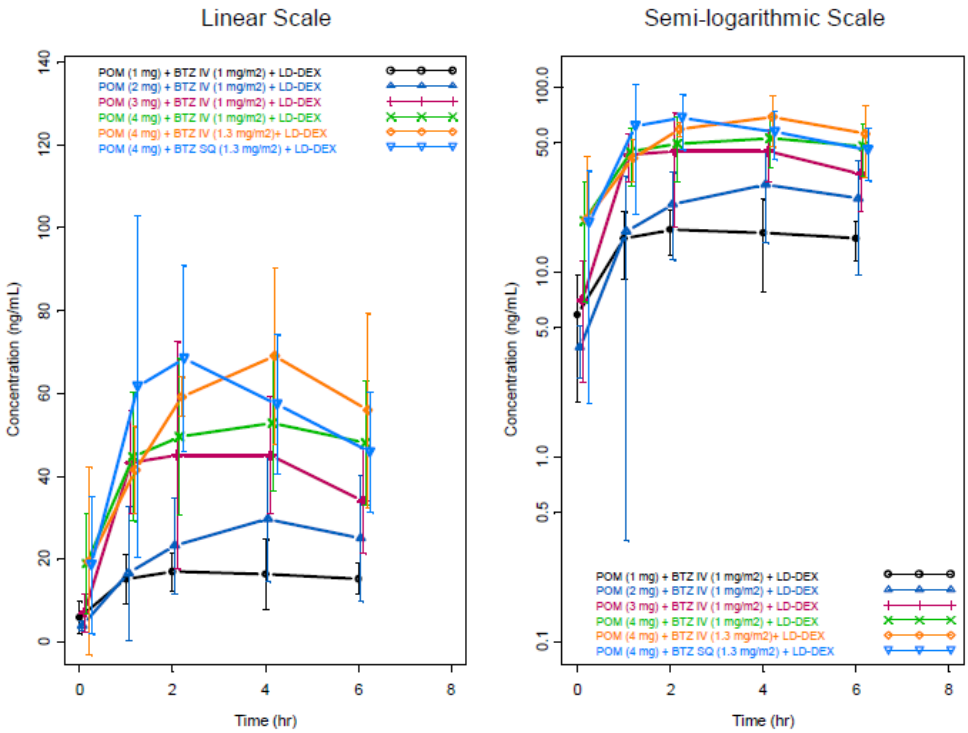


Figure 2 Mean (+ / - SD) Plasma Concentrations of Pomalidomide Time Profiles – Cycle 1 Day 8 (Linear and Semi-log Scales) (PK Population) (Study CC-4047-MM-005)

Table 2 Summary of Pomalidomide Plasma Pharmacokinetic Parameters by Cohort (PK Population) (Study CC-4047-MM-005)

Parameters	Cohort 1	Cohort 2	Cohort 3	Cohort 4	Cohort 5	Exploratory Subcutaneous BTZ Cohort
AUC_{0-t} (h*ug/L) (CV%, N)	86.65 (36.0, 3)	131.11 (40.9, 3)	223.65 (50.5, 3)	271.05 (29.8, 3)	323.05 (28.5, 3)	309.37 (36.4, 12)
C_{max} (ug/L) (CV%, N)	19.04 (27.6, 3)	31.15 (54.2, 3)	48.46 (41.0, 3)	58.83 (16.7, 3)	71.76 (22.5, 3)	73.81 (32.9, 12)
T_{max} (h)[a] (range, N)	4.0 (0.9, 6.0, 3)	4.0 (2.0, 4.0, 3)	2.0 (1.0, 2.0, 3)	2.0 (1.0, 5.8, 3)	4.0 (1.9, 4.0, 3)	1.8 (0.9, 4.2, 12)

AUC_{0-t} = area under the plasma concentration-time curve from time 0 to the last time point; BTZ = bortezomib; C_{max} = maximum plasma drug concentration; CV% = percent coefficient of variation; IV = intravenous; LD-DEX = low-dose dexamethasone; N = number of subjects; PK = pharmacokinetics; POM = pomalidomide; SQ = subcutaneous; T_{max} = time to C_{max}.

[a] Median (min, max, N) data are presented.

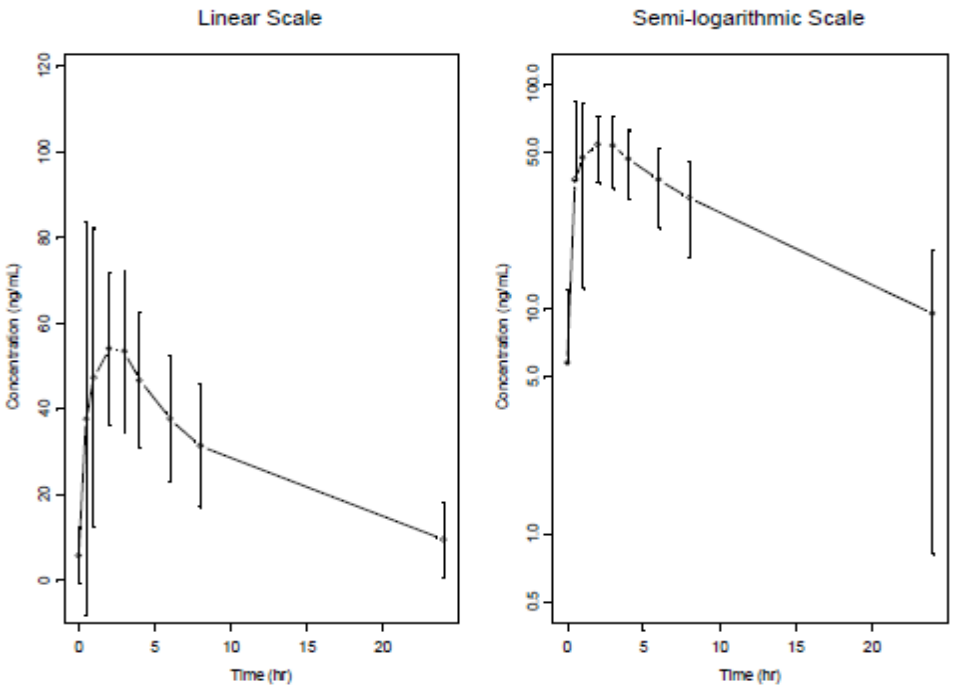
Geometric mean (CV%, N) data are presented.

Cohort 1: POM (1 mg) + BTZ IV (1 mg/m^2) + LD-DEX; Cohort 2: POM (2 mg) + BTZ IV (1 mg/m^2) + LD-DEX; Cohort 3: POM (3 mg) + BTZ IV (1 mg/m^2) + LD-DEX; Cohort 4: POM (4 mg) + BTZ IV (1 mg/m^2) + LD-DEX; Cohort 5: POM (4 mg) + BTZ IV (1.3 mg/m^2) + LD-DEX; Exploratory Subcutaneous BTZ Cohort: POM (4 mg) + BTZ SQ (1.3 mg/m^2) + LD-DEX.

Pharmacokinetic results of pomalidomide from the maximum tolerated dose confirmation cohort

The pomalidomide plasma concentration versus time profiles from the maximum tolerated dose confirmation cohort were characterized by an absorption phase with Tmax ranging from 0.5 to 6.0 hours. Following attainment of Cmax, plasma concentrations of pomalidomide appeared to decline in a mono-phasic manner. The mean t1/2 was 7.12 hours. The mean CL/F was 5.75 L/h. In general, as assessed from the geometric CV%, mild to moderate between-subject variability is noted for both AUC and Cmax with values ranging from 39.8% to 64.5%.

MTD Confirmation Cohort (POM+BTZ IV+ LD-dex)



hr = hour; PK = pharmacokinetics; SD = standard deviation

Figure 3 Mean (+/- SD) Plasma Concentrations of Pomalidomide Time Profiles – Cycle 1 Day 8 (PK Population) (Study CC-4047-MM-005)

Table 3 Summary of Pomalidomide Plasma PK Parameters of Cohort 6 (MTD Confirmation Cohort) (PK Population) (Study CC-4047-MM-005)

Parameters	Mean Value (CV%, N)
$AUC_{0\text{-}inf}$ (h*ug/L)	695.60 (63.9, 6)
$AUC_{0\text{-}t}$ (h*ug/L)	493.01 (64.5, 7)
C_{max} (ug/L)	59.54 (39.8, 7)
T_{max} (h)[a]	2.0 (0.5, 6.0, 7)
$t_{1/2}$ (h)	7.12 (59.6, 6)
CL/F (L/h)	5.75 (63.9, 6)

$AUC_{0\text{-}inf}$ = area under the plasma concentration-time curve from time 0 to infinity; $AUC_{0\text{-}tt}$ = area under the plasma concentration-time curve from time 0 to the last time point; CL/F = apparent total plasma clearance; C_{max} = maximum plasma drug concentration; CV% = percent coefficient of variation; N = number of subjects; PK = pharmacokinetics; $t_{1/2}$ = apparent elimination half-life; T_{max} = time to C_{max}.
a Median (min, max, N) data are presented.
Geometric mean (CV%, N) data are presented.

Additional pharmacokinetic data based on a population-PK (pop-PK) analysis, using a one-compartmental model was submitted. The pop-PK included combined data from 294 patients from studies MM-005 (n=34) and MM-007 (n=260).

Table 4 Population PK parameters of pomalidomide derived from the final PK model

Parameter	Point estimate	RSE%	95% CI
Typical values			
CL/F, Apparent clearance (L/h)	5.60	2.92	5.28 – 5.92
V1/F, Apparent central volume of distribution (L)	78.1	4.76	70.8 – 85.4
Ka, First-order rate of absorption (h^{-1})	2.48	25.8	1.23 – 3.73
Tlag, Absorption lag time (h)	0.395	6.37	0.346 – 0.444
Covariate effects			
BSA (m^2) on CL/F (exponent)	1.10	16.5	0.742 – 1.45
BSA (m^2) on V1/F (exponent)	1.27	15.6	0.882 – 1.66
Interindividual Variability			
Std. dev. of η on CL/F	0.353	9.91	0.285 – 0.422
Std. dev. of η on V1/F	0.176	34.6	0.0565 – 0.295
Std. dev. of η on Ka	1.72	10.3	1.37 – 2.07
Std. dev. of η on Tlag	0 Fixed	NA	NA
Residual Variability			
Std. dev. of ε Additive	0.250	16.7	0.168 – 0.332
Study on additive error model	2.31	17.4	1.52 – 3.10

Objective function value: 234.2995.
BSA = Baseline Body surface area (m^2); CI = confidence interval; CL/F = apparent clearance; Ka = first-order rate of absorption; RSE = relative standard error; Tlag= absorption lag time; V1/F = apparent volume of distribution.

The pomalidomide PK has been characterized in a previously submitted PPK model (Clinical PK/PD Report: CC-4047-MPK-001, procedure EMEA/H/C/2628/II/003 submitted 10 Dec 2013) based on cumulative intensive and sparse PK data collected from multiple studies in both healthy subjects and patients. The results of a PPK analysis, based on data from the CC-4047-MM-005 study and the CC-4047-MM-007 study, (exploring Bayesian individual clearance/exposure based on sparse PK data for exposure-response analysis), supporting the proposed dosage for the pomalidomide/bortezomib/ dexamethasone (PVd) regimen is provided below.

Table 5 Summary of clinical studies included in the Previous PPK analysis (CC-4047-MPK-001) and in the Current PPK analysis (CC-4047-MPK-003)

Previous PPK Analysis (CC-4047-MPK-001)			Current PPK Analysis (CC-4047-MPK-003)		
Studies	**Dose (mg)**	**PK Sampling Time Points (hours)**	**Studies**	**Dose (mg)**	**PK Sampling Time Points (hours)**
CP-006 in HNVs	0.5, 1, 2 mg QD for 5 days	0, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 24 hours on Day 1 0, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 24, 36, 48, 72 hours on Day 5 Predose on Day 3 and 4	**MM-005 in MM patients**	1, 2, 3, 4 mg QD	1) 0, 1, 2, 4, 6 hours on C1D8 in dose determination phase; 2) 0, 0.5, 1, 2, 3, 4, 6, 8, 24 hours on C1D8 in dose confirmation phase
CP-007 in HNVs	3, 4 mg single dose	0, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 8, 12, 16, 24, 36, 48 hours	**MM-007 in MM patients**	4 mg QD	0 and/or 2 hours on C1D1, C1D11, C2D11 and C3D11
MM-001 in MM patients	1, 2, 5, 10 mg QD	1) 0, 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 18, 24, 48 hours on day 1 and 2) 0, 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 18, 24 on day 29			
MM-002 in MM patients	4 mg QD	0, 0.5, 1, 2, 3, 4, 6, 8 hours			
MM-003 in MM patients	4 mg QD	0 and/or 2 hours on C1D1, C1D8, C1D15 and C1D22			
MM-005 in MM patients	1, 2, 3, 4 mg QD	1) 0, 1, 2, 4, 6 hours on C1D8 in dose determination phase; 2) 0, 0.5, 1, 2, 3, 4, 6, 8, 24 hours on C1D8 in dose confirmation phase			

C1D8 = Cycle 1 Day 8; C1D11 = Cycle 1 Day 11; C2D11 = Cycle 2 Day 11; C3D11 = Cycle 3 Day 11; HNV = healthy normal volunteers; MM = multiple myeloma; PPK = population pharmacokinetics; QD = once daily

Table 6 Pharmacokinetic parameter estimates from the sensitivity analysis

	Estimates from previous PPK (CC-4047-MPK-001)[a] (N = 236)			Estimates from supplementing previous model with the current data (N = 508)		
	Estimate	Bootstrap Estimate	95% Bootstrap CI[b]	Estimate	Bootstrap Estimate	95% Bootstrap CI[c]
ka (hr^{-1})	**1.23**	1.23	(1.05, 1.44)	**1.18**	1.19	(1.07, 1.31)
V_2/F (L)	**58.9**	58.91	(56.78, 61.54)	**59.1**	59.09	(57.17, 61.17)
V_3/F (L)	**8.49**	8.53	(7.51, 9.51)	**8.39**	8.37	(7.69, 9.17)
Q/F (L/hr)	**1.01**	1.01	(0.77, 1.29)	**0.986**	0.98	(0.80, 1.20)
CL/F (L/hr)	**8.52**	8.51	(8.04, 8.98)	**8.52**	8.53	(8.15, 8.93)
ALAG1 (hr)	**0.385**	0.38	(0.37, 0.40)	**0.386**	0.39	(0.37, 0.40)
$CL/F_{(patient/HNS)}$	**0.81**	0.81	(0.73, 0.91)	**0.77**	0.79	(0.72, 0.82)
$ALAG1_{patients}$ (hr)	**0.206**	0.21	(0.18, 0.23)	**0.208**	0.208	(0.18, 0.23)
$V_3/F_{(patient/HNS)}$	**8.51**	8.42	(5.89, 11.95)	**8.45**	8.42	(6.28, 10.80)
$Q/F_{(patient/HNS)}$	**3.74**	3.72	(2.46, 5.47)	**3.86**	3.88	(2.89, 5.02)
$V_2/F_{(patient/HNS)}$	**1.19**	1.19	(1.06, 1.32)	**1.17**	1.17	(1.11, 1.26)
ω^2 (ka)	**1.02**	0.998	(0.674, 1.414)	**1.36**	0.041	(0.030, 0.055)
ω^2 (V_2/F)	**0.0488**	0.049	(0.032, 0.070)	**0.0488**	0.059	(0.04, 0.08)
ω^2 (V_2/F): ω^2 (CL/F)	**0.0680**	0.067	(0.042, 0.098)	**0.0593**	0.177	(0.138, 0.224)
ω^2 (CL/F)	**0.178**	0.174	(0.133, 0.232)	**0.181**	1.348	(1.071, 1.676)
δ^2 (HNS)	**0.040**	0.0398	(0.033, 0.047)	**0.04**	0.040	(0.034, 0.047)
δ^2 (Patients)	**0.241**	0.237	(0.195, 0.295)	**0.271**	0.270	(0.238, 0.306)

ALAG1 = lag time; CI = confident interval; CL/F = apparent clearance; $CL/F_{(patient/HNS)}$ = ratios of apparent clearance between MM patients and healthy subjects; IIV = inter-individual variability; ka = absorption rate constant; Q/F = apparent inter-compartmental clearance between the central compartment and the peripheral compartment; $Q/F_{(patient/HNS)}$ = ratios of apparent inter-compartmental clearance between the central compartment and the peripheral compartment between MM patients and healthy subjects; V_2/F = apparent volume of distribution for the central compartment; $V_2/F_{(patient/HNS)}$ = ratios of apparent volume of distribution for the central compartment between MM patients and healthy subjects; V_3/F = apparent volume of distribution for the peripheral compartment; $V_3/F_{(patient/HNS)}$ = ratios of apparent volume of distribution for the peripheral compartment between MM patients and healthy subjects;

[a]Source: Clinical PK/PD Report: CC-4047-MPK-001 (Table 6).

[b]Bootstrap confidence interval values are taken from bootstrap calculation (498 successful out of a total of 500 bootstrap replicates).

[c]Bootstrap confidence interval values are taken from bootstrap calculation (491 successful out of a total of 500 bootstrap replicates).

The reported pomalidomide clearances from various clinical pharmacology studies are displayed in the table below.

Table 7 CL/F reported from clinical pharmacology studies in healthy normal subjects

Study	Dose (mg)	CL/F (L/hr)	Type of Study
CC-4047-CP-004	2	9.85	ADME study
CC-4047-CP-005	2	7.16 (control arm)	Bioequivalence/food effect study
CC-4047-CP-006	0.5, 1 and 2	6.78 (0.5 mg); 9.12 (1 mg) and 7.74 (2 mg)	Multiple ascending dose study
CC-4047-CP-007	3 and 4	8.61 (3 mg control arm) and 8.66 (4 mg control arm)	Bioequivalence study
CC-4047-CP-008	4	8.27 (inhibition control arm) and 7.56 (induction control arm)	Drug-drug interaction study
CC-4047-CP-009	4	8.24 (healthy control group)	Hepatic impairment study
CC-4047-CP-010	4	7.6 (4 mg) and 7.67 (20 mg)	TQT study
CC-4047-CP-011	4	5.38 (food effect control arm) and 5.84 (smoking effect control arm)	Food effect/smoking study
CC-4047-CP-012	4	7.6 (control arm)	Drug-drug interaction study
CC-4047-CP-013	4	6.78 (control arm)	Pediatric formulation study

2.3.3. Pharmacodynamics

No new data have been submitted.

2.3.4. PK/PD modelling

No new data have been submitted.

2.3.5. Discussion on clinical pharmacology

Based on the PK data, pomalidomide exposures increased in a dose dependent manner over the studied dose range. Pomalidomide AUC and Cmax appeared comparable between the IV- and SC-administered BTZ, whereas the Tmax was variable indicating that there is no meaningful impact of BTZ route of administration on POM exposure. Both routes of administration (IV and SC) were used in the pivotal study for BTZ.

The main objective of the population PK analysis was to explore individual exposure using sparse PK data for further exposure-response (ER) analysis to support the proposed dose in the current therapeutic regimen. A small number of subjects (N = 34) contributed limited PK data leading to some bias in the goodness-of-fit for predictions of pomalidomide concentrations at certain earlier points (i.e. absorption phase). The one-compartmental model provided better minimization and more reliable parameter estimates. Additionally, the applicant supplemented the previous two-compartmental model with the current data and showed that the new parameter estimates were generally comparable to those from the previous population PK analysis. This confirms that the current pomalidomide PK data is in good agreement with the previously submitted population pharmacokinetics model. The high ETA shrinkage observed for the parameter V1/F had no impact on the population PK analysis as the applicant used other methods (e.g. objective function) to evaluate the covariate analysis. The estimated apparent clearance (CL/F) varied between studies and it was ranging from 5.38 to 9.85 in the previous studies in healthy normal subjects. Although the apparent clearance estimates from the final popPK model (i.e. 5.6 L/h) is within the lower end of this range, this issue is not further pursued considering the relatively wide therapeutic index and the relatively wide safety margin for pomalidomide treatment.

2.3.6. Conclusions on clinical pharmacology

Overall, the clinical pharmacology data submitted support the new combination.

2.4. Clinical efficacy

2.4.1. Dose response study (MM-005)

This was a Phase 1, multicenter, open-label, dose-escalation study to determine the maximum tolerated dose (MTD) for the combination of pomalidomide, bortezomib and low-dose dexamethasone in subjects with RRMM.

Objectives:

Primary: To determine the MTD for the combination of pomalidomide + intravenous bortezomib + low-dose dexamethasone (Pom + IV BTZ + LD-dex) in subjects with RRMM.

Secondary: To evaluate the safety and efficacy of the combination of Pom + IV BTZ + LD-dex

Exploratory: pharmacokinetics (PK) of POM when administered with BTZ and LD-dex; additional efficacy parameters; safety for the combination of Pom + BTZ + LD-dex when bortezomib is administered subcutaneously.

Methods

A 3 + 3 design was utilized to determine the MTD for Pom + IV BTZ + LD-dex combination treatment in a 21-day treatment cycle. Subjects were treated in 21-day cycles until disease progression or unacceptable toxicity.

Dose-limiting toxicities (DLTs) were assessed to determine MTD during the first treatment cycle. Once the MTD was determined or the maximum planned dose (MPD) was reached without reaching MTD, a cohort of 6 additional subjects was treated at this MTD/MPD level to further confirm the safety and assess preliminary efficacy. An additional cohort of 12 subjects was enrolled to explore the safety for the combination when using SQ BTZ. For this cohort, DLTs were assessed in the first treatment cycle, and the safety data were reviewed after subjects had completed 3 treatment cycles.

Study population

Inclusion criteria

- Age ≥ 18 years with documented diagnosis of MM and measurable disease by serum or urine protein electrophoresis (sPEP or uPEP): sPEP ≥ 0.5 g/dL or uPEP ≥ 200 mg/24 hours.
- At least 1 but no greater than 4 prior lines of anti-myeloma therapies.
- Received at least 2 consecutive cycles of prior treatment with lenalidomide and must have been refractory to their last lenalidomide-containing regimen (either as a single agent or in combination).
- Received at least 2 consecutive cycles of prior treatment with a proteasome inhibitor containing regimen but must not have been refractory to bortezomib (either as a single agent or in combination) under 1.3 mg/m^2 twice weekly dosing schedule.
- Documented progression during or after their last anti-myeloma.
- ECOG performance status score of 0, 1, or 2.

Exclusion criteria

- Documented progressive disease during therapy or within 60 days of the last dose of a bortezomib-containing therapy under the 1.3 mg/m^2 dose twice weekly dosing schedule
- Peripheral neuropathy Grade ≥ 2
- Non-secretory multiple myeloma
- Any of the following laboratory abnormalities: ANC < 1000/µL, Hemoglobin < 8 g/dL (< 4.9 mmol/L), platelet count < 75,000/µL for subjects in whom < 50% of bone marrow nucleated cells are plasma cells; or a platelet count < 30,000/µL for subjects in whom ≥ 50% of bone marrow nucleated cells are plasma cells; corrected serum calcium > 13.5 mg/dL (> 3.4 mmol/L); serum AST or ALT > 3.0 x ULN; serum total bilirubin > 1.5 x ULN; creatinine Clearance <45 mL/min)
- Prior history of malignancies, other than MM, unless free of the disease for ≥ 5 years with the exception of the following non-invasive malignancies: Basal cell carcinoma of the skin, Squamous cell carcinoma of the skin, Carcinoma in situ of the cervix, Carcinoma in situ of the breast, incidental histologic finding of prostate cancer (T1a or T1b) or prostate cancer that is curative.

- Previous therapy with POM
- History of anaphylaxis or hypersensitivity to thalidomide, LEN, bortezomib, boron, mannitol, or dexamethasone
- ≥Grade 3 rash during prior thalidomide or LEN therapy
- Incidence of gastrointestinal disease that may have significantly altered the absorption of POM
- Subjects with any 1 of the following: Congestive heart failure, Myocardial infarction within 12 months prior to starting study treatment, unstable or poorly controlled angina pectoris, including Prinzmetal variant angina pectoris
- Subjects who received any of the following within the last 14 days of initiation of study treatment: plasmapheresis, major surgery (kyphoplasty is not considered major surgery), radiation therapy, antimyeloma drug therapy
- Use of any investigational agents within 28 days or 5 half-lives (whichever is longer) of treatment
- Conditions requiring chronic steroid or immunosuppressive treatment
- Unable/unwilling to undergo protocol required thromboembolism or herpes zoster prophylaxis
- Pregnant or breastfeeding females
- Known seropositive for or active viral infection with HIV or hepatitis B virus

Treatment

All subjects received Pom + BTZ + LD-dex in 21-day cycles until PD or unacceptable toxicity. Dosing modifications and interruptions were permitted throughout the study, except in the first 21-day treatment cycle for DLT evaluation.

- Oral pomalidomide at the dose depending on the cohort on Days 1 to 14
- Bortezomib (IV or SQ depending on the cohort): Cycles 1- 8: 1 mg/m^2 or 1.3 mg/m^2 dose (depending on cohort) on Days 1, 4, 8, and 11 and Cycles 9 and onward: 1 mg/m^2 or 1.3 mg/m^2 dose (depending on cohort) on Days 1 and 8
- Oral LD-dex : Cycles 1- 8: 20 mg/day (≤ 75 years) or 10 mg/day (> 75 years) Days 1, 2, 4, 5, 8, 9, 11 and 12 and Cycles 9 and onward: 20 mg/day (≤ 75 years) or 10 mg/day (> 75 years) Days 1, 2, 8, and 9

Table 8 Dose Escalation (21-day Cycle-MM-005)

Cohort	Oral Pomalidomide (Days 1-14 of a 21-day cycle)	IV Bortezomib (Cycle 1-8: Days 1, 4, 8, 11 of a 21-day cycle; Cycle ≥ 9: Days 1, 8 of a 21-day cycle)	Oral Dexamethasone (Cycle 1-8: Days 1, 2, 4, 5, 8, 9, 11, 12 of a 21-day cycle; Cycle ≥ 9: Days 1, 2, 8, 9 of a 21-day cycle)
1	1 mg	1 mg/m^2	20 mg (subjects ≤ 75years old) 10 mg (subjects > 75 years old)
2	2 mg	1 mg/m^2	20 mg (subjects ≤ 75years old) 10 mg (subjects > 75 years old)
3	3 mg	1 mg/m^2	20 mg (subjects ≤ 75years old) 10 mg (subjects > 75 years old)
4	4 mg	1 mg/m^2	20 mg (subjects ≤ 75years old) 10 mg (subjects > 75 years old)
5[a]	4 mg	1.3 mg/m^2	20 mg (subjects ≤ 75years old) 10 mg (subjects > 75 years old)

[a] The Cohort 5 dose level was the maximum planned dose (MPD) for the combination of Pom + BTZ + LD-Dex.

Measurements

Overall best response was assessed using the International Myeloma Working Group (IMWG) criteria at every cycle on Day 1 starting at Cycle 2 and at the treatment discontinuation visit. An exploratory assessment of response using the European Group for Blood and Marrow Transplantation (EBMT) criteria was also performed. All subjects were assessed every 3 months to determine survival status for at least 5 years after enrollment or longer if clinically indicated.

- Response (IMWG response criteria)
- Overall survival (OS)
- Time to response
- Duration of response

PK samples were collected in Cycle 1 for all subjects enrolled and concentrations of pomalidomide in plasma were determined:

- MTD determination for POM + IV BTZ + LD-dex and exploratory SQ bortezomib cohorts PK Sampling: Cycle 1 Day 8: predose, 1 hour, 2 hours, 4 hours, and 6 hours after administration of pomalidomide.
- MTD/MPD confirmation for POM + IV BTZ + LD-dex cohort PK sampling: Cycle 1 Day 8: predose, 0.5 hour, 1 hour, 2 hours, 3 hours, 4 hours, 6 hours, and 8 hours after administration of pomalidomide and Cycle 1 Day 9: 24 hours post Cycle 1 Day 8 dose but prior to Cycle 1 Day 9 dose.

Statistical methods

Analysis populations:

- Full Analysis Set (FAS): all subjects enrolled in the study.
- Safety Population: all enrolled subjects who received at least 1 dose of the study medications. Subjects were classified according to the initial pomalidomide dose received.
- Efficacy Evaluable (EE): all enrolled subjects who met efficacy eligibility criteria, received at least 1 dose of the study treatment, and had baseline and at least 1 post-baseline efficacy assessment.

Endpoints

Primary: MTD for the combination of Pom + IV BTZ + LD-dex.

Secondary: Safety for the combination of Pom + IV BTZ + LD-dex; Response (IMWG response criteria); OS; Time to response; Duration of response.

Exploratory: PFS (FDA censoring rules;Time-to-progression (TTP); Response (EBMT criteria); Pomalidomide concentrations in plasma; Safety for Pom + SQ BTZ + LD-dex cohort; DLTs in the first cycle for Pom + SQ BTZ + LD-dex cohort.

Results

Analysis Populations

Table 9. Analysis populations (Study MM-005)

	Cohort 1 (N=3) n (%)	Cohort 2 (N=3) n (%)	Cohort 3 (N=3) n (%)	Cohort 4 (N=3) n (%)	Cohort 5 + Confirm (N=10) n (%)	IV Cohort (N=22) n (%)	SQ BTZ Cohort (N=12) n (%)	Total (N=34) n (%)
Full Analysis Set[a]	3	3	3	3	10	22	12	34
Safety Population[b]	3 (100.0)	3 (100.0)	3 (100.0)	3 (100.0)	10 (100.0)	22 (100.0)	12 (100.0)	34 (100.0)
Efficacy Evaluable Population[c]	3 (100.0)	3 (100.0)	3 (100.0)	3 (100.0)	10 (100.0)	22 (100.0)	12 (100.0)	34 (100.0)
DLT Evaluable[d]	3 (100.0)	3 (100.0)	3 (100.0)	3 (100.0)	9 (90.0)	21 (95.5)	12 (100.0)	33 (97.1)
PK Population[e]	3 (100.0)	3 (100.0)	3 (100.0)	3 (100.0)	10 (100.0)	22 (100.0)	12 (100.0)	34 (100.0)

Baseline Characteristics

The majority of subjects were male (58.8%) and white (91.2%); the median age for the overall population was 58.5 years (min, max: 36, 76 years) and approximately 6% of subjects were ≥ 75 years. The median number of prior anti-myeloma regimens was 3. The majority had baseline MM International Stage I (35.3%) or Stage II (20.6%) MM. The median time since diagnosis was 3.4 years. All subjects were either ECOG performance status 0 (55.9%) or 1 (44.1%) at baseline. All subjects had prior exposure to lenalidomide and were refractory to lenalidomide, with 70.6% refractory to lenalidomide on their last regimen. Bortezomib was administered to 97.1% of subjects previously. All subjects had PD after their last myeloma regimen and the majority (91.2%) had progressed ≤ 60 days after their last regimen.The majority of subjects were non-high risk for cytogenetic abnormalities. Mean (± SD) baseline beta-2-microglobulin was 2.9 (± 1.37) mg/L and serum creatinine was 80.6 (22.13) µmol/L.

MTD for the combination treatment

The combination of pomalidomide 4 mg/bortezomib 1.3 mg/m^2/dexamethasone 20 mg (10 mg for subjects > 75 years of age) was the MPD (Cohort 5). DLTs did not occur at any dose level.

Efficacy results (2 Apr 2015 data cut off)

Table 10 Response Rates (Best Response Assessment Using IMWG Criteria) (EE Population-Study MM-005)

	Cohort 1 (N=3) n (%)	Cohort 2 (N=3) n (%)	Cohort 3 (N=3) n (%)	Cohort 4 (N=3) n (%)	Cohort 5 + Confirm (N=10) n (%)	IV Cohort (N=22) n (%)	SQ BTZ Cohort (N=12) n (%)	Total (N=34) n (%)
Response[a]								
sCR	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (10.0)	1 (4.5)	0 (0.0)	1 (2.9)
CR	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (16.7)	2 (5.9)
VGPR	1 (33.3)	0 (0.0)	2 (66.7)	1 (33.3)	4 (40.0)	8 (36.4)	3 (25.0)	11 (32.4)
PR	1 (33.3)	1 (33.3)	1 (33.3)	2 (66.7)	2 (20.0)	7 (31.8)	1 (8.3)	8 (23.5)
SD	1 (33.3)	2 (66.7)	0 (0.0)	0 (0.0)	3 (30.0)	6 (27.3)	6 (50.0)	12 (35.3)
PD	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Dichotomized response								
sCR or CR or VGPR or PR	2 (66.7)	1 (33.3)	3 (100.0)	3 (100.0)	7 (70.0)	16 (72.7)	6 (50.0)	22 (64.7)
SD or PD	1 (33.3)	2 (66.7)	0 (0.0)	0 (0.0)	3 (30.0)	6 (27.3)	6 (50.0)	12 (35.3)

BTZ = bortezomib; CR = complete response; IMWG = International Myeloma Working Group; IV = intravenous; PD = progressive disease; PR = partial response; sCR = Stringent Complete Response; SD = stable disease; SQ = subcutaneous; VGPR = very good partial response

[a] Response is the best assessment of response during the treatment phase of the study.

Source: Table 14.2.1

Data cutoff: 02 Apr 2015

For subjects who had at least PR for the EE population (n=22) median time to response was 4.2 weeks (min, max: 3.0, 22.1 weeks) and median duration of response was 32.3 weeks (95% CI: 19.3, 41.7).

For all cohorts (n=34), median PFS was 31.6 weeks (95% CI: 20.1, 41.7) by IMWG Criteria (EE Population) and median time to progression was 31.9 weeks (95% CI: 20.1, 41.7).

Based on a cutoff date of 02 Apr 2015, 11 (32.4%) subjects had died. Median OS time from Kaplan-Meier estimates has not been reached, but would be expected to be at least 96 weeks, the lower boundary of the 95% CI.

Safety

The most commonly reported (≥ 20% of subjects) adverse events in clinical studies of bortezomib included nausea, diarrhoea, thrombocytopenia, neutropenia, peripheral neuropathy, leukopenia, and lymphopenia. With the addition of pomalidomide, these AEs did not appear to increase in frequency, and in general, occurred at incidence rates between 26.5% (thrombocytopenia) and 38.2% (peripheral sensory neuropathy).

2.4.1. Main study MM-007

Methods

Study MM-007 was a phase 3, multicenter, randomized, open label study to compare the efficacy and safety of pomalidomide, bortezomib and low-dose dexamethasone versus bortezomib and low dose dexamethasone in subjects with relapsed or refractory MM.

Study participants

Inclusion criteria

- Age ≥ 18 years
- Documented diagnosis of MM and have measurable disease by serum or urine protein electrophoresis (sPEP or uPEP): sPEP ≥ 0.5 g/dL or uPEP ≥ 200 mg/24 hours
- Must have had at least 1 but no greater than 3 prior antimyeloma regimens (note: induction with or without bone marrow transplant and with or without maintenance therapy was considered 1 regimen)
- Documented disease progression during or after their last antimyeloma therapy
- Must have received prior treatment with a LEN-containing regimen for at least 2 consecutive cycles
- Eastern Cooperative Oncology Group (ECOG) performance status score of 0, 1, or 2
- Females of childbearing potential (FCBP) must have agreed to utilize 2 reliable forms of contraception simultaneously or practice complete abstinence from heterosexual contact for at least 4 weeks before starting study treatment, while participating in the study treatment phase (including dose interruptions), and for at least 4 weeks after the last dose of POM or 3 months after the last dose of BTZ, whichever was longer, and must have agreed to regular pregnancy testing during this timeframe
- Females must have agreed to abstain from breastfeeding during study treatment and for at least 4 weeks after study treatment discontinuation
- Males must have agreed to use a latex or synthetic condom during any sexual contact with FCBP while participating in the study treatment phase and for at least 4 weeks after the last dose of POM or 3 months after the last dose of BTZ, whichever is longer, even if he has undergone a successful vasectomy

- Males must refrain from donating sperm while on POM and for 4 weeks after discontinuation from this study treatment
- All subjects must have agreed to refrain from donating blood while on study treatment and for 4 weeks after discontinuation from this study treatment

Exclusion criteria

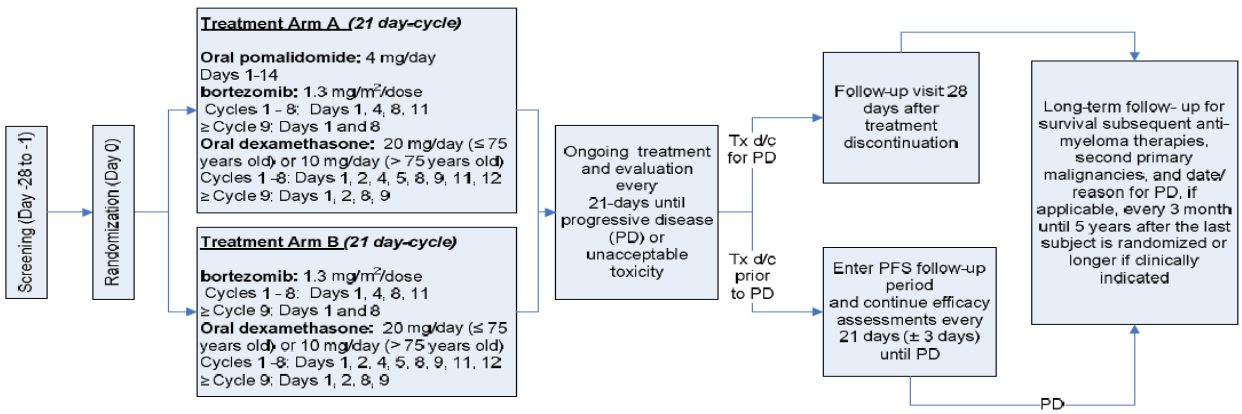
- Documented progressive disease during therapy or within 60 days of the last dose of a bortezomib-containing therapy under the 1.3 mg/m^2 dose twice weekly dosing schedule
- Peripheral neuropathy Grade 3, Grade 4 or Grade 2 with pain within 14 days prior to randomization
- Non-secretory multiple myeloma
- Any of the following laboratory abnormalities:
    - ANC < 1000/µL
    - Hemoglobin < 8 g/dL (< 4.9 mmol/L)
    - Platelet count < 75,000/µL for subjects in whom < 50% of bone marrow nucleated cells are plasma cells; or a platelet count < 30,000/ μL for subjects in whom $\geq$ 50% of bone marrow nucleated cells are plasma cells
    - Corrected serum calcium > 13.5 mg/dL (> 3.4 mmol/L)
    - Serum aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 3.0 x upper limit of normal (ULN)
    - Serum total bilirubin > 1.5 x ULN
- Severe renal impairment (Creatinine Clearance [CrCl] <30 mL/min) requiring dialysis
- Prior history of malignancies, other than MM, unless the subject had been free of the disease for $\geq$ 5 years with the exception of the following non-invasive malignancies: Basal cell carcinoma of the skin, Squamous cell carcinoma of the skin, Carcinoma in situ of the cervix, Carcinoma in situ of the breast, incidental histologic finding of prostate cancer (T1a or T1b) or prostate cancer that is curative
- Previous therapy with POM
- History of anaphylaxis or hypersensitivity to thalidomide, LEN, bortezomib, boron, mannitol, or dexamethasone
- $\geq$ Grade 3 rash during prior thalidomide or LEN therapy
- Incidence of gastrointestinal disease that may have significantly altered the absorption of POM
- Subjects with any 1 of the following:
    - Clinically significant abnormal electrocardiogram (ECG) finding at screening
    - Congestive heart failure (New York Heart Association Class III or IV)
    - Myocardial infarction within 12 months prior to starting study treatment
    - Unstable or poorly controlled angina pectoris, including Prinzmetal variant angina pectoris
- Subjects who received any of the following within the last 14 days of initiation of study treatment:

- Plasmapheresis
- Major surgery (kyphoplasty is not considered major surgery)
- Radiation therapy other than local therapy for myeloma associated bone lesions
- Use of any systemic antimyeloma drug therapy

- Use of any investigational agents within 28 days or 5 half-lives (whichever is longer) of treatment
- Conditions requiring chronic steroid or immunosuppressive treatment, such as rheumatoid arthritis, multiple sclerosis, and lupus, which likely need additional steroid or immunosuppressive treatments in addition to the study treatment. Includes subjects receiving corticosteroids (> 10 mg/day of prednisone or equivalent) within 3 weeks prior to enrollment
- Unable/unwilling to undergo protocol required thromboembolism or herpes zoster prophylaxis
- Pregnant or breastfeeding females
- Known seropositive for or active viral infection with HIV
- Known active viral infection with hepatitis A virus (HAV)
- Known seropositive for or active viral infection with hepatitis B virus (HBV):
  - Subjects HBsAg negative and viral DNA negative were eligible
  - Subjects who had hepatitis B but had received an antiviral treatment and shown non-detectable viral DNA for 6 months were eligible
  - Subjects who were seropositive because of hepatitis B virus vaccine were eligible
- Known seropositive for or active viral infection with hepatitis C virus (HCV):
  - Subjects who had hepatitis C but had received an antiviral treatment and showed no detectable viral ribonucleic acid (RNA) for 6 months were eligible

Treatments

The study design is displayed in figure 4.



d/c = discontinued; PD = progressive disease; PFS = progression-free survival; Tx = treatment

Figure 4. Study design (MM—007)

Arm A:

- POM 4 mg (oral) Days 1 to 14
- BTZ 1.3 mg/m^2/dose (IV or SC): Cycles 1 to 8: Days 1, 4, 8, and 11

  Cycles 9 onwards: Days 1 and 8
- LD-DEX(oral) 20 mg/day (≤ 75 years) or 10 mg/day (> 75 years):

  Cycles 1 to 8: Days 1, 2, 4, 5, 8, 9, 11 and 12,

  Cycles 9 onwards: Days 1, 2, 8, and 9

Arm B:

- BTZ 1.3 mg/m^2/dose (IV or SC): Cycles 1 to 8: Days 1, 4, 8, and 11,

  Cycles 9 onwards; Days 1 and 8
- LD-DEX (oral) 20 mg/day (≤ 75 years) or 10 mg/day (> 75 years):

  Cycles 1 to 8: Days 1, 2, 4, 5, 8, 9, 11 and 12,

  Cycles 9 onwards; Days 1, 2, 8, and 9

There was no limit on the maximum number of cycles for both arms.

Concomitant and permitted medications:

- Herpes Zoster (HZ) prophylaxis for all subjects receiving bortezomib (oral acyclovir or equivalent therapy per institutional guidelines).
- Thromboembolism prophylaxis was required during the study treatment for subjects in arm A. Other subjects in arm B could receive antithrombotic therapy at the discretion of the treating physician.
- Bisphosphonates during the study treatment phase for subjects with myeloma-associated bone disease at the discretion of the Investigator.
- Hematopoietic growth factors (the use of myeloid growth factors was encouraged when the absolute neutrophil count (ANC) was < 1000/µL), platelet or red blood cell (RBC) transfusions at the discretion of the Investigator.
- Radiation therapy to a pathological fracture site or to treat bone pain.

Objectives

The primary objective of the study MM-007 was to compare the efficacy of POM + BTZ + LD-DEX with BTZ + LD-DEX in subjects with RRMM.

The secondary objective was to evaluate the safety and additional efficacy of POM + BTZ + LDDEX versus BTZ + LD-DEX in subjects with relapsed or refractory MM.

Exploratory Objectives

- To explore the pharmacokinetics of pomalidomide and the relationship between drug exposure and response (pharmacodynamic effects, safety and/or efficacy as appropriate) in subjects with relapsed or refractory MM treated with pomalidomide

- To evaluate the differences in pharmacoeconomics of POM + BTZ + LD-DEX versus BTZ + LD-DEX in subjects with relapsed or refractory MM
- To evaluate the differences in clinical benefits of POM + BTZ + LD-DEX versusBTZ + LD-DEX in subjects with relapsed or refractory MM
- To evaluate the differences in key efficacy variables of POM + BTZ + LD-DEX versus BTZ + LD-DEX within defined subgroups
- To evaluate the differences in health-related quality of life of POM + BTZ + LD-DEX versus BTZ + LD-DEX in subjects with relapsed or refractory MM
- To evaluate minimal residual disease (MRD), genomic, molecular/mechanistic and immune biomarkers and their correlation to clinical outcome measures for only those subjects who give their consent (optional).

Outcomes/endpoints

Primary

- PFS: time from randomization to the first documentation of disease progression, based on the IMWG Uniform Response criteria (Durie, 2006), or death whichever occurred earlier.

Secondary

- OS: time from randomization to death due to any cause
- ORR by IMWG response criteria (2006)
- Duration of response: time of the first documented response to confirmed disease progression or death due to any cause for all responders

Exploratory

- ORR by EBMT criteria
- Time-to- treatment response (TTR): time from randomization to the time the response criteria for sCR or CR or VGPR or PR were first met (responders only)
- Time-to-progression (TTP): time from randomization to the first documented disease progression
- Efficacy analysis in subgroups
- PFS after next-line therapy (PFS2): time from randomization to second objective disease progression as per Investigator assessment (during next antimyeloma regimen), or death from any cause, whichever occurred first.
- The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire for Patients with MM (EORTC QLQ-MY20) Module, European Organization for Research and Treatment of Cancer Quality of Life Core 30 (EORTC QLQ-C30) Module, and the European Quality of Life-Five Dimensions (EQ-5D)
- Minimal residual disease (MRD), genomic, molecular/mechanistic and immune biomarkers (optional)
- Time to treatment failure ([TTF]: time from randomization to disease progression (using either IMWG or EBMT criteria), start of another antimyeloma treatment, death, or discontinuation of study treatment or PFS follow-up phase for any reason, whichever was the earliest.

- Healthcare utilization (number days in hospital/high care units/rrgent care visits) during active treatment
- Clinical benefits (improvement in hemoglobin/renal function/ECOG performance status/ hypercalcemia/non-myeloma immunoglobulins)

Sample size

Per protocol Amendment 4, with the assumption of 2-sided significance level of 0.05 and median PFS of 9 versus 12 months in Arms B and A, respectively, a total of 381 PFS events were required to detect approximately 33% increase in median with 80% power. To obtain PFS events from approximately 70% of the ITT population for the final PFS analysis, a total of 544 subjects were required to be randomized (1:1 ratio).

The MAH amended the protocol in Amendment 5 to perform the final PFS analysis earlier due to recently published data from several Phase 3 studies that revealed that the PFS of the BTZ + LD-DEX arm, which requires prior treatment with LEN, was expected to be shorter than the original assumptions of 9 months (relevant median PFS data for BTZ + LD-DEX from Phase 3 Endeavor, Panorama-1 and Castor studies ranging from 7 to 8 months) (Moreau, 2017a; Palumbo, 2016; San-Miguel, 2014). The data cut-off date for the revised final PFS analysis was October 2017, with approximately 320 PFS events projected to be reached, representing an approximate 57% event rate (out of 559 randomized subjects) and 80% power to test a HR of 0.73 (estimated median PFS of 12 months in the POM + BTZ + LD-DEX arm and 8.8 months in the BTZ + LD-DEX arm).

For OS, with the assumption of 2-sided significance level of 0.05 and 1 planned interim analyses at the time of the final PFS analysis, a total of 379 deaths are required to detect approximately 33% increase in median OS (30 to 40 months) with 75% power. The projected events at the time of the OS interim analysis was approximately 50% (191 events).

Randomisation

Randomization was done by a validated interactive response technology system, using randomly permutated blocks within strata, by the following baseline stratification factors:

- Age (≤ 75 years versus > 75 years)
- Number of prior anti-MM regimens (1 versus > 1)
- β2M at screening (< 3.5 mg/L versus ≥ 3.5 mg/L - ≤ 5.5 mg/L versus > 5.5 mg/L)

Blinding (masking)

The study was open-label.

Statistical methods

The efficacy analyses include 1 interim analysis and 1 final analysis for the primary efficacy endpoint, PFS, as well as 1 interim analysis and 1 final analysis for the key secondary endpoint, OS. Type 1 error was controlled for these endpoints and analyses.

1. Intent-to-treat population (ITT): all subjects who were randomized, independent of whether they received study treatment. It was used for the primary efficacy analysis.

2. Safety population: all randomized subjects who receive at least 1 dose of study drug (either POM or BTZ or LD-DEX).

3. Efficacy evaluable population (EE): randomized subjects who received at least 1 dose of study drug, had measurable disease at baseline, and had at least 1 valid post-baseline myeloma response assessment. It was used for exploratory analysis.

Interim analysis

An analysis of PFS was to be performed when approximately 191 PFS events would have been observed. A non-binding stopping boundary was to be applied based on gamma function with gamma = -6. If the p-value of the 2-sided log-rank test for PFS was greater than 0.932, then the futility boundary was crossed.

The ORR analysis and the OS analysis were to be performed with the final PFS analysis in the step-down fashion. The family-wise type I error rate was to be controlled by a step-down approach from PFS to ORR and then to OS comparison.

If the OS analysis crossed the superiority boundary, the OS results would be considered significant in favour of POM + BTZ + LD-DEX. Otherwise the final OS analysis would be performed when 379 deaths are observed. The OS comparison between treatment arms was conducted in which a group sequential test with an overall Type I error probability of 0.05 (two-sided).

Table 11 Nominal Two-Sided P-Value for Rejecting Null (Superiority) for PFS, ORR and OS Analysis (Pocock Type Alpha Spending)

Endpoint	PFS interim	PFS/ORR Final and OS Interim Two-sided nominal P-value	OS Final Two-sided nominal P-value
PFS	Futility Analysis $p > 0.932$	0.05	
ORR		0.05	
OS		0.031	0.028

ORR = overall response rate; OS = overall survival; PFS = progression-free survival

Note: Nominal p-values for superiority and futility computed using the program East Version 6 with Lan-DeMets (1994) spending function (Cytel Statistical Software Company).

Efficacy analyses

The primary efficacy analysis for all endpoints was to be performed based on the ITT population. Exploratory analysis for PFS, ORR and OS were to be performed using the EE population for the final analyses.

For analysis of endpoints with alpha control, statistical tests were to be performed at the 2-sided significance level of 0.05.

Analysis of primary endpoint (PFS assessed by IRAC based on IMWG criteria) was to be calculated using the FDA censoring rules (2007). Additional analysis of PFS by IRAC (EBMT criteria), investigator's assessment (IMWG criteria only) and EMA censoring rules (2013) were also planned, the last two as sensitivity analysis. PFS was to be compared between treatment arms using a log-rank test stratified and Kaplan-Meier method was used to estimate the survival distribution for each arm. The median PFS along with the two-sided 95% CI for the median was to be estimated. A Cox proportional hazards model stratified by stratification factors was to be used to estimate hazard ratio along with 95% CIs. Unstratified log-rank test was performed as a secondary analysis for PFS. Additional analyses for PFS were to be conducted for all possible combinations of assessors (IRAC versus Investigator), criteria (IMWG versus EBMT) and censoring (FDA versus EMA versus sensitivity).

The following censoring rules were to be applied for the analysis of PFS:

Table 12. Censoring rules for PFS

Priority	Situation	FDA Guideline	EMA Guideline	Sensitivity Analysis
1	No baseline assessments and alive after 2 scheduled assessments	IRAC assessment: Censored at date of randomization; Investigator assessment: Not applicable	Same	Same
2	Death within the first two scheduled assessments	Event at date of death	Same	Same
3	New anti-myeloma/non-protocol treatment started prior to progression/death, or new anti-myeloma/non-protocol treatment without progression/death records	Censored at date of last adequate assessment on or before other treatment; if no adequate assessment existed before other treatment then censored at date of randomization	Whether used new anti-myeloma/non-protocol treatment is irrelevant. Check other censoring rules.	FDA Guideline
4	Progression during treatment or PFS follow-up phase after an extended lost-to-follow-up time (two or more missed scheduled assessments)	Censored at date of last adequate assessment with evidence of no progression; if no adequate assessment existed then censored at date of randomization (Note: there should be no response assessment from long-term follow-up phase; if any progression accidentally appeared from long-term follow-up, then it follows the same rule as those during treatment phase).	Event at date of documented progression	FDA Guideline

Priority	Situation	FDA Guideline	EMA Guideline	Sensitivity Analysis
5	Progression documented on scheduled assessments	Event at date of documented progression	Same	Same
6	Progression documented between scheduled assessments	Event at date of documented progression	Same	Event at date of last scheduled adequate assessment prior to the unscheduled assessment when progression is detected; if no adequate assessment at scheduled visits existed prior to the unscheduled assessment, then event at one day after randomization
7	Death during treatment or PFS follow-up phase after an extended lost-to-follow-up time (two or more missed scheduled assessments)	Censored at date of last adequate assessment with evidence of no progression; if no adequate assessment existed then censored at date of randomization	Event at date of death	FDA Guideline
8	Death from the long-term follow-up more than 2 months after the latest of: treatment discontinuation date, or PFS follow-up phase discontinuation date, the overall study treatment end date, and last adequate assessment date during treatment or PFS follow-up phase	Censored at date of last adequate assessment with evidence of no progression; if no adequate assessment existed then censored at date of randomization	Same	Same
9	Death cases not covered in other rows of this table	Event at date of death	Same	Same
10	No progression	Censored at date of last adequate assessment with evidence of no progression; if no adequate assessment existed then censored at date of randomization	Same	Same, except that unscheduled visits are excluded.

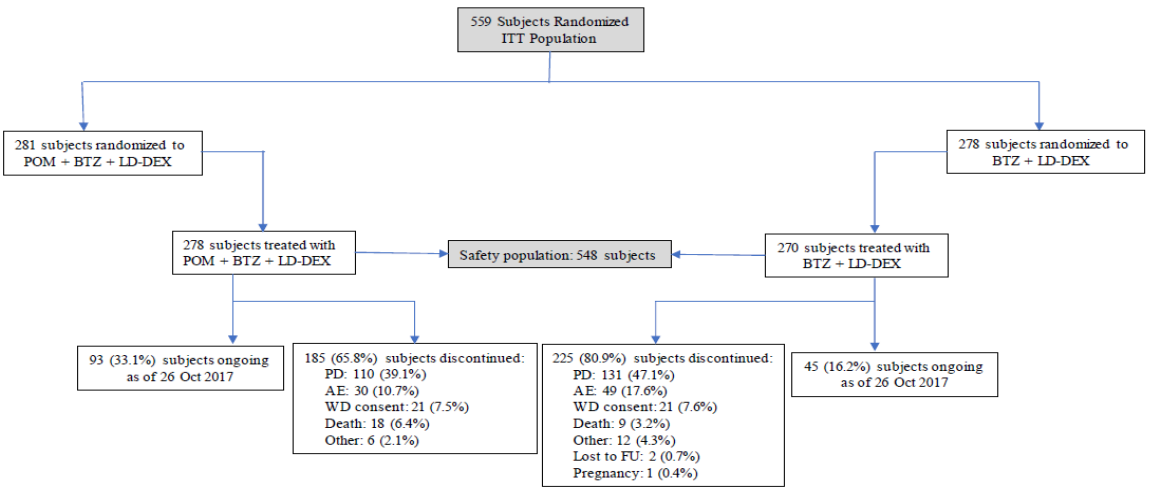
EMA = European Medicines Agency; FDA = Food and Drug Administration; IRAC = Independent Response Adjudication Committee; PFS = progression-free survival

The following subgroup analysis were to be conducted: Region (US versus non-US); Gender (Male versus Female); Age (75 versus > 75 years; 65 versus > 65 years), Race (white versus non-white); Baseline ECOG Performance Status (0 versus > 0); Baseline cytogenetic categories (High risk versus non-high

risk); Number of prior antimyeloma regimens (1 versus > 1; 2 versus > 2); Number of prior antimyeloma lines (1 versus > 1; 2 versus > 2); β2-microglobulin at screening (< 3.5 versus ≥ 3.5 to ≤ 5.5 versus > 5.5 mg/L); Baseline Albumin (< 3.5 versus ≥ 3.5 g/dL); ISS (Stage I versus Stage II versus Stage III); Prior stem cell transplantation (Yes versus No); Baseline creatinine clearance (CrCl) from serum (Cockcroft-Gault) (< 45 versus ≥ 45 mL/min; < 60 versus ≥ 60 mL/min); Refractoriness to LEN in the last LEN-containing regimen (Yes versus No); Refractoriness to last prior antimyeloma therapy before study treatment; Prior exposure to proteasome inhibitors.

Results

Participant flow



AE = adverse event; BTZ = bortezomib; FU = follow-up; ITT = intent-to-treat; LD-DEX = low-dose dexamethasone; PD = progressive disease; POM = pomalidomide; WD = withdrawn.

Percentages shown in parentheses reflect the ITT population
Source: Table 14.1.1.2
Data Cutoff: 26 Oct 2017

Figure 5. Participant flow (Sudy MM-007)

Table 13. Subject disposition (ITT population-Study MM-007)

	POM+BTZ+ LD-DEX N=281	BTZ+LD-DEX N=278	All subjects N=559
Randomized, Not Treated, n (%)	**3 (1.1)**	**8 (2.9)**	**11 (2.0)**
Subjects Treated, n (%)			
Ongoing	93 (33.1)	45 (16.2)	138 (24.7)
Discontinued	185 (65.8)	225 (80.9)	410 (73.3)
Primary Reason for Treatment Discontinuation, n (%)			
Progressive Disease	110 (39.1)	131 (47.1)	241 (43.1)
Adverse Event	30 (10.7)	49 (17.6)	79 (14.1)
Withdrawal of Consent	21 (7.5)	21 (7.6)	42 (7.5)
Death	18 (6.4)	9 (3.2)	27 (4.8)
Other	6 (2.1)	12 (4.3)	18 (3.2)
Lost to Follow-up	0	2 (0.7)	2 (0.4)
Pregnancy	0	1 (0.4)	1 (0.2)
Subjects who Entered Progression-free Follow-up Phase, n (%)			
Ongoing	5 (1.8)	4 (1.4)	9 (1.6)
Discontinued	19 (6.8)	30 (10.8)	49 (8.8)
Primary Reason for PFS Follow-up Phase Discontinuation, n (%)			
Progressive Disease	14 (5.0)	23 (8.3)	37 (6.6)
Other	1 (0.4)	5 (1.8)	6 (1.1)
Withdrawal of Consent	2 (0.7)	2 (0.7)	4 (0.7)
Death	2 (0.7)	0	2 (0.4)
Subjects Discontinued from Study, n (%)	**102 (36.3)**	**110 (39.6)**	**212 (37.9)**
Primary Reason for Discontinuation from Study, n (%)			
Death	87 (31.0)	89 (32.0)	176 (31.5)
Withdrawal of Consent	10 (3.6)	17 (6.1)	27 (4.8)
Lost to Follow-up	3 (1.1)	4 (1.4)	7 (1.3)
Other	2 (0.7)	0	2 (0.4)

Recruitment

Date first subject enrolled: 15 Januray 2013

Last subject visit for final (PFS) data cut-off: 26 October 2017

This study was conducted globally in the US, Europe (including Russia, Turkey, and Israel), Canada and Japan.

Conduct of the study

The original protocol dated 15 October 2012 was amended 5 times prior to the data cut-off of 26 October 2017:

Amendment 1 (27 Mar 2014):

- Based on the safety, efficacy and PK data from SC BTZ cohort in Study MM-005 and general adoption in medical practice of SC BTZ as standard of care due to decreased neurotoxicity, BTZ route of administration was updated from IV to SC in both treatment arms.
- Added exploratory assessments for QoL, biomarker sampling (MRD, genomic, molecular/mechanistic and immune) and PFS2

Amendment 2 (14 Nov 2014):

- Clarified that biomarker study was optional.
- Healthcare resource utilization measurements were added.

Amendment 3 (16 Oct 2015):

- Statistical assumptions were revised by increasing the estimated PFS of arm A from 12 months to 12.6 months (treatment difference increased from 33% to 40% over the control arm), and by reducing the study power from 90% to 85%, which resulted in a sample size reduction from approximately 782 subjects to 450 subjects.
- Timepoints for contraceptive requirements and pregnancy testing for FCBP were updated to be consistent with pomalidomide and bortezomib prescribing information.

Amendment 4 (9 Dec 2015):

- Revisions were made to the overall sample size:
  - The revised sample size assumed a median PFS of 9 months in the arm B versus 12 months in arm A with 80% power at a 2-sided significance level of 5%. This change required 381 PFS events and a total of 544 subjects to be enrolled for an approximate 70% event rate.
  - The interim PFS analysis was to occur when 50% PFS information (191 events) had occurred.
  - The interim OS analysis was to occur when 50% OS information (191 deaths) had occurred.

Amendment 5 (14 Jun 2017):

Due to recently published data from several Phase 3 studies the PFS of arm B was expected to be shorter than the original assumption of 9 months (median PFS from Phase 3 ENDEAVOR, PANORAMA-1 and CASTOR studies ranging from 7 to 8 months) (Moreau, 2017a; Palumbo, 2016; San-Miguel, 2014). Subsequently, the data cutoff date for the revised final PFS analysis was October 2017, by which time approximately 320 PFS events were projected to be reached, representing an approximate 57% event rate (out of 559 randomized subjects). This would allow for 80% power to test a hazard ratio of 0.73 (with an estimated median PFS of 12 months in the POM + BTZ + LD-DEX arm and 8.8 months in the BTZ + LD-DEX arm).

Protocol violations were reported for 63 (11.3%) subjects (35 arm A (12.5%) and 28 arm B (10.1%)). The majority comprised SAEs submitted later than the required timing for 26 subjects (15 arm A and 11 arm B), and Pomalidomide counselling not done in at least 1 visit for 25 subjects (13 arm A and 12 arm B).

Protocol deviation

Table 14. Protocol violations (ITT Population-Study MM-007)

Type of Protocol Violation	N=281 n (%)	N=278 n (%)	N=559 n (%)
Subjects with at Least 1 Protocol Violation	**35 (12.5)**	**28 (10.1)**	**63 (11.3)**
SAE submitted later than required timeline	15 (5.3)	11 (4.0)	26 (4.7)
POM counseling not done	13 (4.6)	12 (4.3)	25 (4.5)
Optional biomarker sample obtained without consent	1 (0.4)	4 (1.4)	5 (0.9)
Did not meet the key safety criteria for taking study drug on C1D1	2 (0.7)	2 (0.7)	4 (0.7)
Incorrect treatment assignment/ incorrect stratification/ randomization error	3 (1.1)	1 (0.4)	4 (0.7)
Did not meet required prior regimens number criterion	1 (0.4)	1 (0.4)	2 (0.4)
Met 1 or more medical history exclusion criterion	2 (0.7)	0	2 (0.4)
Missing baseline skeletal survey	0	2 (0.7)	2 (0.4)
Antithrombotic prophylaxis not given without medical justification	1 (0.4)	0	1 (0.2)
Did not meet the required washout period for prior treatment/procedure	0	1 (0.4)	1 (0.2)

C1D1 = Cycle 1, Day 1; ITT = intent-to-treat; POM = pomalidomide; SAE = serious adverse event
Note; More than one category may be selected per subject.
Source: Table 14.1.12
Data Cutoff: 26 Oct 2017

Baseline data

Table 15. Demographic characteristics (ITT population-Study MM-007)

	POM+BTZ+ LD-DEX N=281	BTZ+LD-DEX N=278	All subjects N=559
Age (years)			
n	281	278	559
Mean (SD)	65.9 (10.13)	66.1 (10.16)	66.0 (10.14)
Median	67.0	68.0	68.0
Min, Max	29, 87	27, 89	27, 89
Age Distribution, n (%)			
≤ 65	123 (43.8)	120 (43.2)	243 (43.5)
> 65	158 (56.2)	158 (56.8)	316 (56.5)
Stratification Factor 1: Age, n (%)			
≤ 75	235 (83.6)	231 (83.1)	466 (83.4)
> 75	46 (16.4)	47 (16.9)	93 (16.6)
Sex, n (%)			
Male	155 (55.2)	147 (52.9)	302 (54.0)
Female	126 (44.8)	131 (47.1)	257 (46.0)
Race, n (%)			
American Indian/Alaska Native	0	0	0
Asian	14 (5.0)	8 (2.9)	22 (3.9)
Black or African American	8 (2.8)	13 (4.7)	21 (3.8)
White	237 (84.3)	234 (84.2)	471 (84.3)
Not Collected or Reported	19 (6.8)	20 (7.2)	39 (7.0)
Other	3 (1.1)	3 (1.1)	6 (1.1)
Ethnicity, n (%)			
Hispanic or Latino	17 (6.0)	14 (5.0)	31 (5.5)
Not Hispanic or Latino	244 (86.8)	241 (86.7)	485 (86.8)
Not Reported	16 (5.7)	21 (7.6)	37 (6.6)
Unknown	4 (1.4)	2 (0.7)	6 (1.1)
Region, n (%)			
US	53 (18.9)	69 (24.8)	122 (21.8)
Non-US	228 (81.1)	209 (75.2)	437 (78.2)

Table 16 Baseline disease characteristics (Study MM-007)

	POM+BTZ+ LD-DEX N=281	BTZ+LD-DEX N=278	All subjects N=559
Time Since Initial Diagnosis (years)			
Mean (SD)	5.16 (3.812)	4.75 (2.921)	4.96 (3.401)
Median (min, max)	4.00 (0.2, 25.9)	4.30 (0.4, 21.8)	4.20 (0.2, 25.9)
Prior MM Radiation Therapies, n (%)	63 (22.4)	61 (21.9)	124 (22.2)
Prior MM Cancer Surgeries, n (%)	17 (6.0)	22 (7.9)	39 (7.0)
Prior Stem Cell Transplant, n (%)	161 (57.3)	163 (58.6)	324 (58.0)
Number of Prior Antimyeloma Regimens			
Mean (SD)	1.9 (0.77)	1.9 (0.79)	1.9 (0.78)
Median (min, max)	2.0 (1, 5)	2.0 (1, 4)	2.0 (1, 5)
Stratification Factor 2: Distribution of Prior Antimyeloma Regimens, n (%)			
1	98 (34.9)	95 (34.2)	193 (34.5)
2	118 (42.0)	107 (38.5)	225 (40.3)
3	64 (22.8)	75 (27.0)	139 (24.9)
> 3	1 (0.4)	1 (0.4)	2 (0.4)
Number of Prior Antimyeloma Lines [a]			
Mean (SD)	1.8 (0.74)	1.8 (0.77)	1.8 (0.76)
Median (min, max)	2.0 (1, 3)	2.0 (1, 4)	2.0 (1, 4)
Distribution of Prior Antimyeloma Lines, n (%)			
1	111 (39.5)	115 (41.4)	226 (40.4)
2	117 (41.6)	104 (37.4)	221 (39.5)
3	53 (18.9)	58 (20.9)	111 (19.9)
> 3	0	1 (0.4)	1 (0.2)
International Staging System at Study Entry [b]**, n (%)**			
Stage I	149 (53.0)	138 (49.6)	287 (51.3)
Stage II	85 (30.2)	90 (32.4)	175 (31.3)
Stage III	47 (16.7)	50 (18.0)	97 (17.4)
ECOG Performance Status, n (%)			
0	149 (53.0)	137 (49.3)	286 (51.2)
1	121 (43.1)	119 (42.8)	240 (42.9)
2	11 (3.9)	22 (7.9)	33 (5.9)

	POM+BTZ+ LD-DEX N=281	BTZ+LD-DEX N=278	All subjects N=559
Cytogenetic Abnormality [c], n (%)			
High Risk	61 (21.7)	49 (17.6)	110 (19.7)
Non-high Risk	137 (48.8)	132 (47.5)	269 (48.1)
Missing or Not Evaluable	83 (29.5)	97 (34.9)	180 (32.2)
Presence of Bone Lesions, n (%)	183 (65.1)	192 (69.1)	375 (67.1)
Presence of Plasmacytoma, n (%)	19 (6.8)	20 (7.2)	39 (7.0)
Stratification Factor 3: Baseline Beta-2-Microglobulin Distribution, n (%)			
< 3.5 mg/L	156 (55.5)	147 (52.9)	303 (54.2)
≥ 3.5 to ≤ 5.5 mg/L	78 (27.8)	81 (29.1)	159 (28.4)
> 5.5 mg/L	47 (16.7)	50 (18.0)	97 (17.4)
Baseline Albumin Distribution, n (%)			
< 3.5 g/dL	49 (17.4)	51 (18.3)	100 (17.9)
≥ 3.5 g/dL	232 (82.6)	227 (81.7)	459 (82.1)
Baseline Renal Function (Cockcroft Gault Creatinine Clearance) (mL/min), n (%)			
< 30	11 (3.9)	10 (3.6)	21 (3.8)
30 to < 45	26 (9.3)	28 (10.1)	54 (9.7)
45 to < 60	54 (19.2)	38 (13.7)	92 (16.5)
60 to < 80	71 (25.3)	80 (28.8)	151 (27.0)
≥ 80	119 (42.3)	122 (43.9)	241 (43.1)

BTZ = bortezomib; ECOG = Eastern Cooperative Oncology Group; ITT = intent-to-treat; LD-DEX = low-dose dexamethasone; max = maximum; min = minimum; MM = multiple myeloma; POM = pomalidomide; SD = standard deviation.

[a] A therapeutic line is defined by subject's progression status. Only a regimen after disease progression is counted as a new line.

[b] International Staging System is calculated using baseline values of albumin and β2-microglobulin.

[c] High-risk is defined as presence of cytogenetic abnormality in at least one or more of the following cytogenetic abnormalities; del(17p) (including monosomy 17), t(4;14) and/or t(14;16). Non-high risk is absence of high risk cytogenetic abnormalities.

Table 17 Exposure and refractoriness to selected prior antimyeloma drugs by treatment arm (ITT Population-MM-007)

	POM+BTZ+ LD-DEX N=281 n (%)	BTZ+LD-DEX N=278 n (%)	All subjects N=559 n (%)
Subjects Exposed to:			
≤ 2 Classes of Prior Anti-MM Drugs	15 (5.3)	19 (6.8)	34 (6.1)
3 Classes of Prior Anti-MM Drugs	43 (15.3)	33 (11.9)	76 (13.6)
4 Classes of Prior Anti-MM Drugs	59 (21.0)	71 (25.5)	130 (23.3)
5 Classes of Prior Anti-MM Drugs	90 (32.0)	88 (31.7)	178 (31.8)
≥ 6 Classes of Prior Anti-MM Drugs	74 (26.3)	67 (24.1)	141 (25.2)
Subjects Exposed to:			
Thalidomide, LEN and Corticosteroids	72 (25.6)	68 (24.5)	140 (25.0)
Lenalidomide and Proteasome Inhibitor	212 (75.4)	213 (76.6)	425 (76.0)
Lenalidomide and Bortezomib	201 (71.5)	203 (73.0)	404 (72.3)
Bortezomib and Dexamethasone	197 (70.1)	200 (71.9)	397 (71.0)
Prior Refractory Status [a]			
Immunomodulatory Agents	202 (71.9)	193 (69.4)	395 (70.7)
Lenalidomide	200 (71.2)	191 (68.7)	391 (69.9)
Thalidomide	15 (5.3)	9 (3.2)	24 (4.3)
Proteasome Inhibitors	37 (13.2)	37 (13.3)	74 (13.2)
Bortezomib [b]	24 (8.5)	32 (11.5)	56 (10.0)
Carfilzomib	5 (1.8)	4 (1.4)	9 (1.6)
Ixazomib	8 (2.8)	2 (0.7)	10 (1.8)

Numbers analysed

	POM+BTZ+ LD-DEX N=281	BTZ+LD-DEX N=278	All subjects N=559
Analysis Populations, n (%)			
ITT Population [a]	281 (100.0)	278 (100.0)	559 (100.0)
Safety Population [b]	278 (98.9)	270 (97.1)	548 (98.0)
Efficacy Evaluable Population [c]	276 (98.2)	266 (95.7)	542 (97.0)

Outcomes and estimation

- *Primary endpoint –Progression free survival (cut-off date of 26 Oct 2017)*

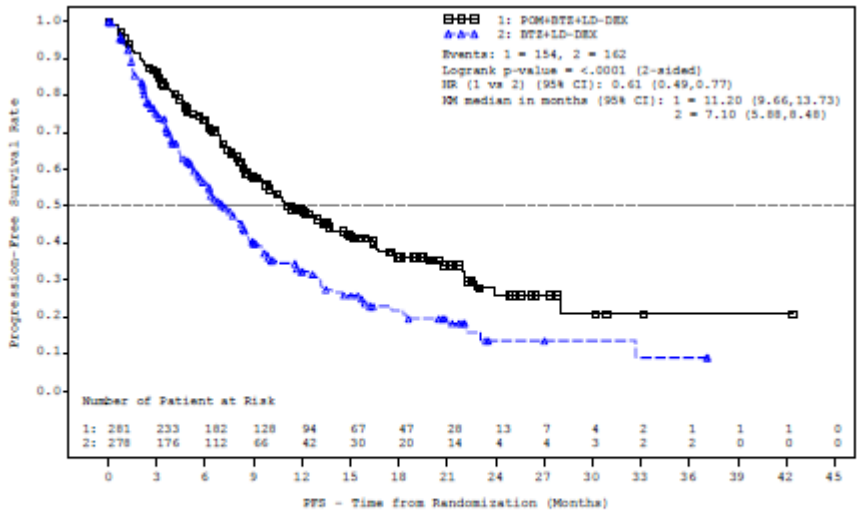
Table 18 Progression-free Survival by IRAC Review Based on IMWG Criteria (Stratified Analysis) Censoring Rule According to FDA Guideline (ITT Population-Study MM-007)

	POM+BTZ+ LD-DEX N=281	BTZ+ LD-DEX N=278	All Subjects N=559
PFS, n (%)	281 (100.0)	278 (100.0)	559 (100.0)
Censored, n (%)	127 (45.2)	116 (41.7)	243 (43.5)
Progressed/Died, n (%)	154 (54.8)	162 (58.3)	316 (56.5)
PFS Time (months)			
Median [a]	11.20	7.10	8.97
[Two-sided 95% CI [b]]	[9.66, 13.73]	[5.88, 8.48]	[8.21, 10.18]
6 Months Event-Free, % (SE)	73.38 (2.72)	56.64 (3.27)	65.55 (2.13)
12 Months Event-Free, % (SE)	49.47 (3.26)	32.45 (3.48)	41.75 (2.40)
Hazard Ratio (POM+BTZ+LD-DEX vs BTZ+LD-DEX) [c] [Two-sided 95% CI]	0.61 [0.49, 0.77]		
p-value [d]	< 0.0001		

BTZ = bortezomib; CI = confidence interval; FDA = Food and Drug Administration; IMWG = International Myeloma Working Group; IRAC = Independent Response Adjudication Committee; ITT = intent-to-treat; LD-DEX = low-dose dexamethasone; PFS = progression-free survival; POM = pomalidomide; SE = standard error

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

[b] 95% confidence interval about the median progression-free survival time.



BTZ = bortezomib; CI = confidence interval; FDA = Food and Drug Administration; HR = hazard ratio; IMWG = International Myeloma Working Group; IRAC = Independent Response Adjudication Committee; ITT = intent-to-treat; KM = Kaplan-Meier; LD-DEX = low-dose dexamethasone; PFS = progression-free survival; POM = pomalidomide
Source: Figure 14.2.1.2.1a
Data cut-off date: 26 Oct 2017

Figure 6 Progression-Free Survival based on IRAC review (IMWG criteria) censoring rule FDA guideline (stratified) (ITT population-Study MM-007)

Multivariate Analysis for Progression-free Survival

Table 19 PFS by IRAC Review IMWG Criteria by Multivariate Cox Proportional Hazards Final Model (ITT Population-Study MM-007)

Model Parameter	Hazard Ratio	95% CI Lower Bound	95% CI Upper Bound	p-value [a]
Treatment Arm: POM+BTZ+LD-DEX versus BTZ+LD-DEX	0.534	0.408	0.699	< 0.001
Age: ≤ 65 versus > 65 years	0.655	0.493	0.871	0.004
Baseline ECOG Performance Status: 0 versus > 0	0.654	0.495	0.865	0.003
Cytogenetics: High Risk versus Non-high Risk	1.411	1.054	1.889	0.021
No. Prior Anti-Myeloma Lines: 1 versus > 1	0.493	0.369	0.660	< 0.001
Albumin: < 3.5 versus ≥ 3.5 (g/dL)	2.045	1.473	2.838	< 0.001
ISS Stage at Study Entry: I & II versus III	0.690	0.494	0.965	0.030

BTZ = bortezomib; CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; IMWG = International Myeloma Working Group; IRAC = Independent Response Assessment Committee; ISS = International Staging system; ITT = intent-to-treat; POM = pomalidomide

[a] The p-value is based on the cox proportional hazard model comparing the hazard functions associated with the model parameter.

Source: Table 14.2.11.1
Data cut-off date: 26 Oct 2017

Table 20 Reasons for Censoring for Progression-free Survival Based on IMWG Criteria Censoring Rule According to FDA Guideline (ITT Population- Study MM-007)

Reason for Censoring	POM+BTZ+ LD-DEX N = 281 n (%)	BTZ+ LD-DEX N = 278 n (%)	All subjects N = 559 n (%)
Progression-free Survival (PFS), n (%)			
Censored	127 (45.2)	116 (41.7)	243 (43.5)
Progressed	133 (47.3)	147 (52.9)	280 (50.1)
Died	21 (7.5)	15 (5.4)	36 (6.4)
Subjects Censored			
Ongoing Without Event at Time of Cutoff	89 (31.7)	43 (15.5)	132 (23.6)
Taking New Anti-MM Therapy	5 (1.8)	19 (6.8)	24 (4.3)
Progression After 2 or More Missed Assessments	4 (1.4)	8 (2.9)	12 (2.1)
Death After 2 or More Missed Assessments	5 (1.8)	1 (0.4)	6 (1.1)
Discontinued Study Without Progression/Death	24 (8.5)	45 (16.2)	69 (12.3)

BTZ = bortezomib; FDA = Food and Drug Administration; IMWG = International Myeloma Working Group; ITT = intent-to-treat; LD-DEX = low-dose dexamethasone; MM = multiple myeloma; PFS = progression-free survival; POM = pomalidomide
Source: Table 14.2.1.3
Data cutoff date: 26 Oct 2017

Table 21 Progression-free Survival by IRAC Review Based on IMWG Criteria (Stratified Analysis) Censoring Rule According to the EMA Guideline (ITT Population- Study MM-007)

	POM+BTZ+ LD-DEX N = 281	BTZ+ LD-DEX N = 278	All Subjects N = 559
PFS	281 (100.0)	278 (100.0)	559 (100.0)
Censored	121 (43.1)	104 (37.4)	225 (40.3)
Progressed/Died	160 (56.9)	174 (62.6)	334 (59.7)
PFS time (months)			
Median [a]	10.74	6.74	8.67
[Two-sided 95% CI [b]]	[9.53, 13.60]	[5.62, 8.21]	[7.85, 9.92]
6-months Event-Free, % (SE)	72.50 (2.73)	55.25 (3.21)	64.31 (2.12)
12-months Event-Free, % (SE)	47.91 (3.23)	31.07 (3.31)	40.09 (2.33)
Hazard Ratio (POM+BTZ+LD-DEX vs BTZ+LD-DEX), [Two-sided 95% CI [c]]	0.60 [0.48, 0.76]		

BTZ = bortezomib; CI = confidence interval; EMA = European Medicines Agency; IMWG = International Myeloma Working Group; IRAC = Independent Response Adjudication Committee; ITT = intent-to-treat; LD-DEX = low-dose dexamethasone; PFS = progression-free survival; POM = pomalidomide; SE = standard error

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

[b] 95% confidence interval about the median progression-free survival time.

[c] Based on Cox proportional hazards model comparing the hazard functions associated with treatment groups, stratified by age (≤ 75 versus > 75), prior number of antimyeloma regimens (1 versus > 1), and β-2 microglobulin at Screening (< 3.5 mg/L versus ≥ 3.5 mg/L to ≤ 5.5 mg/L versus > 5.5 mg/L).

Source: Table 14.2.16.1.1a

Data cutoff date: 26 Oct 2017

Progression-free Survival by Investigator Assessment

Table 22 Progression-free Survival by Investigator Assessment Based on IMWG Criteria (Stratified Analysis) Censoring Rule According to FDA Guideline (ITT Population -Study MM-007)

	POM+BTZ+ LD-DEX N=281	BTZ+ LD-DEX N=278	All Subjects N=559
Progression-free Survival	281 (100.0)	278 (100.0)	559 (100.0)
Censored	124 (44.1)	101 (36.3)	225 (40.3)
Progressed/Died	157 (55.9)	177 (63.7)	334 (59.7)
PFS time (months)			
Median[a]	11.30	6.64	8.57
[Two-sided 95% CI[b]]	[9.43, 13.77]	[5.62, 8.25]	[7.75, 9.86]
6-months Event-Free, % (SE)	73.24 (2.71)	54.84 (3.24)	64.54 (2.13)
12-months Event-Free, % (SE)	49.25 (3.24)	29.45 (3.27)	40.09 (2.34)
Hazard Ratio (POM+BTZ+LD-DEX vs BTZ+LD-DEX) [c], [Two-sided 95% CI]	0.57 [0.46, 0.71]		

BTZ = bortezomib; CI = confidence interval; FDA = Food and Drug Administration; IMWG = International Myeloma Working Group; ITT = intent-to-treat; LD-DEX = low-dose dexamethasone; PFS = progression-free survival; POM = pomalidomide; SE = standard error

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

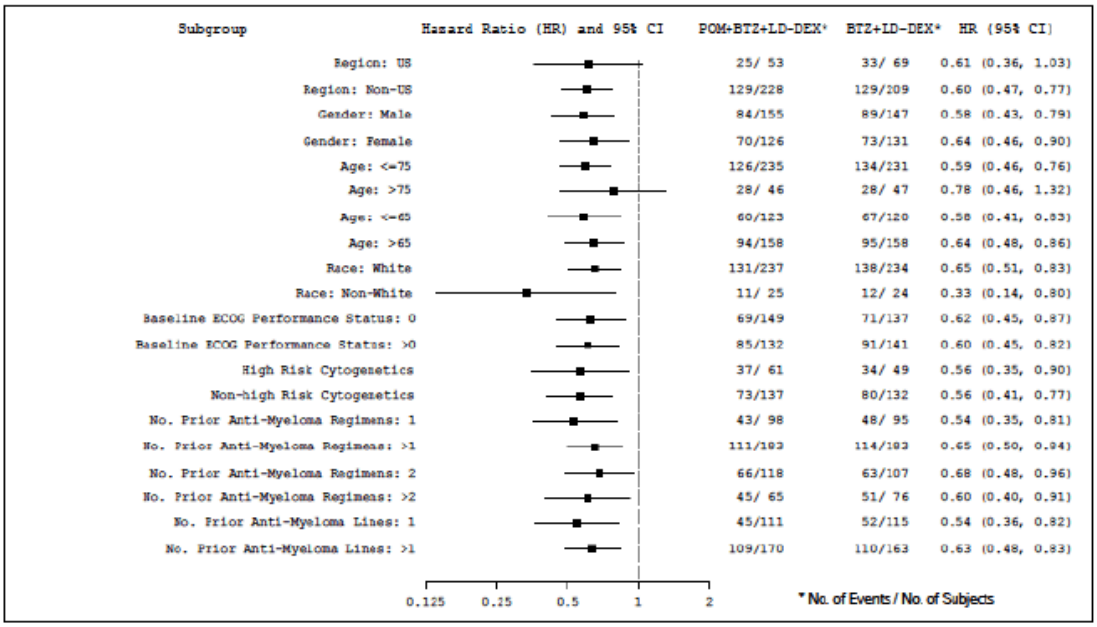
[b] 95% CI about the median progression-free survival time.

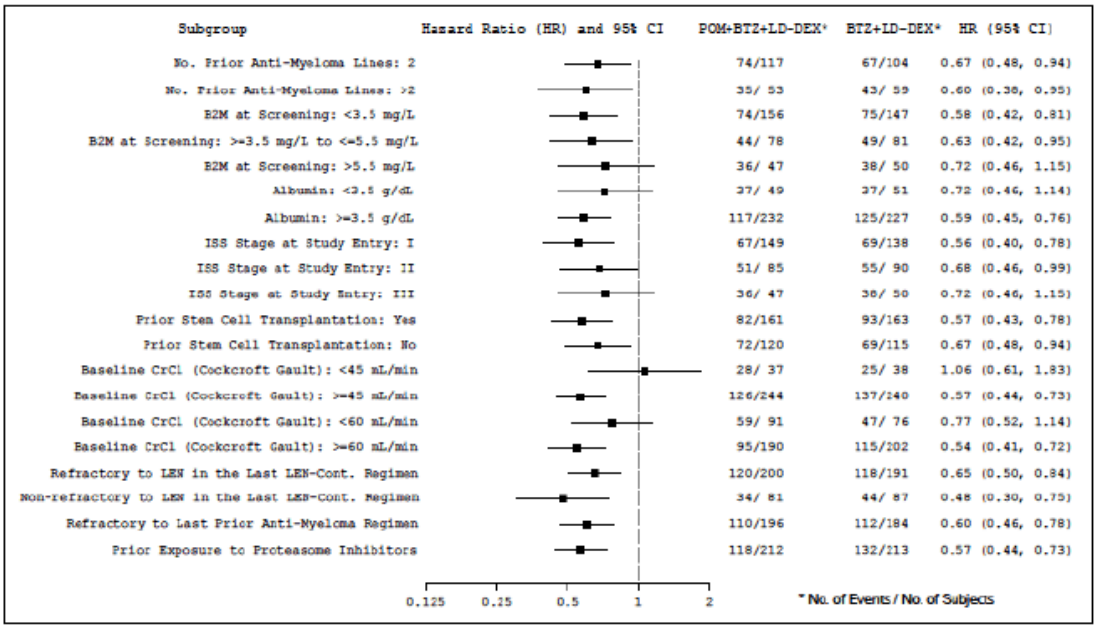
[c] Based on Cox proportional hazards model (stratified hazard ratio).

Source: Table 14.2.6

Data cut-off date: 26 Oct 2017

Progression-free Survival in Pre-specified Subgroups





B2M = β2-microglobulin; BTZ = bortezomib; CI = confidence interval; CrCl = creatinine clearance; ECOG = Eastern Cooperative Oncology Group; FDA = Food and Drug Administration; HR = hazard ratio; IMWG = International Myeloma Working Group; IRAC = Independent Response Adjudication Committee; ISS = International Staging System; ITT = intent-to-treat; LD-DEX = low-dose dexamethasone; LEN = lenalidomide; No. = number; POM = pomalidomide; US = United States

Figure 7 Forest Plot of PFS in Subgroups by IRAC Review IMWG Criteria and FDA Censoring (ITT- Study MM-007)

- *Secondary endpoint- Overall survival*

Table 23. Initial Interim and Updated OS Analyses (Stratified Log-rank Test; ITT Population -Study MM-007)

	Initial Interim Analysis (26 Oct 2017)		Updated Analysis (15 Sep 2018)	
	PVd N=281	Vd N=278	PVd N=281	Vd N=278
Overall Survival, n (%)				
Censored	194 (69.0)	189 (68.0)	165 (58.7)	152 (54.7)
Died	87 (31.0)	89 (32.0)	116 (41.3)	126 (45.3)
Overall Survival Time (months)				
Median [a] [Two-sided 95% CI] [b]	NE [28.48, NE]	31.24 [27.01, NE]	40.54 [29.83, NE]	30.46 [24.61, 35.94]
12-Months event-free, % (SE)	75.01 (2.71)	75.53 (2.75)	75.90 (2.59)	75.19 (2.67)
24-Months event-free, % (SE)	59.47 (3.98)	60.91 (3.79)	60.76 (3.06)	57.69 (3.21)
36-Months event-free, % (SE)	50.55 (6.94)	39.67 (7.87)	52.21 (3.73)	41.97 (4.16)
48-Months event-free, % (SE)	50.55 (6.94)	29.76 (10.42)	46.70 (5.05)	35.50 (4.96)
Hazard ratio (PVd vs Vd) [c] [Two-sided 95% CI]	0.98 [0.73, 1.32]		0.91 [0.70, 1.18]	
p-value [d]	0.894		0.476	

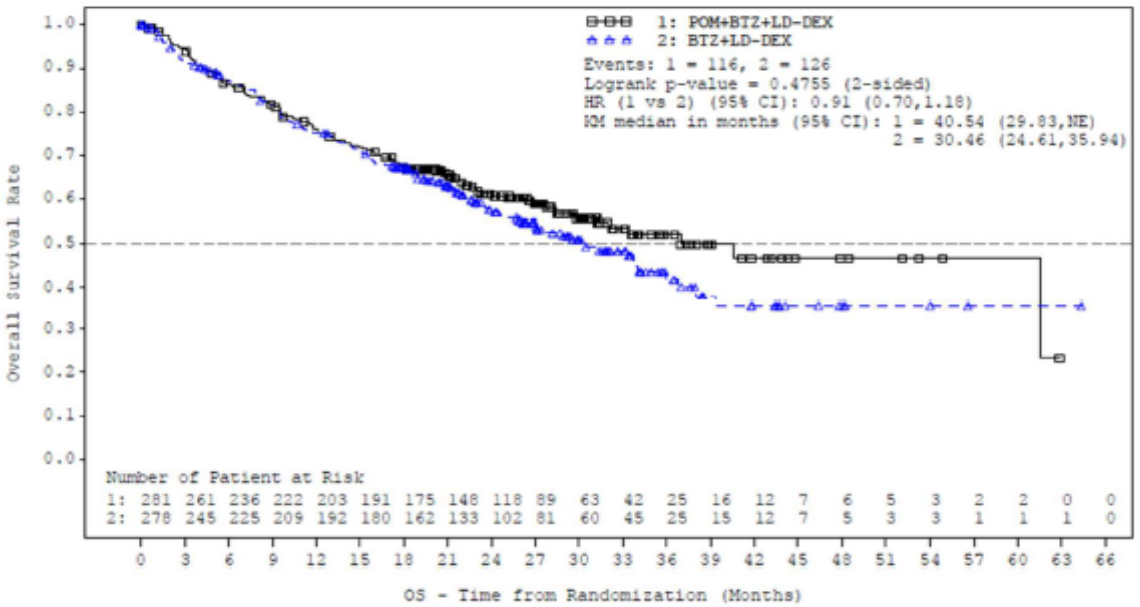
CI = confidence interval; ITT = intent-to-treat; NE = not evaluable; OS = overall survival; PVd = pomalidomide, bortezomib, and low-dose dexamethasone; SE = standard error; Vd = bortezomib and low-dose dexamethasone.

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

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

[c] Based on Cox proportional hazards model comparing the hazard functions associated with treatment groups, stratified by age (≤ 75 versus > 75 years), prior number of antimyeloma regimens (1 versus > 1), and β2-microglobulin at screening (< 3.5 mg/L versus ≥ 3.5 mg/L to ≤ 5.5 mg/L versus > 5.5 mg/L).

[d] The p-value is based on a stratified log-rank test with stratification factors as in the above Cox model.



BTZ = bortezomib; CI = confidence interval; HR = hazard ratio; ITT = intent-to-treat; KM = Kaplan-Meier; LD-DEX = low-dose dexamethasone; NE = not estimable; OS = overall survival; POM = pomalidomide.

Source: Annex 2, Response Figure 14.2.2.2.1

Data cutoff date: 15 Sep 2018

Figure 8: Kaplan-Meier curve for Overall Survival (data cut-off: 15 September 2018 -ITT population- Study MM-007)

Table 24 Interim Overall Survival: Final Multivariate Analysis by Cox Proportional Hazards Model (ITT- Study MM-007)

Model Parameter	Hazard Ratio	95% CI Lower Bound	95% CI Upper Bound	p-value [a]
Treatment Arm: POM+BTZ+LD-DEX vs BTZ+LD-DEX	0.892	0.659	1.206	0.456
Age: ≤ 75 versus >75	0.900	0.620	1.306	0.578
No. Prior Antimyeloma Regimens: 1 versus >1	0.538	0.380	0.760	<0.001
β2-microglobulin: < 3.5 vs ≥ 3.5 mg/L	0.417	0.305	0.570	<0.001
Subsequent Antimyeloma Therapy: Yes versus No (time-dependent)	0.439	0.280	0.688	<0.001

BTZ = bortezomib; CI = confidence interval; ITT = intent-to-treat; LD-DEX = low-dose dexamethasone; NO = number; POM = pomalidomide

[a] The p-value is based on the Cox proportional hazard model comparing the hazard functions associated with the model parameter.

Source: Table 14.2.11.3

Data cut-off date: 26 Oct 2017

- *Secondary endpoint- Response rate*

Table 25 Overall Response Rate by IRAC using IMWG Criteria (Stratified Analysis) (ITT Population- Study MM-007)

	POM+BTZ+ LD-DEX N=281	BTZ+LD-DEX N=278	All Subjects N=559
Overall Response Category, (n %)			
sCR	9 (3.2)	2 (0.7)	11 (2.0)
CR	35 (12.5)	9 (3.2)	44 (7.9)
VGPR	104 (37.0)	40 (14.4)	144 (25.8)
PR	83 (29.5)	88 (31.7)	171 (30.6)
SD	32 (11.4)	106 (38.1)	138 (24.7)
PD	11 (3.9)	16 (5.8)	27 (4.8)
NE / Not Done [a]	7 (2.5)	17 (6.1)	24 (4.3)
Dichotomized Response, n (%)			
sCR or CR or VGPR or PR	231 (82.2)	139 (50.0)	370 (66.2)
SD or PD or NE [a]	50 (17.8)	139 (50.0)	189 (33.8)
Odds Ratio (POM+BTZ+LD-DEX vs BTZ+LD-DEX) [b] [Two-sided 95% CI]	5.02 [3.35, 7.52]		
p-value [c]	<0.001		

BTZ = bortezomib; CI = confidence interval; CR = complete response; IMWG = International Myeloma Working Group; IRAC = Independent Response Adjudication Committee; ITT = intent=to treat; LD-DEX = low-dose dexamethasone; NE = not evaluable; PD = progressive disease; POM = pomalidomide; PR = partial response; sCR = stringent complete response; SD = stable disease; VGPR = very good partial response.

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

[b] Odds ratio is for POM+BTZ+LD-DEX:BTZ+LD-DEX.

[c] P-value is based on a Cochran-Mantel-Haenszel test, stratified by age (≤ 75 versus > 75), prior number of antimyeloma regimens (1 versus > 1), and beta-2 microglobulin at screening (< 3.5 mg/L versus ≥ 3.5 mg/L, ≤ 5.5 mg/L versus > 5.5 mg/L).

Source: Table 14.2.3.1.1a

Data cut-off date: 26 Oct 2017

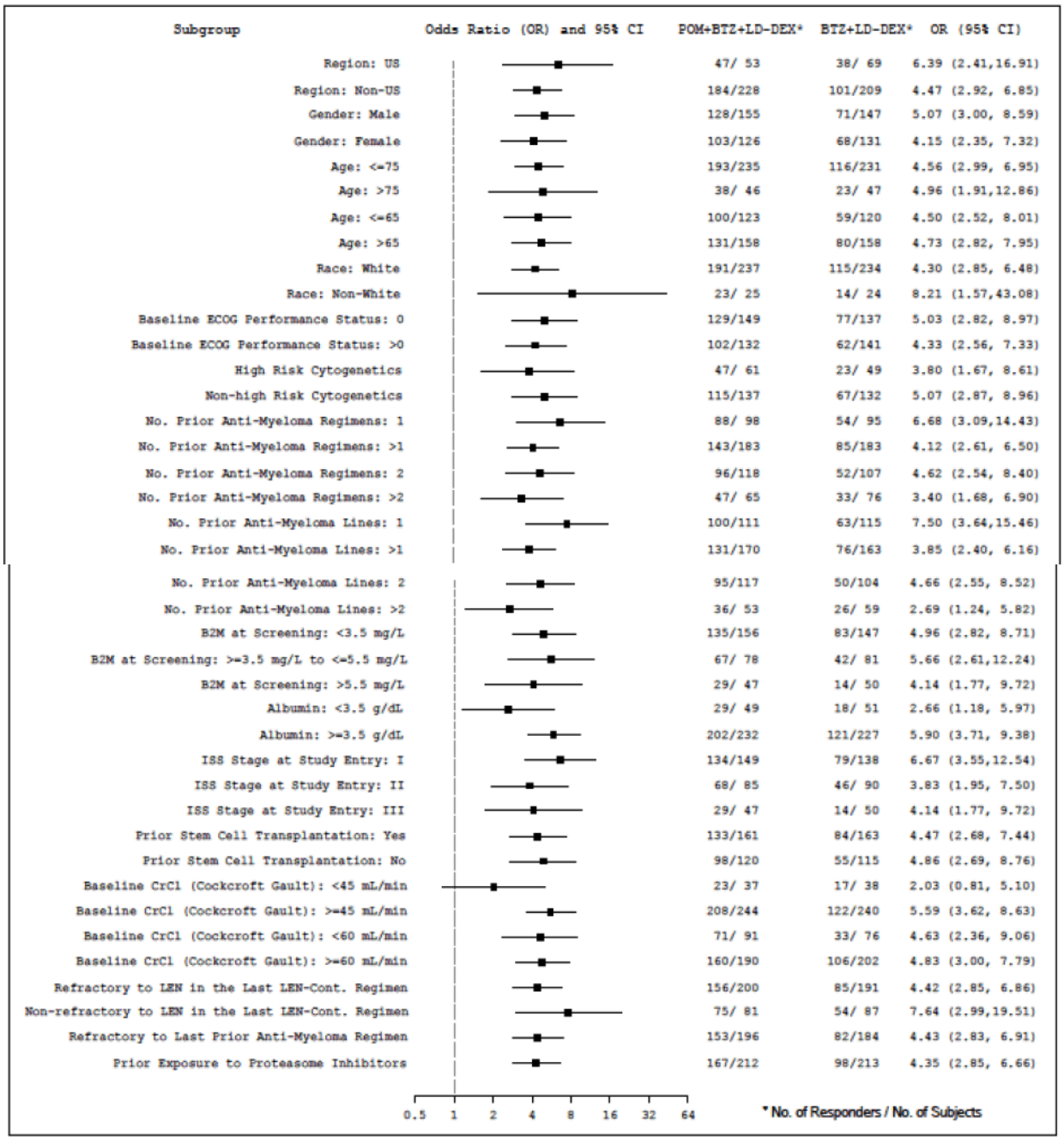


Figure 9: Forest Plot for Overall Response Rates in Subgroups by IRAC (Best Response Using IMWG Criteria) (ITT Population- Study MM-007)

- *Secondary endpoint- Duration of response (DoR)*

Table 26 Duration of Response for Subjects with at Least Partial Response Based on IRAC Assessment Using IMWG Criteria (Study MM-007)

	POM+BTZ+ LD-DEX N=231	BTZ+LD-DEX N=139	All subjects N=370
Duration of Response [a]			
Censored, n (%)	117 (50.6)	68 (48.9)	185 (50.0)
Progressed/Died, n (%)	114 (49.4)	71 (51.1)	185 (50.0)
Duration of Response (months) [a, b]			
Median [c]	13.70	10.94	12.45
Two-sided (95% CI) [d]	[10.94, 18.10]	[8.11, 14.78]	[10.61, 14.82]
6- months Event-Free, % (SE)	77.81 (2.84)	70.38 (4.12)	75.11 (2.35)
12- months Event-Free, % (SE)	54.16 (3.63)	47.98 (4.98)	51.89 (2.93)
Hazard Ratio (POM+BTZ+LD-DEX versus BTZ+LD-DEX) [e] [Two-sided 95% CI]	0.76 [0.56, 1.02]		

BTZ = bortezomib; CI = confidence interval; CR = complete response; IMWG = International Myeloma Working Group; IRAC = Independent Response Adjudication Committee; ITT = intent-to treat; LD-DEX = low-dose dexamethasone; POM = pomalidomide; PR = partial response; sCR = stringent complete response; SE = standard error; VGPR = very good partial response

[a] Only subjects with a response (sCR, CR, VGPR or PR) are included in the analysis.

[b] Response is defined as achieving sCR, CR, VGPR or PR.

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

[d] 95% confidence interval about the median duration of response.

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

Source: Table 14.2.4.1.1a
Data cut-off date: 26 Oct 2017

- *Exploratory endpoint- ORR based on EBMT criteria*

Table 27 ORR by IRAC (Best Response Assessment Using EBMT Criteria) (Stratified Analysis) (ITT Population- StudyMM-007)

	POM+BTZ+ LD-DEX N=281 n (%)	BTZ+ LD-DEX N = 278 n (%)	All subjects N = 559 n (%)
Overall response category			
CR	44 (15.7)	11 (4.0)	55 (9.8)
PR	186 (66.2)	128 (46.0)	314 (56.2)
MR	16 (5.7)	48 (17.3)	64 (11.4)
SD	17 (6.0)	58 (20.9)	75 (13.4)
PD	11 (3.9)	16 (5.8)	27 (4.8)
NE / Not Done [a]	7 (2.5)	17 (6.1)	24 (4.3)
Dichotomized response			
CR or PR	230 (81.9)	139 (50.0)	369 (66.0)
MR or SD or PD or NE / Not Done [a]	51 (18.1)	139 (50.0)	190 (34.0)
Odds Ratio (POM+BTZ+LD-DEX vs BTZ+LD-DEX) [b,c] [Two-sided 95% CI]	4.93 [3.29, 7.39]		

BTZ = bortezomib; CI = confidence interval; CR = complete response; EBMT = European Group for Blood and Marrow Transplantation; IRAC = Independent Response Adjudication Committee; ITT = intent-to-treat; LD-DEX = low-dose dexamethasone; MR = minimal response; NE = not evaluable; PD = progressive disease; POM = pomalidomide; PR = partial response; SD = stable disease; vs = versus

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

[b] Odds ratio is for POM+BTZ+LD-DEX:BTZ+LD-DEX.

[c] Based on a Cochran-Mantel-Haenszel test, stratified by age (≤ 75 versus > 75), prior number of antimyeloma regimens (1 versus > 1), and β2 microglobulin at screening (< 3.5 mg/L versus ≥ 3.5 mg/L, ≤ 5.5 mg/L versus > 5.5 mg/L).

Source: Table 14.2.3.1.1b
Data cut-off date: 26 Oct 2017

• *Exploratory endpoint- Time to response*

Table 28 Time-to-response for Subjects with at Least Partial Response by IRAC Using IMWG Criteria (Study MM-007)

	POM+BTZ+ LD-DEX N=231	BTZ+ LD-DEX N=139	All subjects N=370
Time-to-Response (months) [a,b]			
n	231	139	370
Mean	1.24	1.61	1.38
SD	0.752	1.134	0.931
Median	0.90	1.40	1.05
Min, Max	0.7, 5.7	0.7, 6.8	0.7, 6.8
p-value	< 0.001[c]		

- *Exploratory endpoint- Time to progression*

Table 29 Time-to-progression by IRAC Based on IMWG Criteria (Stratified Analysis) (ITT Population-Study MM-007)

	POM+BTZ+ LD-DEX N=281	BTZ+ LD-DEX N=278	All subjects N=559
Time to Progression			
Censored, n (%)	145 (51.6)	128 (46.0)	273 (48.8)
Progressed, n (%)	136 (48.4)	150 (54.0)	286 (51.2)
Time to Progression (months)			
Median [a]	13.14	7.79	9.92
Two-sided (95% CI) [b]	[10.48, 16.62]	[6.34, 8.71]	[8.57, 11.63]
6-months Event-Free, % (SE)	77.14 (2.63)	59.61 (3.33)	69.03 (2.12)
12-months Event-Free, % (SE)	53.01 (3.36)	34.16 (3.63)	44.51 (2.50)
Hazard Ratio (POM+BTZ+LD-DEX versus BTZ+LD DEX) [c] [Two-sided 95% CI]	0.57 [0.45, 0.72]		

- *Exploratory endpoint- Time to treatment failure*

Table 30 Time-to-Treatment Failure (Stratified Analysis) (ITT Population-Study MM-007)

	POM+BTZ+ LD- DEX N = 281	BTZ+ LD- DEX N=278	All subjects N = 559
Time to Treatment Failure [a]			
Censored	84 (29.9)	39 (14.0)	123 (22.0)
Treatment Failed	197 (70.1)	239 (86.0)	436 (78.0)
Time to Treatment Failure[a] (Months)			
Median[b]	8.54	4.67	6.28
Two-sided (95% CI)[c]	[7.36, 10.12]	[3.84, 5.49]	[5.65, 6.97]
6- months Event-Free, % (SE)	64.02 (2.86)	39.93 (2.94)	52.03 (2.11)
12- months Event-Free, % (SE)	39.69 (3.02)	18.87 (2.46)	29.36 (2.00)
Hazard Ratio (POM+BTZ+LD- DEX versus BTZ+LD-DEX)[d] [Two-sided 95% CI)	0.54 [0.44, 0.65]		

- *Exploratory endpoint- Time to subsequent antimyeloma therapy*

Table 31 Time-to-Subsequent Antimyeloma Therapy (ITT Population-Study MM-007)

	POM+BTZ+ LD-DEX N=281	BTZ+ LD-DEX N=278	All subjects N=559
Time to Subsequent Antimyeloma Therapy[a]			
Censored, n (%)	176 (62.6)	115 (41.4)	291 (52.1)
Used subsequent anti myeloma therapy, n (%)	105 (37.4)	163 (58.6)	268 (47.9)
Time to Subsequent Antimyeloma Therapy (months) [a]			
Median [b]	22.24	8.51	13.96
Two-sided (95% CI) [c]	[17.18, 29.50]	[7.26, 10.02]	[11.43, 15.70]
6- months Event-Free (SE)	86.22 (2.14)	65.34 (3.02)	76.03 (1.89)
12- months Event-Free (SE)	66.65 (3.16)	38.34 (3.35)	52.93 (2.38)
Hazard Ratio (POM+BTZ+LD-DEX versus BTZ+LD-DEX)[d] [Two-sided 95% CI]	0.42 [0.33, 0.54]		

Table 32 Subsequent Antimyeloma Therapy Used by > 5 Subjects by Class and Treatment Arm (ITT Population-Study MM-007)

Class/Preferred Term [a]	POM+BTZ+ LD-DEX N=281	BTZ+LD-DEX N=278	All Subjects N=559
Subjects with at Least 1 Subsequent Antimyeloma Therapy	**105 (37.4)**	**163 (58.6)**	**268 (47.9)**
Corticosteroids	**72 (25.6)**	**137 (49.3)**	**209 (37.4)**
Dexamethasone	65 (23.1)	127 (45.7)	192 (34.3)
Prednisone	7 (2.5)	9 (3.2)	16 (2.9)
Prednisolone	5 (1.8)	6 (2.2)	11 (2.0)
Immunomodulatory Agents	**45 (16.0)**	**129 (46.4)**	**174 (31.1)**
Pomalidomide	21 (7.5)	109 (39.2)	130 (23.3)
Lenalidomide	17 (6.0)	33 (11.9)	50 (8.9)
Thalidomide	9 (3.2)	9 (3.2)	18 (3.2)
Proteasome Inhibitors	**48 (17.1)**	**71 (25.5)**	**119 (21.3)**
Carfilzomib	29 (10.3)	39 (14.0)	68 (12.2)
Bortezomib	26 (9.3)	37 (13.3)	63 (11.3)
Ixazomib/ Ixazomib Citrate	2 (0.7)	8 (2.9)	10 (1.8)
Alkylating Agents	**50 (17.8)**	**58 (20.9)**	**108 (19.3)**
Cyclophosphamide	31 (11.0)	42 (15.1)	73 (13.1)
Melphalan	15 (5.3)	12 (4.3)	27 (4.8)
Bendamustine	10 (3.6)	9 (3.2)	19 (3.4)

Monoclonal Antibodies	**51 (18.1)**	**51 (18.3)**	**102 (18.2)**
Daratumumab	40 (14.2)	30 (10.8)	70 (12.5)
Elotuzumab	9 (3.2)	9 (3.2)	18 (3.2)
Isatuximab	3 (1.1)	6 (2.2)	9 (1.6)
Pembrolizumab	1 (0.4)	6 (2.2)	7 (1.3)
Anthracyclines	**11 (3.9)**	**7 (2.5)**	**18 (3.2)**
Doxorubicin	10 (3.6)	5 (1.8)	15 (2.7)
Stem Cell Transplant	**9 (3.2)**	**8 (2.9)**	**17 (3.0)**
Autologous	7 (2.5)	8 (2.9)	15 (2.7)
Alkaloids	**9 (3.2)**	**7 (2.5)**	**16 (2.9)**
Etoposide	8 (2.8)	6 (2.2)	14 (2.5)
Other	**8 (2.8)**	**5 (1.8)**	**13 (2.3)**
Investigational Drug	3 (1.1)	2 (0.7)	5 (0.9)
HDAC Inhibitors	**2 (0.7)**	**9 (3.2)**	**11 (2.0)**
Panobinostat	1 (0.4)	8 (2.9)	9 (1.6)
Platinum	**6 (2.1)**	**4 (1.4)**	**10 (1.8)**
Cisplatin	6 (2.1)	4 (1.4)	10 (1.8)
Radiotherapy	**1 (0.4)**	**6 (2.2)**	**7 (1.3)**
Radiotherapy	1 (0.4)	6 (2.2)	7 (1.3)
Antimetabolites	**4 (1.4)**	**2 (0.7)**	**6 (1.1)**

- *Exploratory endpoint- Progression-free survival after next-line therapy (PFS_2)*

	POM+BTZ+ LD-DEX N=281	**BTZ+ LD-DEX N=278**	**All subjects N=559**
PFS2[a]			
Censored	169 (60.1)	148 (53.2)	317 (56.7)
Event	112 (39.9)	130 (46.8)	242 (43.3)
PFS2 (months) [a]			
Median [b]	22.44	16.95	20.11
Two-sided (95% CI) [c]	[18.96, NE]	[14.69, 21.09]	[17.35, 22.83]
6- months Event-Free, % (SE)	84.80 (2.16)	83.90 (2.25)	84.35 (1.56)
12- months Event-Free, % (SE)	70.42 (2.86)	63.66 (3.13)	67.12 (2.12)
24-months Event-Free, % (SE)	46.67 (4.17)	36.85 (4.19)	41.91 (2.97)
Hazard Ratio (POM+BTZ+LD-DEX vs BTZ+LD-DEX) [d] [Two-sided 95% CI]	0.76 [0.59, 0.99]		

- *Exploratory endpoint- Quality of life*

Of the ITT population (n = 559), 20% (n = 110) of subjects were not included in the primary HRQoL analyses due to failure to meet the inclusion criteria. The HRQoL evaluable population consisted of 240 and 209 subjects from the POM and control arms, respectively, accounting for 85% and 75% of the ITT population in each respective arm. Global Health Status/QoL of QLQ-C30 showed no clinically meaningful differences between the treatment arms at any cycle. Time to first clinically meaningful worsening have a median time of 3.0 and 3.4 months for the POM and control arms, respectively.

- *Exploratory endpoint- Healthcare Utilization*

During the active treatment period 57.3% and 40.3% of the subjects in the POM + BTZ + LD-DEX and BTZ + LD-DEX groups, respectively, experienced at least one hospitalization. After adjusting for the duration of active treatment between treatment groups, the POM + BTZ + LD-DEX group was found to have a somewhat lower rate of hospitalizations than the BTZ + LD-DEX group (0.149 versus 0.162 hospital admissions per month on treatment; rate ratio: 0.918; 95% CI: 0.665, 1.267).

Summary of main study

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 33 Summary of Efficacy for trial MM-007

Title: A phase 3, multicentre, randomized, open-label study to compare the efficacy and safety of pomalidomide, bortezomib and low-dose dexamethasone versus bortezomib and low-dose dexamethasone in subjects with relapsed or refractory multiple myeloma			
Study identifier	CC-4047-MM-007, EUDRACT 2014-000268-17		
Design	Phase 3, randomised, open-label, multicentre		
	Duration of main phase:		Until disease progression
Hypothesis	Superiority		
Treatments groups	Pom+BTZ+LD-DEX		Pomalidomide (4 mg) on Days 1 – 14 of each 21-day treatment cycle. Bortezomib (1.3 mg/m2/dose): Cycles 1 to 8: Days 1, 4, 8, and 11, for Cycles 9 onwards; Days 1 and 8 Low-dose dexamethasone (20 mg/day) (≤ 75 years old) or 10 mg/day (> 75 years old): Cycles 1 to 8: Days 1, 2, 4, 5, 8, 9, 11 and 12, and for Cycles 9 onwards; Days 1, 2, 8, and 9 281 patients randomized
	BTZ+LD-DEX		Bortezomib (1.3 mg/m2/dose): Cycles 1 to 8: Days 1, 4, 8, and 11, for Cycles 9 onwards; Days 1 and 8 Low-dose dexamethasone (20 mg/day) (≤ 75 years old) or 10 mg/day (> 75 years old): Cycles 1 to 8: Days 1, 2, 4, 5, 8, 9, 11 and 12, and for Cycles 9 onwards; Days 1, 2, 8, and 9 278 patients randomized
Endpoints and definitions	Primary endpoint	PFS	Progression-Free Survival
	Secondary endpoints	ORR DoR OS	Overall Response Rate Duration of Response Overall Survival
	Exploratory endpoint	PFS2	Progression-Free Survival from randomization to progression on next therapy or death
Database lock	26 Oct 2017		

Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat (ITT) population At the time when the number of PFS events for final analysis was reached		
Descriptive statistics and estimate	Treatment group	Pom+BTZ+LD-DEX	BTZ+LD-DEX
	Number of subjects	281	278

variability	PFS n (%) Censored, n(%) Progressed/Died, n(%)		281 (100.0) 127 (45.2) 154 (54.8)	278 (100.0) 116 (41.7) 162 (58.3)
	Median (months)		11.20	7.10
	ORR n (%)		231 (82.2)	139 (50.0)
	DoR Censored, n (%) Progressed/Died, n (%) Median (months) Two-sided 95% CI		117 (50.6) 114 (49.4) 13.70 10.94, 18.10	68 (48.9) 71 (51.1) 10.94 8.11, 14.78
	OS (Interim analysis)* Median (months) Two-sided 95% CI		40.54 (29.83, NE)	30.46 (24.61,35.94)
	PFS2 Median (months)		22.44	16.95
	Two-sided 95% CI		18.96, NE	14.69, 21.09
Effect estimate per comparison	Primary endpoint PFS	Comparison groups	POM+BTZ+LD-DEX v BTZ+LD-DEX	
		HR	0.61	
		95% CI	0.49, 0.77	
		P-value	<0.0001	
	Secondary endpoint ORR	Comparison groups	POM+BTZ+LD-DEX v BTZ+LD-DEX	
		Odds Ratio	5.02	
		95% CI	3.35, 7.52	
		P-value	<0.001	
	Secondary endpoint DoR	Comparison groups	POM+BTZ+LD-DEX v BTZ+LD-DEX	
		HR	0.76	
		95% CI	0.56, 1.02	
		P-value	-	
	Secondary endpoint OS	Comparison groups	POM+BTZ+LD-DEX v BTZ+LD-DEX	
		HR	0.91	
		95% CI	0.70, 1.18	
		Logrank p-value(2-sided)	0.4755	
	Exploratory endpoint PFS2	Comparison groups	POM+BTZ+LD-DEX v BTZ+LD-DEX	
		HR	0.76	
		95% CI	0.59, 0.99	
		P-value	-	
Notes	Subjects were stratified at randomization by age (≤ 75 years old versus > 75 years old), number of prior anti-MM regimens (1 or >1), and baseline β2 microglobulin(< 3.5 mg/L, ≥ 3.5 to ≤ 5.5 mg/L, and > 5.5 mg/L).			

2.4.2. Discussion on clinical efficacy

Design and conduct of clinical studies

This application for a new indication of pomalidomide is supported by a single phase 3 trial (study MM-07) that was designed considering the recommended dose from an adequate phase 1 dose finding study MM-05.

The design of the pivotal study is considered acceptable and the eligibility criteria reflect the intended patient population with RRMM who have received at least one prior regimen, including lenalidomide. The combination of BTZ with DEX is approved in the EU for the treatment of adults with progressive MM who have received at least 1 prior therapy and therefore it is an appropriate comparator. The choice of endpoints with PFS as primary is satisfactory and the duration of study sufficient for assessment.

The methods, conduct, analysis and reporting of results from the pivotal study are appropriate and there are currently no concerns to trigger a GCP inspection. The sample size was amended several times during

this open label study; however these amendments were not based on internal data and are not considered to bias results. It should also be noted that the DMC conducted an interim analysis after 190 events (blinded to the applicant) and the results are consistent with those of the final analysis at 323 events, which provides reassurance that the estimate of treatment effect is not dependent on the final sample size used.

Efficacy data and additional analyses

The pivotal study met its primary endpoint and showed a statistically significant PFS advantage in favour of POM+BTZ+LD-dex with a 39% reduction in risk of death or progression compared to the comparator (HR 0.61(0.49, 0.77, p<0.0001) supported by sensitivity analysis. The PFS advantage was more pronounced in patients with only one prior line of therapy (46% risk reduction) but this is expected as patients tend to become more refractory to new treatments as they receive further lines.

It is clinically relevant that the PFS advantage was seen across subgroups of unfavourable prognosis (e.g. unfavourable cytogenetics), in particular in LEN refractory patients as this drug is widely used in regimens in front/earlier setting. In addition, the PFS2 data showed a 24% risk reduction with POM combination indicating the POM combination does not increase resistance to further treatments.

Results from response rate and other exploratory analysis are also favourable to POM combination.

The interim OS analysis did not show any differences between arms, HR 0.98 (0.73, 1.32) but at the time of cut off 26 October 2017 data was not mature**.** An updated OS analysis based on event rate of 43.3% and after a median follow-up period of 26.2 months has shown a positive trend favouring POM+BTZ+LD-dex supportive of primary analysis. Overall survival data are still immature and the MAH will provide the final OS analysis in Q3 of 2021 tin order to confirm the benefit in terms of OS (see Annex II).

2.4.3. Conclusions on the clinical efficacy

The results of the pivotal trial MM-007 trial are considered of clinical relevance. The statistically significant and clinically relevant improvement in PFS support a clinical benefit associated with the addition of pomalidomide to standard of care regimen BTZ + LD-DEX in relapsed and refractory multiple myeloma patients who have received LEN-based treatments earlier in their treatment pathway, including those who have become LEN-refractory.

The CHMP considers the following measures necessary to address issues related to efficacy in the elderly:

Post-authorisation efficacy study (PAES) MM-007: In order to further investigate the efficacy of pomalidomide in combination with bortezomib and dexamethasone for the treatment of adult patients with multiple myeloma who have received at least one prior treatment regimen including lenalidomide, the MAH should submit the final analysis of OS from the phase 3, randomized, open label study MM-007.

2.5. Clinical safety

Introduction

Safety analyses were based on the safety population, which was defined as all randomized subjects who receive at least 1 dose of study drug (POM, BTZ, or LD-DEX). This safety evaluation included all safety data for the 548 subjects in the safety population as of the data cut-off date of 26 October 2017, including 278 subjects in the POM + BTZ + LD-DEX arm and 270 in the BTZ + LD-DEX.

Patient exposure

Table 34 Dosing Information (Study CC-4047-MM-007) (Safety Population)

	POM + BTZ + LD-DEX N=278			BTZ + LD-DEX N=270	
	POM N=278	BTZ N=277	LD-DEX N=277	BTZ N=270	LD-DEX N=270
Treatment Duration (weeks) [a]					
Median	38.00	33.00	34.00	21.40	21.20
Min, Max	1.1, 187.3	0.4, 147.0	0.4, 144.0	0.4, 164.4	0.3, 164.4
Cumulative Dose (mg) [b]					
Median	521.00	37.20	1088.00	29.45	714.00
Min, Max	4.0, 3164.0	1.3, 133.9	30.0, 3900.0	1.3, 156.0	10.0, 4800.0
Dose Exposure (days) [c]					
Median	154.0	33.0	70.0	24.0	48.0
Min, Max	1, 791	1, 103	2, 205	1, 120	1, 240
Average Daily Dose (mg/day) [d]					
Median	4.00	1.30	17.80	1.30	20.00
Min, Max	1.2, 4.3	0.8, 1.3	5.9, 20.0	0.8, 1.3	4.9, 20.0
Dose Intensity (mg/day) [e]					
Median	2.30	0.20	4.60	0.20	5.50
Min, Max	0.5, 3.1	0.1, 0.4	1.1, 13.3	0.1, 0.4	1.0, 13.3
Relative Dose Intensity [f]					
Median	0.85	0.80	0.80	0.90	0.90
Min, Max	0.2, 1.2	0.3, 1.8	0.2, 1.8	0.4, 1.8	0.3, 1.8
Subjects with at Least 1 Dose Reduction (n, %)	118 (42.4)	148 (53.2)	126 (45.3)	114 (42.2)	89 (33.0)
Number of Dose Reductions – median (min, max)	1.0 (1, 3)	1.0 (1, 2)	1.0 (1, 3)	1.0 (1, 2)	1.0 (1, 4)
Time to First Dose Reduction (days) [g]					
Median	71.0	67.0	64.0	71.0	49.0
Min, Max	22, 879	4, 554	1, 759	21, 264	1, 779
Subjects with at Least 1 Dose Reduction due to AE (n, %)	112 (40.3)	144 (51.8)	114 (41.0)	113 (41.9)	78 (28.9)
Number of Dose Reductions due to AE – median (min-max)	1.0 (1, 3)	1.0 (1, 2)	1.0 (1, 3)	1.0 (1, 2)	1.0 (1, 3)
Time to First Dose Reduction due to AE (days) [g]					
Median	64.5	64.5	74.0	71.0	58.5
Min, Max	22, 879	4, 554	3, 759	21, 264	7, 779
Subjects with at Least 1 Dose Interruption due to AE (n, %)	205 (73.7)	154 (55.4)	132 (47.5)	146 (54.1)	95 (35.2)
Number of Dose Interruptions due to AE – median (min, max)	2.0 (1, 27)	2.0 (1, 14)	1.0 (1, 8)	2.0 (1, 12)	1.0 (1, 10)
Time to First Dose Interruption due to AE (days)					
Median	32.0	34.5	50.0	46.5	56.0
Min, Max	3, 561	4, 519	4, 582	4, 946	4, 1065

BTZ = bortezomib; LD-DEX = low-dose dexamethasone; max = maximum; min = minimum; POM = pomalidomide

[a] Treatment Duration = ((last cycle end date of the study drug) – (the first cycle start date of the study drug) + 1) / 7.
[b] Cumulative Dose is defined as the sum of all doses taken across the treatment period.
[c] Dose exposure is defined as the total number of actual days on drug during the treatment period.
[d] Average Daily Dose is the cumulative dose divided by dose exposure.
[e] Dose intensity is defined as the cumulative dose divided by treatment duration.
[f] Relative dose intensity is defined as dose intensity divided by planned dose intensity.
[g] Time to the first dose reduction and/or interruption is defined as the time from the first dose date of the study medication to the start date of the first observed dose reduction and/or interruption, respectively.

Adverse events

Table 35. Overview of TEAE (Study CC-4047-MM-007) (Safety Population)

	POM+BTZ+LD-DEX N=278 n (%)	BTZ+LD-DEX N=270 n (%)
Subjects with at Least 1 TEAE	**277 (99.6)**	**264 (97.8)**
Subjects with at Least 1 TEAE Related to Any Study Drug	**267 (96.0)**	**226 (83.7)**
Related to POM	229 (82.4)	N/A
Related to BTZ	242 (87.1)	219 (81.1)
Related to DEX	219 (78.8)	175 (64.8)
Subjects with at Least 1 NCI CTCAE Grade 3-4 TEAE	**251 (90.3)**	**190 (70.4)**
Subjects with at Least 1 NCI CTCAE Grade 3-4 TEAE Related to Any Study Drug	**215 (77.3)**	**126 (46.7)**
Related to POM	167 (60.1)	N/A
Related to BTZ	159 (57.2)	112 (41.5)
Related to DEX	105 (37.8)	69 (25.6)
Subjects with at least 1 NCI CTCAE Grade 5 TEAE	**27 (9.7)**	**12 (4.4)**
Subjects with at Least 1 Serious TEAE	**159 (57.2)**	**114 (42.2)**
Subjects with at Least 1 Serious TEAE Related to any Study Drug	**83 (29.9)**	**41 (15.2)**
Related to POM	67 (24.1)	N/A
Related to BTZ	51 (18.3)	33 (12.2)
Related to DEX	46 (16.5)	32 (11.9)
Subjects with at Least 1 TEAE Leading to Discontinuation of Any Study Drug	**80 (28.8)**	**51 (18.9)**
TEAE Leading to Discontinuation of POM	31 (11.2)	N/A
TEAE Leading to Discontinuation of BTZ	67 (24.1)	50 (18.5)
TEAE Leading to Discontinuation of DEX	47 (16.9)	51 (18.9)
Subjects with at Least 1 TEAE leading to Dose Reduction of POM, BTZ or DEX	**200 (71.9)**	**139 (51.5)**
TEAE Leading to Dose Reduction of POM	113 (40.6)	N/A
TEAE Leading to Dose Reduction of BTZ	145 (52.2)	112 (41.5)
TEAE Leading to Dose Reduction of DEX	118 (42.4)	78 (28.9)
Subjects with at Least 1 TEAE Leading to Dose Interruption of Any Drug	**244 (87.8)**	**181 (67.0)**
TEAE Leading to Interruption of POM	223 (80.2)	N/A
TEAE Leading to Interruption of BTZ	223 (80.2)	175 (64.8)
TEAE Leading to Interruption of DEX	209 (75.2)	160 (59.3)

BTZ = bortezomib; LD-DEX = low-dose dexamethasone; N/A = not applicable; NCI CTCAE = National Cancer Institute Common Terminology Criteria Version 4.0 for Adverse Events; POM = pomalidomide; TEAE = treatment-emergent adverse event.

A TEAE is defined as any AE occurring or worsening on or after the first treatment of study medication and within 28 days after the latest of the last dose date of any study drug

Table 36 TEAE Reported in ≥ 5% of Subjects in Either Treatment Arm by System Organ Class and Preferred Term (Study MM-007) (Safety Population)

System Organ Class/Preferred Term[a]	POM+BTZ +LD-DEX N=278 n (%)	BTZ+LD-DEX N=270 n (%)
Subjects with at Least 1 TEAE	**277 (99.6)**	**264 (97.8)**
Infections and Infestations	**223 (80.2)**	**175 (64.8)**
Upper respiratory tract infection	58 (20.9)	48 (17.8)
Pneumonia	53 (19.1)	37 (13.7)
Bronchitis	39 (14.0)	19 (7.0)
Viral upper respiratory tract infection	31 (11.2)	14 (5.2)
Urinary tract infection	27 (9.7)	25 (9.3)
Influenza	27 (9.7)	15 (5.6)
Respiratory tract infection	23 (8.3)	12 (4.4)
Conjunctivitis	21 (7.6)	16 (5.9)
Lower respiratory tract infection	22 (7.9)	7 (2.6)
General Disorders and Administration Site Conditions	**213 (76.6)**	**172 (63.7)**
Fatigue	103 (37.1)	71 (26.3)
Edema peripheral	94 (33.8)	54 (20.0)
Pyrexia	64 (23.0)	32 (11.9)
Asthenia	48 (17.3)	48 (17.8)
Non-cardiac chest pain	14 (5.0)	13 (4.8)
Nervous System Disorders	**205 (73.7)**	**163 (60.4)**
Peripheral sensory neuropathy	133 (47.8)	100 (37.0)
Dizziness	48 (17.3)	28 (10.4)
Headache	31 (11.2)	25 (9.3)
Tremor	30 (10.8)	8 (3.0)
Syncope	17 (6.1)	11 (4.1)
Peripheral sensorimotor neuropathy	16 (5.8)	12 (4.4)
Hypoaesthesia	7 (2.5)	15 (5.6)
Dysgeusia	18 (6.5)	8 (3.0)
Paraesthesia	16 (5.8)	5 (1.9)

System Organ Class/Preferred Term[a]	POM+BTZ +LD-DEX N=278 n (%)	BTZ+LD-DEX N=270 n (%)
Gastrointestinal Disorders	**195 (70.1)**	**168 (62.2)**
Diarrhoea	94 (33.8)	81 (30.0)
Constipation	102 (36.7)	65 (24.1)
Nausea	49 (17.6)	54 (20.0)
Vomiting	32 (11.5)	27 (10.0)
Abdominal pain	27 (9.7)	18 (6.7)
Abdominal pain upper	22 (7.9)	15 (5.6)
Stomatitis	17 (6.1)	1 (0.4)
Dry mouth	16 (5.8)	10 (3.7)
Abdominal distension	15 (5.4)	6 (2.2)
Dyspepsia	14 (5.0)	25 (9.3)
Blood and Lymphatic System Disorders	**187 (67.3)**	**143 (53.0)**
Neutropenia	130 (46.8)	29 (10.7)
Thrombocytopenia	102 (36.7)	103 (38.1)
Anaemia	79 (28.4)	73 (27.0)
Leukopenia	32 (11.5)	9 (3.3)
Musculoskeletal and Connective Tissue Disorders	**171 (61.5)**	**119 (44.1)**
Back pain	52 (18.7)	36 (13.3)
Muscular weakness	38 (13.7)	13 (4.8)
Pain in extremity	33 (11.9)	36 (13.3)
Arthralgia	32 (11.5)	31 (11.5)
Muscle spasms	26 (9.4)	14 (5.2)
Bone pain	22 (7.9)	15 (5.6)
Musculoskeletal pain	17 (6.1)	14 (5.2)
Myalgia	14 (5.0)	10 (3.7)

System Organ Class/Preferred Term[a]	POM+BTZ +LD-DEX N=278 n (%)	BTZ+LD-DEX N=270 n (%)
Metabolism and Nutrition Disorders	**144 (51.8)**	**113 (41.9)**
Hypokalaemia	43 (15.5)	30 (11.1)
Hyperglycaemia	40 (14.4)	30 (11.1)
Decreased appetite	23 (8.3)	26 (9.6)
Hypomagnesaemia	19 (6.8)	7 (2.6)
Hypocalcemia	18 (6.5)	9 (3.3)
Hypophosphataemia	16 (5.8)	8 (3.0)
Respiratory, Thoracic and Mediastinal Disorders	**141 (50.7)**	**107 (39.6)**
Cough	57 (20.5)	40 (14.8)
Dyspnoea	56 (20.1)	33 (12.2)
Psychiatric Disorders	**95 (34.2)**	**86 (31.9)**
Insomnia	45 (16.2)	53 (19.6)
Depression	15 (5.4)	7 (2.6)
Anxiety	13 (4.7)	16 (5.9)
Skin and Subcutaneous Tissue Disorders	**91 (32.7)**	**59 (21.9)**
Rash	26 (9.4)	8 (3.0)
Injury, Poisoning and Procedural Complications	**85 (30.6)**	**56 (20.7)**
Accidental overdose	23 (8.3)	5 (1.9)
Fall	17 (6.1)	10 (3.7)
Vascular Disorders	**79 (28.4)**	**52 (19.3)**
Hypotension	24 (8.6)	14 (5.2)
Hypertension	18 (6.5)	17 (6.3)
Deep vein thrombosis	14 (5.0)	5 (1.9)
Investigations	**70 (25.2)**	**67 (24.8)**
Weight decreased	16 (5.8)	17 (6.3)
Weight increased	14 (5.0)	17 (6.3)
Cardiac Disorders	**63 (22.7)**	**37 (13.7)**
Atrial fibrillation	26 (9.4)	5 (1.9)
Renal and Urinary Disorders	**52 (18.7)**	**28 (10.4)**
Acute kidney injury	15 (5.4)	10 (3.7)

BTZ = bortezomib; LD-DEX = low-dose dexamethasone; MedDRA = Medical Dictionary for Regulatory Activities; POM = pomalidomide; TEAE = treatment-emergent adverse event

[a] System organ classes and preferred terms are coded using the MedDRA dictionary Version 20.0, and are listed in decreasing order of frequency for the POM+BTZ+LD-DEX column. A subject with multiple occurrences of the same preferred term is counted only once in that preferred term.

TEAE related to study drug

Pomalidomide

A total of 229 (82.4%) subjects experienced at least 1 TEAE considered related to pomalidomide and the most frequently reported (at least 10% of the subjects) TEAEs included neutropenia (37.8%), thrombocytopenia (28.1%), fatigue (21.9%), constipation (18.0%), diarrhea (14.4%), and anemia and peripheral sensory neuropathy (13.3% each).

Table 37 Treatment-emergent Adverse Events (All Grades) Considered Related to Pomalidomide by the Investigator that Occurred in ≥ 5% of Subjects by System Organ Class and Preferred Term (Study CC-4047-MM-007) (Safety Population)

System Organ Class/Preferred Term[a]	POM+BTZ+LD-DEX N=278 n (%)
Subjects with at Least 1 TEAE Related to POM	**229 (82.4)**
Blood and Lymphatic System Disorders	**138 (49.6)**
Neutropenia	105 (37.8)
Thrombocytopenia	78 (28.1)
Anaemia	37 (13.3)
Leukopenia	22 (7.9)
General Disorders and Administration Site Conditions	**100 (36.0)**
Fatigue	61 (21.9)
Asthenia	17 (6.1)
Pyrexia	16 (5.8)
Gastrointestinal Disorders	**94 (33.8)**
Constipation	50 (18.0)
Diarrhoea	40 (14.4)
Nausea	20 (7.2)
Infections and Infestations	**77 (27.7)**
Pneumonia	22 (7.9)
Nervous System Disorders	**71 (25.5)**
Peripheral sensory neuropathy	37 (13.3)
Dizziness	16 (5.8)

BTZ = bortezomib; LD-DEX = low-dose dexamethasone; MedDRA = Medical Dictionary for Regulatory Activities; POM = pomalidomide; TEAE = treatment-emergent adverse event

[a] System organ classes and preferred terms are coded using the MedDRA dictionary version 20.0, and are listed in decreasing order of frequency. A subject with multiple occurrences of the same preferred term is counted only once in that preferred term, in the highest grade category.

The following Grade 3 or 4 TEAEs were reported more frequently (a difference of at least 2% points) in the POM + BTZ + LD-DEX arm than in the BTZ + LD-DEX arm:

- Blood and lymphatic system disorders: neutropenia (41.7% versus 8.5%), leukopenia (5.4% versus 1.9%), and febrile neutropenia (3.2% versus none),
- Infections and infestations: pneumonia (11.5% versus 6.3%),
- Metabolism and nutrition disorders: hyperglycemia (9.0% versus 5.2%), hypokalaemia (6.1% versus 4.1%), and hypophosphatemia (4.0% versus 1.9%),
- Nervous system disorders: peripheral sensory neuropathy (8.3% versus 4.4%) and syncope (5.0% versus 2.2%),
- General disorders and administration site conditions: fatigue (8.3% versus 3.7%),
- Gastrointestinal disorders: diarrhea (7.2% versus 3.3%) and constipation (2.5% versus 0.4%),

- Respiratory, thoracic and mediastinal disorders: pulmonary embolism (4.0% versus 0.4%),
- Cardiac disorders: atrial fibrillation (3.2% versus 0.7%),
- Renal and urinary disorders: vascular disorders (6.1% versus 3.0%)
- Skin and subcutaneous disorders: rash (2.2% versus none).

Bortezomib

A total of 242 (87.1%) subjects in the POM arm and 219 (81.1%) subjects in the control experienced at least 1 TEAE considered related to bortezomib. The most frequently reported (at least 10% of the subjects) in the POM arm were peripheral sensory neuropathy (43.5%), neutropenia (25.5%), thrombocytopenia (25.2%), fatigue (20.9%), constipation (19.8%), and diarrhea (16.2%); In the control, were peripheral sensory neuropathy (34.1%), thrombocytopenia (30.0%), fatigue (15.6%), constipation (13.0%), and diarrhea (12.6%).

Dexamethasone

A total of 219 (78.8%) subjects in the POM arm and 175 (64.8%) subjects in control experienced at least 1 TEAE considered related to dexamethasone. The most frequently reported (at least 10% of the subjects) in the POM arm were peripheral edema (20.9%), insomnia (13.3%), and hyperglycemia (12.6%). In the control, the most frequently reported was insomnia (17.8%).

Table 38 TEAE of Common Terminology Criteria Grade 3 or 4 Severity Reported in ≥ 2% in Either Treatment Arm (Study CC-4047-MM-007) (Safety Population)

System Organ Class/Preferred Term[a]	POM+BTZ+LD-DEX N=278 n (%)	BTZ+LD-DEX N=270 n (%)
Subjects with at Least 1 NCI CTCAE Grade 3 or 4 TEAE	**251 (90.3)**	**190 (70.4)**
Blood and Lymphatic System Disorders	**154 (55.4)**	**112 (41.5)**
Neutropenia	116 (41.7)	23 (8.5)
Thrombocytopenia	76 (27.3)	79 (29.3)
Anaemia	39 (14.0)	38 (14.1)
Leukopenia	15 (5.4)	5 (1.9)
Lymphopenia	12 (4.3)	8 (3.0)
Febrile neutropenia	9 (3.2)	0 (0.0)
Infections and Infestations	**86 (30.9)**	**48 (17.8)**
Pneumonia	32 (11.5)	17 (6.3)
Influenza	7 (2.5)	4 (1.5)
Sepsis	6 (2.2)	1 (0.4)
Metabolism and Nutrition Disorders	**71 (25.5)**	**49 (18.1)**
Hyperglycaemia	25 (9.0)	14 (5.2)
Hypokalaemia	17 (6.1)	11 (4.1)
Hypophosphataemia	11 (4.0)	5 (1.9)
Hyponatremia	7 (2.5)	8 (3.0)
Hyperkalaemia	7 (2.5)	2 (0.7)
Hyperuricaemia	2 (0.7)	7 (2.6)
Nervous System Disorders	**57 (20.5)**	**32 (11.9)**
Peripheral sensory neuropathy	23 (8.3)	12 (4.4)
Syncope	14 (5.0)	6 (2.2)
General Disorders and Administration Site Conditions	**50 (18.0)**	**31 (11.5)**
Fatigue	23 (8.3)	10 (3.7)
Asthenia	8 (2.9)	8 (3.0)
Pyrexia	6 (2.2)	2 (0.7)
General physical health deterioration	3 (1.1)	7 (2.6)
Gastrointestinal Disorders	**36 (12.9)**	**19 (7.0)**
Diarrhoea	20 (7.2)	9 (3.3)
Constipation	7 (2.5)	1 (0.4)
Respiratory, Thoracic and Mediastinal Disorders	**24 (8.6)**	**13 (4.8)**
Pulmonary embolism	11 (4.0)	1 (0.4)
Dyspnoea	8 (2.9)	3 (1.1)
Cardiac Disorders	**22 (7.9)**	**12 (4.4)**
Atrial fibrillation	9 (3.2)	2 (0.7)
Cardiac failure	3 (1.1)	2 (0.7)
Renal and Urinary Disorders	**19 (6.8)**	**6 (2.2)**
Acute kidney injury	9 (3.2)	4 (1.5)
Vascular disorders	**17 (6.1)**	**8 (3.0)**
Hypertension	8 (2.9)	4 (1.5)
Skin and Subcutaneous Tissue Disorders	**9 (3.2)**	**0 (0.0)**
Rash	6 (2.2)	0 (0.0)

Serious adverse event / deaths / other significant events

Deaths

Table 39 Summary of Deaths (Study CC-4047-MM-007) (Safety Population)

n (%)	PVd N = 278	Vd N = 270
All deaths	**86 (30.9)**	**86 (31.9)**
Within 60 days of first dose	10 (3.6)	13 (4.8)
Within 100 days of first dose	20 (7.2)	22 (8.1)
Deaths during treatment (within 28 days of last dose)	**27 (9.7)**	**12 (4.4)**
Within 60 days of first dose	8 (2.9)	10 (3.7)
Within 100 days of first dose	15 (5.4)	12 (4.4)
Deaths during follow-up (> 28 days of last dose)	**59 (21.2)**	**74 (27.4)**

Table 40 Cause of Death Over Entire Study Period (Study CC-4047-MM-007) (Safety Population)

System Organ Class/Preferred Term[a]	POM+BTZ+LD-DEX N=278 n (%)	BTZ+LD-DEX N=270 n (%)
Number of Subjects Died	86 (30.9)	86 (31.9)
Neoplasms Benign, Malignant and Unspecified (Incl Cysts and Polyps)	**53 (19.1)**	**59 (21.9)**
Plasma cell myeloma	50 (18.0)	59 (21.9)
Metastases to meninges	1 (0.4)	0 (0.0)
Plasma cell leukaemia	1 (0.4)	0 (0.0)
Scrotal cancer	1 (0.4)	0 (0.0)
Infections and Infestations	**15 (5.4)**	**13 (4.8)**
Pneumonia	3 (1.1)	4 (1.5)
Septic shock	3 (1.1)	0 (0.0)
Escherichia sepsis	1 (0.4)	2 (0.7)
Sepsis	1 (0.4)	2 (0.7)
Clostridium difficile colitis	1 (0.4)	0 (0.0)
H1N1 influenza	1 (0.4)	0 (0.0)
Infection	1 (0.4)	0 (0.0)
Influenza	1 (0.4)	0 (0.0)
Pneumonia cytomegaloviral	1 (0.4)	0 (0.0)
Staphylococcal sepsis	1 (0.4)	0 (0.0)
Streptococcal sepsis	1 (0.4)	0 (0.0)
Lower respiratory tract infection	0 (0.0)	2 (0.7)
Bronchopulmonary aspergillosis	0 (0.0)	1 (0.4)
Lung infection	0 (0.0)	1 (0.4)
Staphylococcal bacteraemia	0 (0.0)	1 (0.4)

System Organ Class/Preferred Term[a]	POM+BTZ+LD-DEX N=278 n (%)	BTZ+LD-DEX N=270 n (%)
General Disorders and Administration Site Conditions	**9 (3.2)**	**5 (1.9)**
Death	9 (3.2)	4 (1.5)
General physical health deterioration	0 (0.0)	1 (0.4)
Cardiac Disorders	**4 (1.4)**	**3 (1.1)**
Cardiac arrest	3 (1.1)	1 (0.4)
Cardio-respiratory arrest	1 (0.4)	0 (0.0)
Myocardial infarction	0 (0.0)	1 (0.4)
Pericardial effusion	0 (0.0)	1 (0.4)
Respiratory, Thoracic and Mediastinal Disorders	**2 (0.7)**	**0 (0.0)**
Acute pulmonary oedema	1 (0.4)	0 (0.0)
Respiratory failure	1 (0.4)	0 (0.0)
Nervous System Disorders	**1 (0.4)**	**1 (0.4)**
Cerebral haemorrhage	1 (0.4)	0 (0.0)
Encephalopathy	0 (0.0)	1 (0.4)
Immune System Disorders	**1 (0.4)**	**0 (0.0)**
Graft versus host disease	1 (0.4)	0 (0.0)
Injury, Poisoning and Procedural Complications	**1 (0.4)**	**0 (0.0)**
Subdural haematoma	1 (0.4)	0 (0.0)
Investigations	**0 (0.0)**	**1 (0.4)**
Morganella test positive	0 (0.0)	1 (0.4)
Metabolism and Nutrition Disorders	**0 (0.0)**	**1 (0.4)**
Hypernatraemia	0 (0.0)	1 (0.4)
Musculoskeletal and Connective Tissue Disorders	**0 (0.0)**	**1 (0.4)**
Osteorrhagia	0 (0.0)	1 (0.4)
Renal and Urinary Disorders	**0 (0.0)**	**1 (0.4)**
Chronic kidney disease	0 (0.0)	1 (0.4)
Vascular Disorders	**0 (0.0)**	**1 (0.4)**
Shock haemorrhagic	0 (0.0)	1 (0.4)

Serious adverse events (SAEs)

Table 41 TE SAE in ≥ 1% of Subjects in Either Arm (Study CC-4047-MM-007) (Safety Population)

System Organ Class/Preferred Term [a]	POM+BTZ+LD-DEX N=278 n (%)	BTZ+LD-DEX N=270 n (%)
Subjects with at Least One Treatment Emergent Serious Adverse Events	**159 (57.2)**	**114 (42.2)**
Infections and Infestations	**90 (32.4)**	**48 (17.8)**
Pneumonia	32 (11.5)	17 (6.3)
Influenza	8 (2.9)	4 (1.5)
Lower respiratory tract infection	8 (2.9)	2 (0.7)
Respiratory tract infection	6 (2.2)	0 (0.0)
Septic shock	6 (2.2)	0 (0.0)
Sepsis	5 (1.8)	1 (0.4)
Clostridium difficile colitis	4 (1.4)	0 (0.0)
Bronchitis	3 (1.1)	2 (0.7)
Infection	3 (1.1)	1 (0.4)
Lung infection	3 (1.1)	1 (0.4)
Upper respiratory tract infection	2 (0.7)	3 (1.1)
Cardiac Disorders	**25 (9.0)**	**9 (3.3)**
Atrial fibrillation	7 (2.5)	2 (0.7)
Cardiac failure	3 (1.1)	2 (0.7)
General Disorders and Administration Site Conditions	**24 (8.6)**	**20 (7.4)**
Pyrexia	11 (4.0)	5 (1.9)
General physical health deterioration	5 (1.8)	9 (3.3)
Non-cardiac chest pain	3 (1.1)	2 (0.7)
Death	3 (1.1)	0 (0.0)
Nervous System Disorders	**20 (7.2)**	**17 (6.3)**
Syncope	6 (2.2)	5 (1.9)
Respiratory, Thoracic and Mediastinal Disorders	**18 (6.5)**	**12 (4.4)**
Pulmonary embolism	8 (2.9)	1 (0.4)
Dyspnoea	4 (1.4)	1 (0.4)
Pleural effusion	2 (0.7)	3 (1.1)
Gastrointestinal Disorders	**17 (6.1)**	**14 (5.2)**
Diarrhoea	5 (1.8)	6 (2.2)
Renal and Urinary Disorders	**14 (5.0)**	**6 (2.2)**
Acute kidney injury	8 (2.9)	6 (2.2)
Blood and Lymphatic System Disorders	**11 (4.0)**	**10 (3.7)**
Anaemia	3 (1.1)	5 (1.9)
Febrile neutropenia	5 (1.8)	0 (0.0)
Thrombocytopenia	1 (0.4)	3 (1.1)
Hyperviscosity syndrome	0 (0.0)	3 (1.1)
Neoplasms benign, Malignant and Unspecified (Incl Cysts and Polyps)	**10 (3.6)**	**6 (2.2)**
Basal cell carcinoma	4 (1.4)	1 (0.4)
Metabolism and Nutrition Disorders	**10 (3.6)**	**7 (2.6)**
Hyperglycaemia	3 (1.1)	1 (0.4)
Musculoskeletal and Connective Tissue Disorders	**10 (3.6)**	**6 (2.2)**
Back pain	3 (1.1)	1 (0.4)
Vascular Disorders	**8 (2.9)**	**7 (2.6)**
Deep vein thrombosis	4 (1.4)	4 (1.5)
Hypotension	3 (1.1)	1 (0.4)
Injury, Poisoning and Procedural Complications	**6 (2.2)**	**9 (3.3)**
Femur fracture	1 (0.4)	3 (1.1)

Other significant events

Table 42 TEAE of interest category (Study CC-4047-MM-007) (Safety Population)

Event of Interest Category/ Preferred Term[a]	ALL TEAEs		Grade 3 or 4 TEAEs[b]		Serious TEAEs	
	POM+ BTZ+ LD-DEX N=278 n (%)	BTZ+ LD-DEX N=270 n (%)	POM+ BTZ+ LD-DEX N=278 n (%	BTZ+ LD-DEX N=270 n (%)	POM+ BTZ+ LD-DEX N=278 n (%)	BTZ+ LD-DEX N=270 n (%)
Subjects with at Least 1 TEAE of Interest	**273 (98.2)**	**243 (90.0)**	**208 (74.8)**	**137 (50.7)**	**114 (41.0)**	**71 (26.3)**
Infections and Infestations	223 (80.2)	175 (64.8)	86 (30.9)	48 (17.8)	90 (32.4)	48 (17.8)
Peripheral Neuropathy	154 (55.4)	117 (43.3)	32 (11.5)	14 (5.2)	2 (0.7)	1 (0.4)
Neutropenia	142 (51.1)	36 (13.3)	121 (43.5)	28 (10.4)	7 (2.5)	0
Thrombocytopenia	102 (36.7)	106 (39.3)	76 (27.3)	80 (29.6)	1 (0.4)	3 (1.1)
Somnolence including dizziness and confusion	57 (20.5)	34 (12.6)	3 (1.1)	2 (0.7)	1 (0.4)	2 (0.7)
Bleeding	48 (17.3)	43 (15.9)	3 (1.1)	7 (2.6)	3 (1.1)	6 (2.2)
Cardiac arrhythmia	44 (15.8)	16 (5.9)	14 (5.0)	4 (1.5)	13 (4.7)	4 (1.5)
Venous thromboembolic event	32 (11.5)	7 (2.6)	15 (5.4)	2 (0.7)	12 (4.3)	4 (1.5)
Hepatic disorders	27 (9.7)	16 (5.9)	8 (2.9)	10 (3.7)	1 (0.4)	3 (1.1)
Angioedema	18 (6.5)	10 (3.7)	0	0	0	0
Acute renal failure	17 (6.1)	14 (5.2)	10 (3.6)	6 (2.2)	9 (3.2)	6 (2.2)
Cardiac failure	12 (4.3)	4 (1.5)	5 (1.8)	4 (1.5)	6 (2.2)	4 (1.5)
Cataract	10 (3.6)	0 (0.0)	3 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)
Herpes zoster virus infection	8 (2.9)	4 (1.5)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
Acute diffuse infiltrative pulmonary disease/Interstitial lung disease	7 (2.5)	3 (1.1)	3 (1.1)	2 (0.7)	1 (0.4)	2 (0.7)
Cerebrovascular accident	4 (1.4)	1 (0.4)	2 (0.7)	1 (0.4)	3 (1.1)	1 (0.4)
Arterial thromboembolic event	3 (1.1)	4 (1.5)	1 (0.4)	3 (1.1)	2 (0.7)	3 (1.1)
Myocardial infarction	3 (1.1)	3 (1.1)	2 (0.7)	3 (1.1)	3 (1.1)	2 (0.7)
Thyroid disorders	2 (0.7)	4 (1.5)	1 (0.4)	0 (0.0)	0 (0.0)	1 (0.4)
Severe skin reactions	2 (0.7)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
Gastrointestinal perforation	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Guillain-Barre syndrome	1 (0.4)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.4)	0 (0.0)
Hypersensitivity	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Tumour lysis syndrome	1 (0.4)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.4)	0 (0.0)
Pericardial disease	0 (0.0)	2 (0.7)	0 (0.0)	2 (0.7)	0 (0.0)	1 (0.4)
Teratogenicity	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.4)

BTZ = bortezomib; LD-DEX = low-dose dexamethasone; MedDRA = Medical Dictionary for Regulatory Activities; POM = pomalidomide; TEAE = treatment-emergent adverse event

[a] Preferred terms are coded using the MedDRA dictionary Version 20.0. Categories are listed in decreasing order of frequency for the first POM+BTZ+LD-DEX column. A subject was counted only once for multiple events within preferred term/system organ class.

[b] Graded using National Cancer Institute Common Terminology Criteria Version 4.0 for Adverse Events.

- *Neutropenia and thrombocytopaenia*

Table 43 TEAE of Interest – Neutropenia (Study CC-4047-MM-007) (Safety Population)

TEAE of Interest Category/ Preferred Term[a]	ALL TEAEs		Grade 3 or 4 TEAEs[b]		Serious TEAEs	
	POM+ BTZ+ LD-DEX N=278 n (%)	BTZ+ LD-DEX N=270 n (%)	POM+ BTZ+ LD-DEX N=278 n (%	BTZ+ LD-DEX N=270 n (%)	POM+ BTZ+ LD-DEX N=278 n (%)	BTZ+ LD-DEX N=270 n (%)
Neutropenia	**142 (51.1)**	**36 (13.3)**	**121 (43.5)**	**28 (10.4)**	**7 (2.5)**	**0 (0.0)**
Neutropenia	130 (46.8)	29 (10.7)	116 (41.7)	23 (8.5)	1 (0.4)	0 (0.0)
Leukopenia	32 (11.5)	9 (3.3)	15 (5.4)	5 (1.9)	0 (0.0)	0 (0.0)
Febrile neutropenia	9 (3.2)	0 (0.0)	9 (3.2)	0 (0.0)	5 (1.8)	0 (0.0)
Neutrophil count decreased	2 (0.7)	1 (0.4)	2 (0.7)	1 (0.4)	1 (0.4)	0 (0.0)

In patients receiving combination therapy with pomalidomide in clinical studies, thrombocytopenia occurred in 27.0-36.7% of patients. Thrombocytopenia was Grade 3 or 4 in 20.7-27.3% of patients, led to pomalidomide discontinuation in 0.7% of patients and was serious in 0.4-1.7% of patients.

- *Infection*

In patients receiving combination therapy with pomalidomide in clinical studies, infection occurred in 55.0-80.2% of patients (24.0-30.9% Grade 3 or 4). Upper respiratory tract infection and pneumonia were the most frequently occurring infections. Fatal infections (Grade 5) occurred in 2.7-4.0% of patients. Infections led to pomalidomide discontinuation in 2.0-2.9% of patients.

- *Bleeding*

Haemorrhagic disorders have been reported with pomalidomide, especially in patients with risk factors such as concomitant medicinal products that increase susceptibility to bleeding. Haemorrhagic events have included epistaxis, intracranial haemorrhage and gastrointestinal haemorrhage.

- *Venous Thromboembolic Events*

In patients receiving combination therapy with pomalidomide in clinical studies, venous thromboembolic events (VTE) occurred in 3.3-11.5% of patients (1.3-5.4% Grade 3 or 4). VTE was reported as serious in 1.7-4.3% of patients, no fatal reactions were reported, and VTE was associated with pomalidomide discontinuation in up to 1.8% of patients.

- *Peripheral Neuropathy*

In study CC-4047-MM-007, peripheral neuropathy occurred in 55.4 % of patients who received pomalidomide in combination with bortezomib and low-dose dexamethasone (Pom+Btz+LD-Dex) and 43.3% of patients receiving bortezomib and low-dose dexamethasone (Btz + LD-Dex). Peripheral neuropathy was reported as Grade 3 in 10.8% of patients in the Pom + Btz + LD-Dex arm and 5.2% in the Btz + LD-Dex arm. Grade 4 was reported infrequently; 0.7% of patients in Pom + Btz + LD-Dex arm and none in Btz + LD-Dex arm. Exposure-adjusted rates were comparable across treatment arms. Approximately 30% of the patients experiencing peripheral neuropathy had a history of neuropathy at baseline. Peripheral neuropathy led to discontinuation of bortezomib in approximately 12.9% of patients, pomalidomide in 1.8% and dexamethasone in 2.2 - 8.9% of patients, respectively.

Table 44 Permanent study drug discontinuation, dose reduction, and dose interruption due to TEAEs in the events of interest category of peripheral neuropathy (Study CC-4047-MM-007) (Safety Population)

	PVd N = 278 n (%)	Vd N = 270 n (%)	All subjects N = 548 n (%)
Permanent discontinuation			
Pomalidomide	5 (1.8)	NA	
Dexamethasone	6 (2.2)	24 (8.9)	30 (5.5)
Bortezomib	36 (12.9)	26 (9.6)	62 (11.3)
Dose reduction(s)			
Pomalidomide	5 (1.8)	NA	
Dexamethasone	3 (1.1)	5 (1.9)	8 (1.5)
Bortezomib	77 (27.7)	70 (25.9)	147 (26.8)
Dose interruption(s)			
Pomalidomide	16 (5.8)	NA	
Dexamethasone	14 (5.0)	23 (8.5)	37 (6.8)
Bortezomib	44 (15.8)	34 (12.6)	78 (14.2)

NA = not available; PVd = pomalidomide, bortezomib, and low-dose dexamethasone; TEAE = treatment-emergent adverse event; Vd = bortezomib and low-dose dexamethasone.
Source: CSR MM-007 Table 14.3.2.16.9; Annex 1, Response Table 14.1 and Response Table 14.2
Data cutoff date: 26 Oct 2017

- *Second Primary Malignancies (SPM)*

Table 45 Summary of Frequencies and Incidence Rates of Second Primary Malignancies (Study CC-4047-MM-007) (Safety Population)

	POM + BTZ + LD-DEX (N = 278)			BTZ + LD-DEX (N = 270)		
SPM Category	n (%)	IR per 100 PY[a]	(95% CI)	n (%)	IR per 100 PY[a]	(95% CI)
Hematologic Malignancies	1 (0.4)	0.29	(0.04 – 2.07)	0 (0.0)	--	--
AML	0 (0.0)	--	--	0 (0.0)	--	--
MDS to AML	0 (0.0)	--	--	0 (0.0)	--	--
MDS	1 (0.4)	0.29	(0.04 – 2.07)	0 (0.0)	--	--
B-cell malignancies	0 (0.0)	--	--	0 (0.0)	--	--
Solid Tumors	1 (0.4)	0.29	(0.04 – 2.07)	1 (0.4)	0.30	(0.04 – 2.14)
Invasive SPMs	**2 (0.7)**	**0.58**	**(0.15 – 2.33)**	**1 (0.4)**	**0.30**	**(0.04 – 2.14)**
Non-Invasive SPMs (Non-melanoma skin cancer)	7 (2.5)	2.10	(1.00 – 4.40)	3 (1.1)	0.92	(0.30 – 2.84)
TOTAL SPMs	**9 (3.2)**	**2.70**	**(1.41 – 5.20)**	**4 (1.5)**	**1.22**	**(0.46 – 3.25)**

Laboratory findings

Hematology

The percentages of subjects with Grade 3 or 4 hemoglobin, lymphocyte, and platelet values were similar in the POM + BTZ + LD-DEX and BTZ + LD-DEX treatment arms. Substantially higher percentages of subjects in the POM + BTZ + LD-DEX arm than in the BTZ + LD-DEX arm experienced Grade 3 leukocyte

and Grade 3 and Grade 4 neutrophil values. Neutropenia (PT) was reported as a TEAE in 130 (46.8%) subjects in the POM + BTZ + LD-DEX arm and 29 (10.7%) subjects in the BTZ + LD-DEX arm.

Clinical Chemistry

For most tests, the percentages of subjects with Grade 3 or 4 values were relatively low and similar in the 2 treatment arms. Test with the largest differences in subjects with Grade 3 values between the POM + BTZ + LD-DEX and BTZ + LD-DEX treatment arms was calcium (14 subjects [5.1%] versus 4 subjects [1.5%]).

One subject in the POM + BTZ + LD-DEX arm was reported with Grade 4 calcium at baseline; the value shifted to Grade 3 postbaseline. Two subjects in the POM + BTZ + LD-DEX arm were reported with Grade 4 calcium corrected for albumin at baseline. The value shifted to Grade 3 postbaseline for 1 subject and the other subject had additional Grade 4 values postbaseline. One subject in the POM + BTZ + LD-DEX arm was reported with Grade 4 magnesium at baseline; the subject had additional Grade 4 readings postbaseline. Seven subjects in the POM + BTZ + LD-DEX arm and 2 subjects in the BTZ + LD-DEX were reported with Grade 4 urate at baseline. In the POM + BTZ + LD-DEX arm, the values shifted to normal postbaseline for 1 subject and Grade 1 postbaseline for 3 subjects. Three other subjects in the POM + BTZ + LD-DEX arm and the 2 subjects in the BTZ + LD-DEX arm had additional Grade 4 values postbaseline.

Safety in special populations

No clinically meaningful differences were noted in the safety profile of POM + BTZ + LD-DEX when analyzed by age (≤ 75 years, > 75 years; ≤ 65 years, > 65 years).

Safety related to drug-drug interactions and other interactions

Not applicable.

Discontinuation due to adverse events

Table 46. Overview of discontinuation due to adverse events (Study CC-4047-MM-007) (Safety Population)

	POM+BTZ+LD-DEX N=278 n (%)	BTZ+LD-DEX N=270 n (%)
Subjects with at Least 1 TEAE Leading to Discontinuation of Any Study Drug	**80 (28.8)**	**51 (18.9)**
TEAE Leading to Discontinuation of POM	31 (11.2)	NA
TEAE Leading to Discontinuation of BTZ	67 (24.1)	50 (18.5)
TEAE Leading to Discontinuation of DEX	47 (16.9)	51 (18.9)

Table 47 TEAE Leading to Discontinuation of Pomalidomide in ≥1% of the Subjects by System Organ Class and Preferred Term (Study CC-4047-MM-007) (Safety Population)

System Organ Class/Preferred Term[a]	POM+BTZ+LD-DEX N=278 n (%)
Subjects with at Least 1 TEAE Leading to Discontinuation of POM	31 (11.2)
Nervous System Disorders	7 (2.5)
Peripheral sensory neuropathy	3 (1.1)
General Disorders and Administration Site Conditions	6 (2.2)
Fatigue	4 (1.4)
Respiratory, Thoracic and Mediastinal Disorders	4 (1.4)
Pulmonary embolism	3 (1.1)

Post marketing experience

Since the initial marketing authorization, 77,428 patients have been exposed to pomalidomide. The safety profile has been well defined in the RRMM population and is discussed in the most recent periodic safety update report (PSUR) (version 8) for the reporting period 8 February 2017 to 7 February 2018.

2.5.1. Discussion on clinical safety

Safety data from a total of 548 subjects were included in this report in order to evaluate the safety profile of POM together with standard background therapy, 278 subjects received POM in combination with standard background therapy (POM+BTZ+LD-DEZ) and 270 subjects received background therapy alone (BTZ+LD-DEX). The number of exposed subjects and degree of exposure is considered sufficient to evaluate the safety of POM in combination with the background therapies.

Treatment was generally well tolerated and the median relative dose intensity was high for POM (0.8), and was comparable for both BTZ (0.8 versus 0.9) and DEX (0.8 vs 0.9) in the POM + BTZ + LD-DEX vs the BTZ + LD-DEX arm, respectively. Treatment duration of BTZ (33.0 versus 21.4 weeks) and DEX (34.0 versus 21.2 weeks) was substantially longer in the POM + BTZ + LD-DEX arm compared to the BTZ + LD-DEX arm, indicating that triplet therapy allowed for longer usage and higher cumulative doses of BTZ and DEX.

Overall, the most frequently reported ADRs (all grades) by preferred term in the POM + BTZ + LD-DEX arm were peripheral sensory neuropathy (47.8%), neutropenia (46.8%), fatigue (37.1%), thrombocytopenia and constipation (36.7% each), peripheral edema and diarrhea (33.8%). In the BTZ + LD-DEX arm, the 5 most frequently reported TEAEs were thrombocytopenia (38.1%), peripheral sensory neuropathy (37.0%), diarrhea (30.0%), anemia (27.0%), and fatigue (26.3%).

Infections occurred frequently in both arms; 80.2% all grades and 30.9% Grade 3 or 4 in the POM + BTZ + LD-DEX arm compared with 64.8% all grades and 17.8% Grade 3 or 4 in the BTZ + LD-DEX arm; however, exposure-adjusted rates were similar between the 2 treatment arms. Most subjects in both treatment arms who developed infections did not have a concurrent Grade 3 or 4 neutropenia. Infections seldom led to treatment discontinuation or death during the treatment period.

Neutropenia occurred more frequently in the POM + BTZ + LD-DEX arm; Grade 3 or 4 neutropenia occurring in 41.7% of subjects in the POM + BTZ + LD-DEX arm compared to the 8.5% in the BTZ + LD-DEX arm. The frequency of febrile neutropenia was low; 3.2% in the POM + BTZ + LD-DEX arm and

no recorded events in the BTZ + LD-DEX arm. Most subjects who developed a Grade 3 or 4 neutropenia did not develop concurrent infections in either arm. The frequency of thrombocytopenia was similar (36.7% in the POM + BTZ + LD-DEX arm compared with 39.3% in the BTZ + LD-DEX arm); and bleeding events occurred at similar rates between treatment arms (17.3% versus 15.9%, respectively). Neutropenia and thrombocytopenia occurred most frequently in the first 2 cycles of treatment with pomalidomide.

Peripheral neuropathy occurred more frequently in the POM + BTZ + LD-DEX arm (55.4%) compared to the BTZ + LD-DEX arm (43.3%); however, exposure-adjusted rates were comparable across treatment arms. Approximately 30% of the subjects experiencing PN already had a history of neuropathy at baseline. Peripheral neuropathy was reported as Grade 3 or 4 in relatively few subjects (11.5% and 5.2%, respectively).

Venous thromboembolic events, including deep venous thrombosis and pulmonary embolus, occurred more frequently in the POM + BTZ + LD-DEX arm than in the BTZ + LD-DEX arm (11.5% versus 2.6%). None of these events in either arm resulted in death.

Cardiac arrhythmias occurred more frequently in the POM + BTZ + LD-DEX arm (15.8%) compared to the BTZ + LD-DEX arm (5.9%), driven primarily by atrial fibrillation (9.4% versus 1.9%, respectively). Grade 3 or 4 atrial fibrillation occurred infrequently in both treatment arms (3.2% versus 0.7%). Most subjects who developed atrial fibrillation had a history of cardiac disorders, and/or other comorbidities that could increase the risk of developing atrial fibrillation.

Ventricular arrhythmias were infrequently (< 1.0%) reported and at similar rates between treatment arms.

In summary, 172 (31.4%) deaths occurred in the safety population over the entire study period, at a comparable rate across treatment arms (30.9% and 31.9%, respectively). The most common cause of death in both treatment arms was progression of MM; particularly plasma cell myeloma (18.0% and 21.9% of subjects in the POM + BTZ + LD-DEX and BTZ + LD-DEX arms, respectively), and plasma cell leukemia and metastases to the meninges (due to MM) in 1 subject each for the POM + BTZ + LD-DEX arm. Death due to infections and infestations occurred in 5.4% and 4.8%, of subjects respectively, not unexpectedly as infection is the leading cause of death in patients with myeloma (Nucci, 2009).

More deaths were reported during the treatment period in the POM + BTZ + LD-DEX arm compared with the BTZ + LD-DEX arm (9.7% versus 4.4%). This observation likely reflects the substantially longer treatment duration in the POM + BTZ + LD-DEX arm compared with the BTZ + LD-DEX arm (median treatment duration 38 weeks versus 21 weeks, respectively). In support of this observation, the incidence of all deaths and on-treatment deaths during the first 60 and 100 days of treatment were comparable across treatment arms. More deaths occurred during the follow-up phase in the BTZ + LD-DEX arm compared with the POM + BTZ + LD-DEX arm (74 [27.4%]) versus 59 [21.2%]), again potentially reflecting the difference in study treatment duration between arms. Most of these deaths were due to plasma cell myeloma.

2.5.2. Conclusions on clinical safety

The safety profile of POM + BTZ + LD-DEX was consistent with the well-established safety profiles of each drug in the triplet therapy. There is no new safety concern arising from the data in the new population of RRMM patients after at least one prior treatment. Toxicities were generally manageable with dose reductions and interruptions, and study drug discontinuations due to AEs were infrequently reported. Data from POM + BTZ + LD-DEX define a manageable safety profile with no clinically relevant differences from the current product information for POM + DEX and BTZ.

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 MAH submitted an updated RMP (version 15.0 and 15.1) with this application.

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

The PRAC considered that the risk management plan version 15.1 is acceptable.

The CHMP endorsed the Risk Management Plan version 15.1 with the following content:

2.6.1. Safety Specification

Table 48 Summary of safety concerns

Important Identified Risks	– Teratogenicity – Severe infection due to neutropenia and pancytopenia – Thrombocytopenia and bleeding – Cardiac failure – Non-melanoma skin cancer
Important Potential Risks	– Other second primary malignancies – Cardiac arrhythmia
Missing Information	– None

The safety concerns are unchanged from those relating to the current indication, which is in line with the CHMP assessment that the safety profile of the triplet combination of pomalidomide + bortezomib + dexamethasone is in line with the safety profile of each drug.

2.6.2. Pharmacovigilance Plan

Table 49 On-going and planned additional PhV studies/activities in the Pharmacovigilance Plan

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Category 1 – Imposed Mandatory Additional Pharmacovigilance Activities which are Conditions of the Marketing Authorisation				
Study CC-4047-MM-015 Started	– Monitor incidence of ADRs in "real world situation" – Monitor implementation and compliance of Celgene PPP	Teratogenicity, severe infection due to neutropenia and pancytopenia, thrombocytopenia and bleeding, cardiac failure, NMSC, other SPM, cardiac arrhythmia.	Started patient recruitment 26 Jun 2014	31 Aug 2023 (Final report) Updates with PSURs
Category 2 – Imposed Mandatory Additional Pharmacovigilance Activities which are Specific Obligations in the Context of a Conditional Marketing Authorisation or a Marketing Authorisation under Exceptional Circumstances				
None	Not available	Not available	Not available	Not available
Category 3 – Required Additional Pharmacovigilance Activities				
Solicited reporting of SPM in all Celgene sponsored clinical studies Started	– Monitor incidence of SPM in the clinical trial setting	NMSC, other SPM	Please note: Ongoing. Safety updates to be submitted with future PSURs	PSUR/DSUR cycle

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Long-term follow-up of SPM in all Celgene-sponsored clinical studies Started	– Long-term follow-up of SPM in all Celgene-sponsored clinical studies	NMSC, other SPM	Please note: Ongoing. Safety updates to be submitted with future PSURs	PSUR/DSUR cycle

There are no new studies in the Pharmacovigilance Plan which is agreed.

2.6.3. Risk Minimisation measures

Table 50 Summary of risk minimisation measures

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Important Identified Risks		
Teratogenicity	**Routine Risk Minimisation Activities:** SmPC – Contraindicated in pregnant women and in women of childbearing potential, unless all the conditions of the PPP are met. Pomalidomide is also contraindicated in male patients unable to follow or comply with the required contraceptive measures (Section 4.3). – Warnings: criteria for women of non-childbearing potential, counselling, contraception, pregnancy testing, precautions for men, additional precautions, prescription duration (Section 4.4). – Stringent controls are required to ensure exposure of an unborn child to pomalidomide does not occur (Section 4.4). These include: counselling, contraception, pregnancy testing, precautions for men, additional precautions and prescription duration. PL – The PL warns of the potential teratogenic effects of pomalidomide and the need to avoid pregnancy. **Additional Risk Minimisation Activities:** Celgene PPP – Educational Programme o DHPC prior to launch ('Dear HCP' Letter). o HCP kit to include booklet. o Treatment algorithm, pregnancy reporting form, Patient Card and/or equivalent tool, and Patient Brochure. – Therapy management o Criteria for determining women of childbearing potential, contraceptive measures and pregnancy testing for women of childbearing potential. o Advice in SmPC, DHPC and educational materials. – System to ensure appropriate measures have been completed o Patient Card to document childbearing status, counselling and pregnancy testing.	**Routine Pharmacovigilance Activities Beyond Adverse Reactions Reporting and Signal Detection:** – Expedited reporting of all pregnancies and abnormal pregnancy test results – Optimise data collection and reporting of pregnancies by use of pregnancy report forms in HCP Kits – Follow-up of abnormal pregnancy test results – Follow-up of all pregnancies until outcome is known. – Follow-up of infant until one year after delivery – Root cause analysis of failed Celgene PPP as part of standard follow-up – Review of PSURs (periodic and cumulative). **Additional Pharmacovigilance:** Study CC-4047-MM-015: Noninterventional postauthorisation registry of patients treated with pomalidomide for RRMM to monitor incidence of ADRs in "real world situation" and to monitor implementation and compliance of the Celgene PPP on a country basis in agreement with the relevant NCA (ie, monitoring of Patient Card completion).

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Severe Infection due to Neutropenia and Pancytopenia	**Routine Risk Minimisation Activities:** SmPC – Dose modification advice for neutropenia (Section 4.2). – Warning of neutropenia, and advice for blood tests at baseline, weekly for the first 8 weeks and monthly thereafter (Section 4.4). – Warning regarding HBV reactivation and advice that HBV status should be established before treatment (Section 4.4). – Neutropenia, pancytopenia and infections and infestations are listed as ADRs and neutropenia and infection are discussed in Section 4.8. PL – Advice to patients including a warning that the doctor is advised to check if the patient has ever had hepatitis B infection prior to starting pomalidomide treatment. – A warning that pomalidomide may cause a reduction in the number of RBCs, WBCs, and platelets at the same time (pancytopenia), and describes possible symptoms. **Additional Risk Minimisation Activities:** – None proposed.	**Routine Pharmacovigilance Beyond Adverse Reactions Reporting and Signal Detection:** – If there is a change in nature or frequency observed or significant clinical findings emerge, these events will be analysed in the PSURs. – Additional information from ongoing clinical trials. – Event specific questionnaire for the collection of the AE and follow-up. **Additional Pharmacovigilance:** Study CC-4047-MM-015: Noninterventional postauthorisation registry of patients treated with pomalidomide for RRMM to monitor incidence of ADRs in "real world" situation.
Thrombocytopenia and Bleeding	**Routine Risk Minimisation Activities:** **SmPC** – Dose modification advice for thrombocytopenia (Section 4.2). – Warning of thrombocytopenia, and advice for blood tests at baseline, weekly for the first 8 weeks and monthly thereafter. Advice to monitor for signs of bleeding (Section 4.4) – Thrombocytopenia, intracranial haemorrhage and gastrointestinal haemorrhage are listed as ADRs and discussed in Section 4.8. PL – The PL warns that pomalidomide may cause a fall in the number of cells that help to stop bleeding, and lists bleeding within the skull, nosebleeds and bleeding from the bowels or stomach as possible side effects. **Additional Risk Minimisation Activities:** – HCP additional educational materials. – Patient brochure.	**Routine Pharmacovigilance Beyond Adverse Reactions Reporting and Signal Detection:** – If there is a change in nature or frequency observed or significant clinical findings emerge, these events will be analysed in the PSURs – Additional information from ongoing clinical trials – Event specific questionnaire for the collection of the AE and follow-up. **Additional Pharmacovigilance:** Study CC-4047-MM-015: Noninterventional postauthorisation registry of patients treated with pomalidomide for RRMM to monitor incidence of ADRs in "real world" situation.

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Cardiac Failure	**Routine Risk Minimisation Activities:** SmPC – Section 4.4 of the SmPC provides warnings and precautions regarding treating patients with cardiac risk factors, and advice regarding periodic monitoring for signs or symptoms of cardiac failure. – Listed as an ADR in Section 4.8. PL – A warning regarding heart failure is included in the PL. **Additional Risk Minimisation Activities:** – HCP additional educational materials.	**Routine Pharmacovigilance Beyond Adverse Reactions Reporting and Signal Detection:** – If there is a change in nature or frequency observed or significant clinical findings emerge, these events will be analysed in the PSURs – Additional information from ongoing clinical trials – Event specific questionnaire for the collection of the AE and follow-up. **Additional Pharmacovigilance:** Study CC-4047-MM-015: Noninterventional postauthorisation registry of patients treated with pomalidomide for RRMM to monitor incidence of ADRs in "real world" situation.
Non-melanoma Skin Cancer	**Routine Risk Minimisation Activities:** SmPC – Section 4.4 contains a warning that SPM, such as NMSC, have been reported in patients receiving pomalidomide; physicians should carefully evaluate patients before and during treatment using standard cancer screening for occurrence of SPM and institute treatment as indicated. – BCC of the skin and SCC of the skin are listed as ADRs in Section 4.8. PL – A warning regarding BCC and SCC is included in the PL. **Additional Risk Minimisation Activities:** – None proposed.	**Routine Pharmacovigilance Beyond Adverse Reactions Reporting and Signal Detection:** – If there is a change in nature or frequency observed or significant clinical findings emerge, these events will be analysed in the PSURs – Event specific questionnaire for the collection of the AE and follow-up. **Additional Pharmacovigilance:** – Study CC-4047-MM-015: Noninterventional postauthorisation registry of patients treated with pomalidomide for RRMM to monitor incidence in "real world" situation – Solicited reporting in all Celgene-sponsored clinical studies (status of studies will be updated with each PSUR cycle) – Long-term (at least 5 years from the date of the randomisation of the last patient in the study) follow-up in all Celgene-sponsored clinical studies
Important Potential Risks		
Other Second Primary Malignancies	**Routine Risk Minimisation Activities:** SmPC – Section 4.4 states that SPM have been reported in patients receiving pomalidomide, and warns that physicians should carefully evaluate patients before and during treatment using standard cancer screening for occurrence of SPM	**Routine Pharmacovigilance Beyond Adverse Reactions Reporting and Signal Detection:** – If there is a change in nature or frequency observed or significant clinical findings emerge, these events will be analysed in the PSURs – Event specific questionnaire for the collection of the AE and follow-up.

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Other Second Primary Malignancies (Continued)	and institute treatment as indicated. – Preclinical safety data discussed in Section 5.3. PL – A warning regarding BCC and SCC is included in the PL. **Additional Risk Minimisation Activities:** None proposed.	**Additional Pharmacovigilance:** – Study CC-4047-MM-015: Noninterventional postauthorisation registry of patients treated with pomalidomide for RRMM to monitor incidence in "real world" situation – Solicited reporting in all Celgene-sponsored clinical studies (status of studies will be updated with each PSUR cycle) – Long-term (at least 5 years from the date of the randomisation of the last patient in the study) follow-up in all Celgene-sponsored clinical studies Invasive SPM will be considered important medical events.
Cardiac Arrhythmia	**Routine Risk Minimisation Activities:** SmPC – AF listed as an ADR in Section 4.8. PL – Listed in PL. **Additional Risk Minimisation Activities:** – None proposed.	**Routine Pharmacovigilance Beyond Adverse Reactions Reporting and Signal Detection:** – If there is a change in nature or frequency observed or significant clinical findings emerge, these events will be analysed in the PSURs – Additional information from ongoing clinical trials – Event specific questionnaire for the collection of the AE and follow-up. **Additional Pharmacovigilance:** Study CC-4047-MM-015: Noninterventional postauthorisation registry of patients treated with pomalidomide for RRMM to monitor incidence of ADRs in "real world" situation.
Missing Information		
Not applicable.		

The risk minimisation measures are unchanged from those that are in place for the current indication and the MAH is not proposing any additional risk minimisation measures for the new indication, which is agreed.

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.3, 4.4, 4.5, 4.8 and 5.1 of the SmPC have been updated. The Package Leaflet is updated in accordance.

As a result the MAH submitted a request to add 14-capsule pack sizes for the 1 mg, 2 mg, 3 mg and 4 mg Imnovid strengths to support the new proposed posology and pomalidomide dose modification which was accepted by the CHMP. The SmPC, Labelling and Package leaflet are updated in accordance. The RMP version 15.1 has also been updated.

Update on Annex II to include post-authorisation efficacy study.

In addition, changes related to section 5.1 of the SmPC have been made with regard to pomalidomide mechanism of action based on literature data.

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

Pomalidomide is currently approved in combination with dexamethasone for the treatment of RRMM after at least two prior regimens, including both lenalidomide and bortezomib, and with disease progression on last therapy.

The proposed new indication of pomalidomide is in combination with bortezomib and dexamethasone for the treatment of adults with MM who have received at least one prior treatment regimen, including lenalidomide.

3.1.2. Available therapies and unmet medical need

Lenalidomide-based therapy is a major current standard of care in MM, and it is expected that the vast majority of patients will receive LEN for the treatment of newly diagnosed and/or early relapsed refractory MM. Consequently, the treatment where LEN is no longer an option, including refractory patients, represent a clinically relevant population. Currently, although there are no treatments that were developed to specifically address this patient population there are some therapy regimens available for lenalidomide refractory patients (e.g. daratumumab or carfilzomib based regimens).

The combination of lenalidomide and dexamethasone is approved as second line treatment in the EU. There are several regimens approved in EU as second line treatment in RRMM that include the

combination of LEN + Dex + a third agent (daratumumab, elotuzumab, carfilzomib, ixazomib). Bortezomib (monotherapy or in combination with dexamethasone or doxorubicin) is also authorised as second line therapy. However, none of these regimens are specifically indicated in lenalidomide refractory patients.

3.1.3. Main clinical studies

The clinical package of Imnovid for the proposed indication was primarily supported by data from a single phase 3 randomized clinical study MM-007 that compared the efficacy and safety of the triplet pomalidomide +bortezomib + dexamethasone to the doublet of bortezomib + dexamethasone in patients who had received at least 1 prior regimen that included lenalidomide.

3.2. Favourable effects

- Statistically significant improvement in PFS with the POM combination with a reduction of the risk of progression or death by 39% in ITT population compared to BTZ+DEX (median 11.2 months versus 7.10 months, HR 0.61 (0.49 to 0.77), p< 0.0001) supported by positive results in sensitivity analysis.
- The PFS favourable effect with POM combination is maintained in key subgroups of high prognostic risk (> 65 years, refractory to LEN, refractory to last prior antimyeloma therapy, unfavourable cytogenetics).
- Statistically significant improvement in overall response rate (sCR+CR+VGPR+PR) with the POM combination (ORR 82.2% versus 50.0 %, OR 5.02 (3.35 to 7.52), p<0.001). Consistent results in all subgroups analysis.
- For subjects with at least PR the duration of response was longer for POM combination (median 13.7 months versus 10.94 months, HR 0.76 (0.56 to 1.02) and the time to response was shorter for POM combination (median 0.9 months versus 1.4 months; p<0.001).
- Time to progression was longer for POM combination (median 13.14 months versus 7.79 months, HR 0.57 (0.45 to 0.72)).
- Time to treatment failure was longer for POM combination (median 8.54 months versus 4.67 months, HR 0.54 (0.44 to 0.65)).
- Treatment with POM combination prolongs the time to next anti-myeloma therapy by 58% (median 22.24 months versus 8.51 months; HR 0.42 (0.33 to 0.54)).
- PFS after next line therapy (PFS2) showed an advantage for POM combination (median 22.44 months versus 16.95 months, HR 0.76 (0.59 to 0.99)).

3.3. Uncertainties and limitations about favourable effects

The interim of OS analysis (176 events) did not cross the pre-specified boundary for superiority of the POM combination (HR 0.98; 95% CI: 0.73 to 1.32). An updated analysis based on data cut off 15 September 2018 showed a positive trend in favour of PVd with median OS 40.5 months for the PVd arm and 30.5 months for the Vd arm (HR 0.91; 95% CI: 0.70 to 1.18). Overall survival data are still immature and the MAH will provide the final OS analysis (expected after 379 events) in Q3 of 2021 (see Annex II).

3.4. Unfavourable effects

The most frequently reported (at least 10% of the subjects) pomalidomide-related TEAEs included neutropenia (37.8%), thrombocytopenia (28.1%), fatigue (21.9%), constipation (18.0%), diarrhea (14.4%), and anemia and peripheral sensory neuropathy (13.3% each).

The following Grade 3 or 4 ADRs were reported more frequently in the POM + BTZ + LD-DEX arm than in the BTZ + LD-DEX arm: peripheral sensory neuropathy (8.3% vs 4.4%), neutropenia (41.7% vs 8.5%), fatigue (8.3% vs 3.7%), constipation(2.5% vs 0.4%), diarrhoea (7.2% vs 3.3%) and peripheral oedema (1.8% vs 0.7%).

The most frequent serious ADR reported was pneumonia. Other reported adverse reactions were in line with the safety profile of each drug (e.g. venous thromboembolism, cataract, secondary primary malignancies).

3.5. Uncertainties and limitations about unfavourable effects

There are no uncertainties and limitations about unfavourable effects.

3.6. Effects Table

Table 51. Effects Table for Imnovid for the treatment of patients with MM who have received at least one prior regimen including lenalidomide (Study MM-007 -data cut-off:26 October 2017)

Effect	Short Description	Unit	Bortezomib +Dexamethasone N=270	Pomalidomide+ Bortezomib +Dexamethasone N=278	Uncertainties / Strength of evidence	References
Favourable Effects						
PFS	Median time from randomization to progression or death	Months	7.10 (5.88, 8.48)	11.2 (9.66, 13.73)	HR= 0.61 [0.49 to 0.77]; P<0.0001 Results supported by sensitivity and exploratory analysis	See 'clinical efficacy' section
OS	Median time from randomization to death of any cause	Months	30.46 (24.61,35.94)	40.54 (29.83, NE)	HR=0.91 (0.70 to 1.18); Logrank p-value(2-sided) = 0.4755 The OS data are not mature	
Unfavourable Effects						
Peripheral sensory neuropathy	Incidence of grade 3 or 4 ADRs	%	4.4	8.3		See 'clinical safety' section
Neutropaenia	Incidence of grade 3 or 4 ADRs	%	8.5	41.7		

Fatigue	Incidence of grade 3 or 4 ADRs	%	3.7	8.3		
Constipation	Incidence of grade 3 or 4 ADRs	%	0.4	2.5		
Diarrhoea	Incidence of grade 3 or 4 ADRs	%	3.3	7.2		
Peripheral oedema	Incidence of grade 3 or 4 ADRs	%	0.7	1.8		

Abbreviations: NE: not estimable; OS: overall survival; PFS: progression-free survival data

Cut-off dates: efficacy: PFS and safety: 26 Oct 2017, OS: 15 Sep 2018.

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The addition of POM to BTZ + DEX results in an improvement in PFS, including patients refractory to LEN. As LEN based regimens are used earlier in the treatment of MM and many patients become refractory to LEN the proposed POM combination is an option of interest in this patient population. The positive PFS results are supported by sensitivity and exploratory analysis and other secondary endpoints.

The unfavourable effects of the POM combination are in line with the known safety profile of each drug. The higher frequency of reported AEs should be viewed in the context of larger treatment duration compared to BTZ+ DEX. The toxicity is well managed with supportive care and dose interruptions and to a lower extent dose reductions. No new safety concerns have been reported.

3.7.2. Balance of benefits and risks

The benefit-risk balance of pomalidomide in combination with bortezomib and dexamethasone for the treatment of adult patients with multiple myeloma who have received at least one prior treatment regimen including lenalidomide is considered positive.

3.7.3. Additional considerations on the benefit-risk balance

Not applicable.

3.8. Conclusions

The overall B/R of Imnovid 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
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.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	I
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 for Imnovid to include a new indication: treatment in combination with bortezomib and dexamethasone of adult patients with multiple myeloma who have received at least one prior treatment regimen including lenalidomide; as a consequence, sections 4.1, 4.2, 4.3, 4.4, 4.5, 4.8 and 5.1 of the SmPC are updated. The Annex II is also updated to include a new post-authorisation efficacy study (PAES) as an obligation of the marketing authorisation. As a further consequence, new 14-capsule pack sizes for the 1 mg, 2 mg, 3 mg and 4 mg Imnovid strengths were included to support the new proposed posology and pomalidomide dose modification. The SmPC, Labelling and Package leaflet are updated in accordance. Finally, section 5.1 of the SmPC is updated in order to update the information on pomalidomide mechanism of action based on literature data. The RMP version 15.1 has also been updated.

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

This CHMP recommendation is subject to the following new condition:

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

Obligation to conduct post-authorisation measures

The MAH shall complete, within the stated timeframe, the below measures:

Description	Due date
• Post-authorisation efficacy study (PAES) MM-007: In order to further investigate the efficacy of pomalidomide in combination with bortezomib and dexamethasone for the treatment of adult patients with multiple myeloma who have received at least one prior treatment regimen including lenalidomide, the MAH should submit the final analysis of OS from the phase 3, randomized, open label study MM-007.	30 September 2021

Similarity with authorised orphan medicinal products

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

Additional market protection

Furthermore, the CHMP reviewed the data submitted by the MAH, taking into account the provisions of Article 14(11) of Regulation (EC) No 726/2004, and considers, by consensus, that the new therapeutic indication brings significant clinical benefit in comparison with existing therapies.

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 for Imnovid to include a new indication: treatment in combination with bortezomib and dexamethasone of adult patients with multiple myeloma who have received at least one prior treatment regimen including lenalidomide; as a consequence, sections 4.1, 4.2, 4.3, 4.4, 4.5, 4.8 and 5.1 of the SmPC are updated. The Annex II is also updated to include a new post-authorisation efficacy study (PAES) as an obligation of the marketing authorisation. As a further consequence, new 14-capsule pack sizes for the 1 mg, 2 mg, 3 mg and 4 mg Imnovid strengths were included to support the new proposed posology and pomalidomide dose modification. The SmPC, Labelling and Package leaflet are updated in accordance. Finally, section 5.1 of the SmPC is updated in order to update the information on pomalidomide mechanism of action based on literature data. The RMP version 15.1 has also been updated.

Summary

Please refer to the published Assessment Report Imnovid-H-2682-II-31/G.