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POMALIDOMIDE

RISK MANAGEMENT PLAN

Version Number: 17.0

Data-lock Point for this RMP: 07-Feb-2022

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LIST OF ABBREVIATIONS

Term	Definition
ADL	Activities of daily living
ADR(s)	Adverse drug reaction(s)
AE(s)	Adverse event(s)
AF	Atrial fibrillation
ALF	Acute liver failure
ALT	Alanine aminotransferase
AME	Absorption, metabolism and elimination
AML	Acute myeloid leukaemia
ASCT	Autologous stem cell transplantation
ASR	Age-standardised incidence rates
ATC	Anatomical Therapeutic Chemical Classification
ATRIA	AnTicoagulation and Risk Factors in Atrial Fibrillation
ATU	Autorisations temporaires d'utilisation (temporary authorisations for use)
AUC_{24h}	Area under the concentration-time curve over 24 hours
BCC	Basal cell carcinoma
BCRP	Breast cancer resistance protein
BIPN	Bortezomib-induced peripheral neuropathy
BMS	Bristol Myers Squibb
BMT	Bone marrow transplant
C_1 INH	C_1 esterase inhibitor protein
CHD	Coronary heart disease
CHF	Congestive heart failure
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CIOMS	Council for International Organizations of Medical Sciences
C_{max}	Maximum observed plasma concentration
CNS	Central nervous system
CSR	Clinical study report
CU	Compassionate use
CVA	Cerebrovascular accident
CYP/CYP450	Cytochrome P450
DHPC	Direct Healthcare Professional Communication
DILI	Drug-induced liver injury
DNA	Deoxyribonucleic acid

Term	Definition
DRESS	Drug reaction with eosinophilia and systemic symptoms
DSUR	Development Safety Update Report
DVT	Deep vein thrombosis
E+R	Evaluation plus reporting
EC	European Commission
ECG	Electrocardiogram
EEA	European Economic Area
EMA	European Medicines Agency
EPAR	European public assessment report
EROS	European Registers of Stroke
EU	European Union
EURD	European Union Reference Date
FCBP	Females of childbearing potential
FDA	Food and Drug Administration
G-CSF	Granulocyte colony-stimulating factor
GPRD	General Practice Research Database
GVHD	Graft versus host disease
GVP	Good Pharmacovigilance Practices
HBeAg	Hepatitis B e antigen
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
hCG	Human chorionic gonadotrophin
HCP	Healthcare professional
HEK293 cells	Human embryonic kidney cells
hERG	Human ether-à-go-go-related gene
HIV	Human immunodeficiency virus
HLGT	High level group term
HLT	High level term
HMRN	Haematological Malignancy Research Network
HSCT	Haematopoietic stem cell transplantation
IIT	Investigator-initiated trial
IMiD	Immunomodulatory drugs
INN	International Nonproprietary Name
IV	Intravenous
MAA	Marketing Authorisation Application

Term	Definition
MAH	Marketing Authorisation Holder
MDS	Myelodysplastic syndrome(s)
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial infarction
MM	Multiple myeloma
MONICA	Multinational MONItoring of trends and determinants in Cardiovascular disease
MRC	Medical Research Council
NA	Not available
NCA(s)	National Competent Authority(ies)
NCI	National Cancer Institute
NEC	Not elsewhere classified
NHANES	National Health and Nutrition Examination Survey
NHL	Non-Hodgkin's lymphoma
NMSC	Non-melanoma skin cancer
NOAEL	No observable adverse effect level
NPP	Named patient programme(s)
NSAID	Non-steroidal anti-inflammatory drug
NZ	New Zealand
OAT	Organic anion transporter
OATP	Organic anion transporter protein
OCT	Organic cation transporter
OR	Odds ratio
OS	Overall survival
PASS	Postauthorisation safety study
PBd/PVd	Pomalidomide plus bortezomib and low-dose dexamethasone
PDCO	Paediatric Committee
P-gp	P-glycoprotein
PI	Product Information
PL	Package leaflet
PPP	Pregnancy Prevention Programme
PRAC	Pharmacovigilance Risk Assessment Committee
PSUR	Periodic Safety Update Report
PT	Preferred term
Q(1-4)	Quarter (1-4)
QD	Once daily

Term	Definition
QPPV	Qualified Person for Pharmacovigilance
RBC	Red blood cell
RMP	Risk Management Plan
ROW	Rest of world
RR	Relative risk
RRMM	Relapsed and refractory multiple myeloma
SAE(s)	Serious adverse event(s)
SC	Subcutaneous
SCC	Squamous cell carcinoma
SCT(s)	Stem cell transplantation(s)
SD	Standard deviation
SEER	Surveillance, Epidemiology and End Results
SIR	Standardised incidence ratio
SJS	Stevens-Johnson syndrome
SmPC	Summary of Product Characteristics
SMQ	Standardised MedDRA query
SPM	Second primary malignancies
SSPU	Supply for single patient use
TEE(s)	Thromboembolic event(s)
TEN	Toxic epidermal necrolysis
TIPN	Thalidomide-induced peripheral neuropathy
TLS	Tumour lysis syndrome
t_{max}	Time of maximum observed plasma concentration
TSH	Thyroid-stimulating hormone
UGIB	Upper gastrointestinal bleeding
UK	United Kingdom
US/USA	United States/United States of America
Vd	Bortezomib and low-dose dexamethasone
VZV	Varicella zoster virus
WBC	White blood cell
WCBP	Women of childbearing potential
WHO	World Health Organization

EU RISK MANAGEMENT PLAN (RMP) FOR POMALIDOMIDE

RMP version to be assessed as part of this application:

Version Number: 17.0Data-lock Point for this RMP: 07-Feb-2022 Date of Final Sign-off: 07-Jul-2023

Rationale for submitting an updated RMP:

- Update of milestone due date for Study CC-4047-MM-015 in Part III and Annex 2.

Summary of Significant Changes in this RMP

Part/Module	Summary of Major Changes	Version # / Date of Positive Opinion for Module Update
Part II Safety Specification		
SI Epidemiology of the indication(s) and target population(s)	No changes.	V16.5 / 08-Jun-2023
SII Non-clinical part of the safety specification	No significant changes.	V15.1 / 13-May-2019
SIII Clinical trial exposure	No changes.	V15.1/13-May-2019
SIV Populations not studied in clinical trials	No changes.	V15.1/13-May-2019
SV Post-authorization experience	No changes.	V16.5 / 08-Jun-2023
SVI Additional EU requirements for the safety specification	No changes.	V15.1/13-May-2019
SVII Identified and potential risks	No changes.	V15.1/13-May-2019
SVIII Summary of the safety concerns	No changes.	V15.1/13-May-2019
Part III Pharmacovigilance Plan	Update of milestone due date for Study CC-4047-MM-015.	V17.0 / pending
Part IV Plan for post-authorization efficacy studies	No changes.	V15.1/13-May-2019
Part V Risk Minimization Measures	No changes.	V16.5 / 08-Jun-2023
Part VI Summary of the Risk Management Plan	No changes.	V16.5 / 08-Jun-2023
Part VII Annexes		
ANNEX 2 Tabulated summary of planned, ongoing, and completed pharmacovigilance study programme	Update of milestone due date for Study CC-4047-MM-015.	V 17.0/ pending

Summary of Significant Changes in this RMP

Part/Module	Summary of Major Changes	Version # / Date of Positive Opinion for Module Update
ANNEX 3 Protocols for proposed, ongoing, and completed studies in the pharmacovigilance plan	No changes.	V15.1/13-May-2019
ANNEX 4 Specific adverse drug reaction follow-up forms	No changes.	V16.5 / 08-Jun-2023
ANNEX 5 Protocols for proposed and on-going studies in RMP Part IV	Not applicable.	V15.1/13-May-2019
ANNEX 6 Details of proposed additional risk minimisation activities	No changes.	V16.5 / 08-Jun-2023
ANNEX 7 Other supporting data	No changes.	V16.5 / 08-Jun-2023
ANNEX 8 Summary of changes to the risk management plan over time	Updated to reflect changes in the RMP.	V17.0/ pending

Other RMP versions under evaluation:

RMP Version Number	Submitted on	Procedure Number
None		

Details of the currently approved RMP:

Version number: 16.5

Approved with procedure: EMEA/H/C/002682/II/0047

Date of approval (opinion date): 08-Jun-2023 (CHMP Positive Opinion)

EU RMP Contact Person: Priv. Doz. Dr. Stefan Kaehler, EU QPPV

QPPV oversight declaration: The content of this RMP has been reviewed and approved by the marketing authorization holder´s QPPV. The electronic signature is available on file.

1 PART 1: PRODUCT OVERVIEW

Table 1-1: Product Details

Active substance(s) (INN or common name)	Pomalidomide
Pharmacotherapeutic group(s) (ATC Code)	Immunosuppressants, other immunosuppressants L04 AX06
Marketing Authorisation	Bristol-Myers Squibb Pharma EEIG
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	IMNOVID®
Marketing authorization procedure	Central Marketing Authorisation granted; Authorisation Number (s) EU/1/13/850/001-008
Brief description of the product	Pomalidomide (also called CC-4047) is an analog of thalidomide with tumouricidal, immunomodulatory, anti-angiogenic, and anti-inflammatory properties. The multiple pharmacological properties of pomalidomide suggested a potential therapeutic benefit in patients with MM. The activity of pomalidomide, and other immunomodulatory compounds, is exerted through binding to cereblon, a component of an E3 ligase complex that includes DNA damage-binding protein 1, cullin 4, and Roc1. In the presence of pomalidomide in vitro, substrate proteins Aiolos and Ikaros are targeted for ubiquitination and subsequent degradation leading to direct anti-myeloma cytotoxic and immunomodulatory effects. Pomalidomide enhanced T cell- and natural killer cell-mediated immunity and inhibited production of pro-inflammatory cytokines (eg, tumor necrosis factor alpha and interleukin 6) by monocytes. Additionally, pomalidomide retained activity in lenalidomide-resistant MM cell lines, despite reduced cereblon expression. In vivo, pomalidomide therapy reduced the levels of Ikaros in patients with relapsed, lenalidomide-refractory MM.
Hyperlink to the Product Information	Refer to proposed PI
Indication(s) in the EEA	**Current:** <u>Pomalidomide in combination therapy with dexamethasone</u> Imnovid in combination with dexamethasone is indicated in 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. <u>Pomalidomide in combination therapy with bortezomib and dexamethasone</u> 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.

Table 1-1: Product Details

Dosage in the EEA	**Current:** Pomalidomide in combination therapy with dexamethasone The recommended starting dose of Imnovid is 4 mg QD taken orally on Days 1 to 21 of repeated 28-day cycles. The recommended dose of dexamethasone is 40 mg orally QD on Days 1, 8, 15 and 22 of each 28-day treatment cycle. Treatment with pomalidomide combined with dexamethasone should be given until disease progression or until unacceptable toxicity occurs. Pomalidomide in combination therapy with bortezomib and dexamethasone The recommended starting dose of Imnovid is 4 mg QD taken orally on Days 1 to 14 of repeated 21-day cycles. The recommended starting dose of bortezomib is: • For Cycles 1 to 8: 1.3 mg/m^2/dose IV or SC on Days 1, 4, 8 and 11 of a 21-day cycle. • For Cycle 9 and onwards: 1.3 mg/m^2/dose IV or SC on Days 1 and 8 of a 21-day cycle. The recommended dose of dexamethasone is: • For Cycles 1 to 8: 20 mg/day (≤ 75 years old) or 10 mg/day (> 75 years old) taken orally on Days 1, 2, 4, 5, 8, 9, 11 and 12 of a 21-day cycle. • For Cycle 9 and onwards: 20 mg/day (≤ 75 years old) or 10 mg/day (> 75 years old) taken orally on Days 1, 2, 8 and 9 of a 21-day cycle. Treatment with pomalidomide combined with bortezomib and dexamethasone should be given until disease progression or until unacceptable toxicity occurs.
Pharmaceutical form (s) and strength(s)	**Current:** Hard capsules, available in 1, 2, 3 and 4 mg.
Is/will the product be subject to additional monitoring in the EU?	Yes

2 PART II: SAFETY SPECIFICATION

Approved Indications:

Pomalidomide in combination therapy with dexamethasone

Imnovid in combination with dexamethasone is indicated in 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.

Pomalidomide in combination therapy with bortezomib and dexamethasone

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.

2.1 Epidemiology of the Indication(s) and Target Population(s)

Table 2.1-1: Epidemiology of Patients with Multiple Myeloma

Multiple Myeloma	
Incidence and Prevalence	• MM accounts for about 10% to 18% of haematologic malignancies.[1,2] • The HMRN was established in 2004 to provide robust generalisable data to inform clinical practice and research. The data are collected in the UK but estimates are extrapolated to Europe. Based on the most recent estimates (2014), the annual incidence of MM is 6.5 per 100,000 persons. The 3-year, 5-year and 10-year prevalence estimates were: 16.4 per 100,000 persons, 22.6 per 100,000 persons and 29.9 per 100,000 persons respectively.[3] • Crude and ASR of MM in the population of the EU – 28 states are 6.6 and 3.0 per 100,000, respectively, based upon estimates obtained from GLOBOCAN 2012.[4] – The 1-year, 3-year, and 5-year number of persons with MM and prevalence proportions of MM (ages 15 years and older) in the EU-28 countries were 5.8 per 100,000 persons, 13.4 per 100,000 persons and 18.0 per 100,000 persons, respectively.[4] • Gains in survivorship associated with new therapies will increase the prevalence of MM.
Demographics of the population: age, gender, racial and/or ethnic origin	• MM incidence rates among males and females in Europe rise with increasing age intervals: 0.0 (ages 0 to 14 years), 0.2 (ages 15 to 39 years), 1.3 (ages 40 to 44 years), 2.9 (ages 45 to 49 years), 5.2 (ages 50 to 54 years), 8.1 (ages 55 to 59 years), 12.3 (ages 60 to 64 years), 17.9 (ages 65 to 69 years), 24.6 (ages 70 to 74 years), 31.0 (ages 75 years and older).[4] • The ASR incidence of MM in men in the EU-28 countries is 3.7, based upon the diagnosis of MM in 18,043 men. MM accounted for 1.3% of all malignancies in men.[4] • The ASR incidence of MM in women in the EU-28 countries is 2.5, based upon the diagnosis of MM in 15,599 women. MM accounts for 1.4% of all malignancies in women.[4] • Analysing 18,824 MM registrations with ethnicity obtained by linkage to the English Hospital Episodes Statistics Database, Shirley[5] reported markedly higher incidence rates of MM in Black African men (ASR 8.6 per 100,000) and Black Caribbean men (8.3) relative to White men (3.7). Similar results were obtained with MM incidence rates in Black African women (5.8) and Black Caribbean women (5.7) were compared to White women (2.4). This pattern is similar to that reported in the United States (US), where incidence rates of MM are markedly higher in Black men compared to White men (15.9 versus 7.8 per 100,000) and in Black women compared to White women (11.4 versus 4.6 per 100,000, respectively).[6] Racial differences in rates were also observed in the US population.[7] • According to the HMRN, the incidence of MM increases with age from a low of 0.09 per 100,000 (30 to 34 years old) to 36.24 per 100,000 (≥80 years old). Among males, the annual ASR incidence was 9.7 per 100,000 while for females, it was 5.8 per 100,000.[3]

Table 2.1-1: Epidemiology of Patients with Multiple Myeloma

Multiple Myeloma	
Risk factors for the disease	• Age is the most important risk factor for MM, although race and gender are also important. While strong familial clustering of MM suggests that underlying genetic factors are important, findings from studies of lifestyle, dietary, occupational and environmental risk factors have been inconsistent.[8,7]
Main treatment options	• Thalidomide, bortezomib, lenalidomide, panobinostat, carfilzomib, pomalidomide, daratumumab, elotuxumab, and ixazomib per the approved indication.
Mortality and morbidity (natural history)	• Crude and age-standardised mortality rates of MM in the EU-28 population are 4.0 and 1.6 per 100,000, respectively, based upon estimates obtained from GLOBOCAN 2012. Within the EU-28 population, 20,462 men and women died with MM in 2012. The cumulative mortality risk of MM (ages 0 to 74 years) is 0.17%.[4] • According to GLOBOCAN 2012, MM accounts for 1.2% of all deaths among persons with invasive malignancy in the European population.[4] • Between 1989 and 2009, 1206 patients with MM were identified through the Modena Cancer Registry,[9] corresponding to periods of conventional therapy (1988 to 1996), high dose melphalan and ASCT (1997 to 2005) and novel agents (2006 to 2009). Relative survival and OS improved over the years, with little change noted for patients aged ≥ 75 years. The survival of MM patients aged < 65 years and, in particular, 65 to 74 years improved over time, especially after 2006. • The most recent data from the European Society for Bone and Marrow Transplantation registry (2006 to 2010) reported 5 year OS in MM transplant recipients as follows: 61.5% (< 40 years of age), 62.8% (40 to 49 years). 59.9% (50 to 59 years), 58.8% (60 to 64 years), 53.3% (65 to 69 years), 49.7% (≥ 70 years).[10] • In a retrospective analysis of MM patients who received HSCT, median OS was 79.5 months in those < 60 years of age and 63.4 months in those ≥ 60 years of age.[11]
Important co-morbidities	• Renal impairment;[12,13,14] • Peripheral neuropathy;[15,16,17] • TEEs;[18,19,20,21] • Anaemia, leukopenia and infection;[14,22,23] • SPM;[24,25,26,27,28,29] • Gastrointestinal haemorrhage;[30,31] • GvHD.[32,33] • Bone diseases.[34,35,36]

2.2 Nonclinical Part of the Safety Specification

Full details of the nonclinical safety data for pomalidomide are presented in the Nonclinical Overview (MAA, Module 2, Section 2.4 Nonclinical Overview).

A summary of the nonclinical findings and their relevance to human usage is outlined in Table 2.2-1.

Table 2.2-1: Summary of Significant Non-clinical Safety Findings

Key Safety Findings (from Nonclinical Studies)	Relevance to human usage
Toxicity Studies: • Single and Repeat-dose Toxicity Single-dose oral and IV studies in mice and rats indicated that pomalidomide is well tolerated and acute oral minimum lethal dose was > 2000 mg/kg, and acute IV minimum lethal dose was > 80 mg/kg for mice, and > 50 mg/kg for rats. Pomalidomide was well-tolerated by rats up to the highest dosage tested in repeat-dose studies of durations from 7 days to 6 months. No adverse effects were observed up to 5000 mg/kg/day in the 7-day study, 2000 mg/kg/day in the 28-day study, 1500 mg/kg/day in the 90-day study and 1000 mg/kg/day in the 6-month study. In the 6-month study, the dosage of 1000 mg/kg/day resulted in a mean AUC24h of 70270 g•h/mL on Day 180 (175-fold higher exposure relative to a 4 mg clinical dose). In monkeys, pomalidomide was evaluated in repeat-dose studies with durations of 14 days at doses from 50 to 1200 mg/kg/day, 28 days at doses from 30 to 300 mg/kg/day and from 0.2 and 2 mg/kg/day, 90 days at doses from 0.05 to 10 mg/kg/day, and 9 months at doses from 0.05 to 1 mg/kg/day. In these studies, the monkey exhibited greater sensitivity to pomalidomide effects compared to the rat, and morbidity and mortality were associated with doses at 1 and 10 mg/kg/day in the 9-month and 3-month studies, respectively. The primary toxicities observed in monkeys were associated with the haematopoietic/lymphoreticular systems. The major findings were decreased RBC parameters (RBC count, haemoglobin, and haematocrit), decreased WBC counts (neutrophils, lymphocytes, and monocytes), and histologic lymphoid depletion (lymph nodes, spleen, thymus, and gut-associated lymphoid tissue). In addition, increased incidences of loose and watery stool leading to weight loss were often observed and contributed to poor clinical conditions. In the 9-month toxicity study in monkeys, the longest duration study completed, pomalidomide was administered orally at 0.05, 0.1, and 1 mg/kg/day. Test article-related morbidity and early euthanasia (3/sex) were observed in the 1 mg/kg/day group and were attributed to immunomodulation/immunosuppression associated with pomalidomide administration (decreased peripheral blood lymphocytes, histologic lymphoid depletion, and hypocellularity of bone marrow). These immunosuppressive effects were associated with staphylococcal infection and chronic inflammation of the large intestine. In addition, one female administered 1 mg/kg/day was euthanised on Day 253 and exhibited changes consistent with AML (extreme leukocytosis, multiple organ infiltrates, and bone marrow blast infiltration). Based upon the known association in humans of AML with immunosuppression and the low incidence of this neoplastic change in cynomolgus macaques, this event was	In clinical studies of pomalidomide, neutropenia was the most frequently reported Grade 3/4 adverse reaction in subjects with RRMM, followed by thrombocytopenia. The SmPC states that patients should be monitored for haematological adverse reactions, especially neutropenia (Section 4.4). Dose modifications may be required (SmPC, Section 4.4 and 4.2). Neutropenia and infection are included in Section 4.8 of the SmPC. A finding consistent with AML in one animal was unexpected and significant; however the specific level of risk this animal finding potentially represents for humans treated with pomalidomide is currently unknown. Some data in humans suggest rare cases of AML may be correlated with intense immune suppression. [37] Whether this played a role in the disease resembling AML in this monkey is unknown, however, studies of cytogenetics were normal and clonality could not be proven. Consequently, a leukemoid reaction to the drug, infection, both or another cause cannot be excluded. The specific level of risk this animal finding potentially poses for humans is currently uncertain. There is no corroborative evidence from current pomalidomide clinical experience regarding pomalidomide and the development of AML.

Table 2.2-1: Summary of Significant Non-clinical Safety Findings

Key Safety Findings (from Nonclinical Studies)	Relevance to human usage
considered treatment-related. The 1 mg/kg/day dose resulted in a mean AUC24h of 6540 ng•h/mL in female monkeys on Day 272 (16-fold higher exposure relative to a 4 mg clinical dose). NOAEL in this study was 0.1 mg/kg/day, corresponding to Day 272 mean pomalidomide AUC24h of 219 ng•h/mL (0.5-fold exposure ratio relative to a 4 mg clinical dose). In the surviving animals, there were no treatment-related changes in body weight, electrocardiography, blood pressure measurements, ophthalmology, and urinalysis. Other minor changes present at the scheduled sacrifice included villous atrophy of the small intestine and minimal or mild bile duct proliferation. Evaluation of recovery animals indicated that all treatment-related findings were reversible after 8 weeks of dosing cessation, except for proliferation of intrahepatic bile ducts observed in 1 animal in the 1 mg/kg/day group. Pomalidomide was also assessed for immunotoxicity in monkeys after treatment at 2 mg/kg/day for 28 days. Immunotoxicologic effects related to pomalidomide treatment included increased large unstained cells, decreases in peripheral lymphocytes populations (correlating to bone marrow hypocellularity), alterations to the primary and secondary humoral immune system, thymic organ weight decreases (macroscopic finding of small thymus), and histological findings consistent with general lymphoid depletion in the thymus, spleen, and the mandibular and mesenteric lymph nodes. There were no effects on granulocyte, monocyte, or natural killer cell function. All findings at 2 mg/kg/day demonstrated full recovery after a 30-day drug-free period, with the exception of the decreased CD20+ B lymphocytes (partial recovery observed) and reduced thymus weights; minimal/mild histological changes in the lymph nodes also indicated that there were partial recoveries of these effects.	
• Reproductive and Developmental Toxicity In a fertility and early embryonic development study in rats, pomalidomide was administered to males and females at dosages of 25, 250, and 1000 mg/kg/day. Male rats were dosed beginning 28 days before cohabitation and continuing through the day before necropsy; female rats were dosed beginning 14 days before cohabitation, during the mating period, and until Gestation Day 7. Uterine examination on Gestation Day 13 showed a decrease in mean number of viable embryos and an increase in post-implantation loss at all dosage levels. Therefore, the NOAEL for these observed effects was < 25 mg/kg/day (AUC24h was 39960 ng•h/mL at this lowest dose tested, and the exposure ratio was 99-fold relative to a 4 mg clinical dose). When treated males on this study were mated with untreated females, all uterine parameters were comparable to the controls. Based on these results, the observed effects were attributed to the treatment of females. Pomalidomide was found to be teratogenic in both rats and rabbits when administered during the period of major organogenesis. In the	Pomalidomide must not be taken during pregnancy, since a teratogenic effect is expected. Pomalidomide is structurally related to thalidomide, a known human teratogen that causes severe life-threatening birth defects (SmPC, Section 4.4). The conditions of the PPP must be fulfilled for all patients.

Table 2.2-1: Summary of Significant Non-clinical Safety Findings

Key Safety Findings (from Nonclinical Studies)	Relevance to human usage
rat embryofoetal developmental toxicity study, malformations of absence of urinary bladder, absence of thyroid gland, and fusion and misalignment of lumbar and thoracic vertebral elements (central and/or neural arches) were observed at all dosage levels (25, 250, and 1000 mg/kg/day). There was no maternal toxicity observed in this study. Therefore, the maternal NOAEL was 1000 mg/kg/day, and the NOAEL for developmental toxicity was < 25 mg/kg/day (AUC_{24h} was 34340 ng•h/mL on Gestation Day 17 at this lowest dose tested, and the exposure ratio was 85-fold relative to a 4 mg clinical dose). In rabbits, pomalidomide at dosages ranging from 10 to 250 mg/kg produced embryo foetal developmental malformations. Increased cardiac anomalies were seen at all doses with significant increases at 250 mg/kg/day. At 100 and 250 mg/kg/day, there were slight increases in post-implantation loss and slight decreases in foetal body weights. At 250 mg/kg/day, foetal malformations included limb anomalies (flexed and/or rotated fore- and/or hind-limbs, unattached or absent digit) and associated skeletal malformations (not ossified etacarpal, misaligned phalanx and metacarpal, absent digit, not ossified phalanx, and short not ossified or bent tibia); moderate dilation of the lateral ventricle in the brain; abnormal placement of the right subclavian artery; absent intermediate lobe in the lungs; low-set kidney; altered liver morphology; incompletely or not ossified pelvis; an increased average for supernumerary thoracic ribs and a reduced average for ossified tarsals. Slight reduction in maternal body weight gain, significant reduction in triglycerides, and significant decrease in absolute and relative spleen weights were observed at 100 and 250 mg/kg/day. The maternal NOAEL was 10 mg/kg/day, and the developmental NOAEL was < 10 mg/kg/day (AUC_{24h} was 418 ng•h/mL on Gestation Day 19 at this lowest dose tested, which was similar to that obtained from a 4 mg clinical dose).	
• Nephrotoxicity Not applicable as no separate studies were performed to investigate nephrotoxicity. The repeat-dose toxicity studies, described above, did, however, assess all organ systems.	Caution should be exercised when treating patients with renal impairment. Clinical studies in MM patients with moderate and severe renal impairment are ongoing (CC-4047-MM-008 [38] and CC-4047-MM-013). [39] A meta-analysis combining pharmacokinetics data from both of these studies is complete with a final report (CC-4047-MPK-002). [40] No dose adjustment of pomalidomide is required for patients with renal impairment. On haemodialysis days, patients should take their pomalidomide dose following haemodialysis (SmPC, Section 4.2).
• Hepatotoxicity Not applicable as no separate studies were performed to investigate hepatotoxicity. The repeat-dose toxicity studies, described above, did, however, assess all organ systems.	Caution should be exercised when treating patients with hepatic impairment. A clinical study in healthy subjects with varying degrees of hepatic impairment is

Table 2.2-1: Summary of Significant Non-clinical Safety Findings

Key Safety Findings (from Nonclinical Studies)	Relevance to human usage
	complete with a final clinical study report (CSR; CC-4047-CP-009).[41]
• Genotoxicity/Carcinogenicity Pomalidomide was not mutagenic in bacterial and mammalian mutation assays, and did not induce chromosomal aberrations in human peripheral blood lymphocytes or micronuclei formation in polychromatic erythrocytes in bone marrow of rats administered doses up to 2000 mg/kg/day.	The negative results achieved in genotoxicity studies of pomalidomide suggest that a risk of mutagenic or clastogenic potential is absent and provides some assurance that pomalidomide may not be carcinogenic.
General Safety Pharmacology Pomalidomide had no effects on CNS and respiratory function in rats at oral doses up to 2000 mg/kg. Pomalidomide up to 87.5 µM did not produce any statistically significant hERG current blockade in HEK293 cells expressing hERG channels, indicating a low potential to block cardiac IKr (rapidly activating component of cardiac delayed rectifier K+ current) in vitro. In anesthetised dogs, pomalidomide had no effects on QTc following IV administration at dose levels of up to 25 mg/kg. However, the NOAEL in this study is considered to be 10 mg/kg based on the changes in respiratory rate and blood pressure observed in 1 of 4 dogs in the 25 mg/kg group. No significant differences from vehicle controls were observed in the remaining 3 dogs. In a conscious, telemetry-instrumented male monkey study, pomalidomide at oral doses ranging from 0.2 to 10 mg/kg had no adverse pharmacodynamic effects on cardiovascular function, electrocardiographic and haemodynamic parameters, or respiration. Cardiovascular assessment (vital signs, ECG, respiration, and heart rate) conducted in the 1-, 3- and 9-month monkey studies indicated no pomalidomide-related cardiovascular changes at doses up to 2 mg/kg/day for up to 3 months, and up to 1 mg/kg/day after 9 months (Cmax = 1249 and 653 ng/mL; both sexes combined, at 2 and 1 mg/kg/day respectively).	The negative results achieved in the cardiovascular studies of pomalidomide suggest no effect of pomalidomide on vital signs, ECG, respiration and heart rate. The doses tested translated into a human with approximately 70 kg body weight were up to 140 mg/day for 3 months and up to 70 mg/day after 9 months. A clinical study in healthy subjects to investigate the effects of pomalidomide on the QT interval is complete with a final CSR (CC-4047-CP-010).[42] Pomalidomide does not appear to have an effect on QTc prolongation. In the pomalidomide clinical studies, Cmax was approximately 76 ng/mL after 8 days dosing with 4 mg pomalidomide in MM subjects.
Mechanisms for Drug Interactions In the human AME study, CYP dependent metabolites accounted for approximately 43% of the excreted radioactivity, while non-CYP dependent hydrolytic metabolites accounted for 25%, and excretion of unchanged pomalidomide accounted for 10%. Since pomalidomide was eliminated in humans via multiple pathways and several CYP enzymes were capable of metabolising pomalidomide, namely CYP1A2, CYP3A4, and to a minor extent CYP2C19 and CYP2D6, it is not anticipated that inhibitors of these CYPs will have a significant impact on pomalidomide pharmacokinetics. No pharmacokinetic interaction was observed between pomalidomide (4 mg) and dexamethasone (20 to 40 mg), a weak to moderate inducer of CYP3A in MM subjects (see Section 11.6 of the CC-4047-MM-002 CSR[43]; SmPC, Section 4.5). Pomalidomide (up to 30 µM) produced no direct inhibition of CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19,	The potential for clinically relevant drug-drug interactions when pomalidomide is coadministered with substrates of CYP enzymes, P-gp, or other drug transporters (BCRP, organic anion transporter protein OATP] OATP1B1, OATP1B3, OCT2 and OAT1 and OAT3) is low, but has not been evaluated clinically. Co-administration of pomalidomide with the strong CYP3A4/5 and P-gp inhibitor ketoconazole, or the strong CYP3A4/5 inducer carbamazepine, had no clinically relevant effect on exposure to pomalidomide. Co-administration of the strong CYP1A2 inhibitor fluvoxamine with

Table 2.2-1: Summary of Significant Non-clinical Safety Findings

Key Safety Findings (from Nonclinical Studies)	Relevance to human usage
CYP2D6, CYP2E1, and CYP3A4/5 in human liver microsomes. Furthermore, little to no time-dependent inhibition of CYP1A2, CYP2C9, CYP2C19, CYP2D6 or CYP3A4/5 was observed with pomalidomide at concentrations up to 30 μM. In human hepatocyte cultures, pomalidomide (0.3 to 3 μM, three day treatment) did not induce the catalytic activities of CYP1A2, CYP2B6, CYP2C9, CYP2C19 and CYP3A4/5 to a notable extent. Since the mean C_{max} value following multiple daily doses of 5 mg to subjects with MM was approximately 50 ng/mL (0.2 μM), pomalidomide is unlikely to cause inhibition or induction of CYP enzyme activities at clinically relevant concentrations. Pomalidomide (up to 10 μM) is not an inhibitor of P-glycoprotein (P-gp) and is not anticipated to cause drug-drug interactions at therapeutic doses when administered with substrates of P-gp. Pomalidomide is a substrate of P-gp in vitro, but intestinal absorption did not appear to be limited by this. In the human AME study, at least 70% of the dose was absorbed, indicating good oral absorption. The potential for clinically relevant drug-drug interactions when pomalidomide is coadministered, with inhibitors of P-gp is low, but has not been evaluated clinically. Pomalidomide (at 2 and 20 μM) did not inhibit BCRP, OATP1B1, OATP1B3 and OCT2 transporter mediated activities. Pomalidomide weakly (approximately 26% to 30%) inhibited OAT1 and OAT3 activities at the 20 μM concentration, with no inhibition observed at 2 μM. Pomalidomide is not anticipated to cause drug-drug interactions at therapeutic doses when administered with substrates of BCRP, OATP1B1, OATP1B3, OCT2, OAT1 and OAT3.	pomalidomide in the presence of ketoconazole, increased exposure to pomalidomide by 107% with a 90% CI [91% to 124%] compared to pomalidomide plus ketoconazole. Co-administration of the strong CYP1A2 inhibitor fluvoxamine with pomalidomide, increased exposure to pomalidomide by 125% with a 90% CI [98% to 157%] compared to pomalidomide. If strong inhibitors of CYP1A2 (eg, ciprofloxacin, enoxacin and fluvoxamine) are co-administered with pomalidomide, the dose of pomalidomide should be reduced to 50% (SmPC, Sections 4.5 and 5.2).
Other Toxicity-related Information or Data • Preclinical Pharmacokinetics and Metabolism Pomalidomide is a chiral molecule that contains an equal mixture of the S-enantiomer and the R-enantiomer. Interconversion of the enantiomers occurred gradually in buffer at neutral pH (non-enzymatic interconversion), more rapidly in vitro in plasma (presumably due to enzymatic interconversion), and in vivo in monkeys following IV or oral administration of the individual enantiomers. Following IV administration of pomalidomide to rats and monkeys, the systemic clearance was low (< 1/6th liver blood flow) and the volume of distribution was moderate (2- to 4-fold body water volume). The terminal half-life of pomalidomide was approximately 6 h in rats and 4 to 7 h in monkeys. Following oral dosing to animals, pomalidomide (racemate) was absorbed at a moderate rate, with median time of maximum observed plasma concentration values of 2 to 4 h. The oral bioavailability of a 2 mg/kg dose of pomalidomide in monkeys was approximately 100%. However, at a higher dose of 100 mg/kg in both rats and monkeys, the	Metabolites observed in humans are similar to those observed in animals and have thus been adequately characterised with regard to their potential toxicity. As pomalidomide has been observed in milk from lactating rats and can cross the placenta, it must not be administered to pregnant or lactating females.

Table 2.2-1: Summary of Significant Non-clinical Safety Findings

Key Safety Findings (from Nonclinical Studies)	Relevance to human usage
oral bioavailability of pomalidomide was low (< 20%), suggesting oral bioavailability may be solubility limited. Pomalidomide plasma protein binding was low to moderate in animals and humans, ranging from approximately 12% to 59% at concentrations between 30 and 1000 ng/mL. Following a single oral administration of [14C]pomalidomide (100 mg/kg) to pigmented male Long-Evans rats, compound-derived radioactivity was widely distributed into tissues, with most tissue concentrations peaking at 3 hours and decreasing to below quantifiable levels (< 0.418 µg equiv/g) by 12 hours postdose. The highest measured tissue concentrations occurred in the kidney and in gastrointestinal organs. Radioactivity was present in the bile and the urinary bladder indicating liver and kidney are involved in excretion. Most tissues had moderate levels of radioactivity, including liver, endocrine glands, secretory glands, and pigmented skin. Pomalidomide-derived radioactivity was observed in the spinal cord and brain, with tissue to blood ratios between 0.27 and 0.43 at 3 hours postdose. These data indicate good distribution of pomalidomide-related material into most tissues. Additional studies to investigate the penetration of pomalidomide into the CNS were performed in rats and mice. Brain to plasma/blood ratios ranged from 0.39 to 0.49 in these studies, indicating moderate distribution into the brain. Following daily oral administration of pomalidomide from Gestation Day 7 through Gestation Day 20 as part of a developmental toxicity dose-range finding study in pregnant rabbits, foetal plasma pomalidomide concentrations were approximately 50% of the maternal Cmax at all dosages (5 to 250 mg/kg/day), indicating that pomalidomide crossed the placenta. Following a single oral administration of pomalidomide to lactating rats approximately 14 days postpartum, pomalidomide was transferred into milk, with milk to plasma ratios of 0.63 to 1.46. During in vitro incubation of [14C]pomalidomide in cell-free medium, multiple degradation products were formed due to non-enzymatic hydrolysis of the glutarimide and phthalidmide rings of pomalidomide. The levels of some hydrolysis products were increased in the presence of hepatocytes, indicating they may be formed enzymatically as well as non-enzymatically. The extent of pomalidomide metabolism was low in human hepatocytes, with metabolites formed via hydroxylation of the phthalimide ring and glucuronidation of these hydroxylated metabolites. Following oral administration of [14C]pomalidomide to rats or monkeys, > 80% of the circulating radioactivity was characterised as unchanged pomalidomide. With the exception of a hydroxylated metabolite in male rats, all plasma metabolites were present at < 10% relative to parent compound. In rats, [14C]pomalidomide was poorly absorbed following an oral dose (100 mg/kg), with faecal radioactivity containing primarily unchanged, and likely unabsorbed pomalidomide, while in monkeys, unchanged pomalidomide in faeces represented < 5% of the dose. In both species, urinary radioactivity contained primarily metabolites and urinary excretion of parent compound was a minor	

Table 2.2-1: Summary of Significant Non-clinical Safety Findings

Key Safety Findings (from Nonclinical Studies)	Relevance to human usage
elimination pathway. In rats and monkeys, the primary pathways for metabolism of [14C]pomalidomide included hydroxylation of the phthalimide ring, glucuronidation of the hydroxylated metabolites, hydrolysis of the glutarimide ring, and hydrolysis of the phthalimide ring. Following administration of a single oral 2 mg [14C]pomalidomide dose to healthy male subjects, pomalidomide was the predominant circulating radioactive component, accounting for approximately 70% of the circulating radioactivity. The metabolic pathways observed were the same as those observed in rats and monkeys and no circulating human metabolites were present at > 10% relative to parent or relative to total radioactivity. Based on the in vivo rat, monkey and human metabolism data, there were no unique or disproportionate metabolites observed in humans. Following oral (10 mg/kg) or IV (1 mg/kg) administration of [14C]pomalidomide to rats or monkeys, excretion of radioactivity was rapid and nearly complete (> 90%). In rats, the predominant route of elimination was in the faeces following oral administration and in urine following IV administration. Based on excretion data from bile duct cannulated male and female rats, approximately 28% of orally administered [14C]pomalidomide was absorbed. In monkeys, the primary route of elimination was via the urine, which contained approximately 72% of the radioactive dose following either oral or IV administration, demonstrating that at least 72% of the drug was absorbed following oral administration. These data indicate that urine is the primary route of elimination for circulating pomalidomide related material in both species, with the urinary radioactivity consisting mainly of metabolites rather than parent compound. Following administration of a single oral [14C]pomalidomide dose to healthy male subjects, the excretion profile was similar to monkeys, with 73% of the radioactive dose eliminated in urine, but urinary excretion of unchanged drug was < 3%.	

2.3 Clinical Trial Exposure

2.3.1 Clinical Study Information

The data presented in this section represent the primary studies (CC-4047-MM-002 [hereafter referred to as MM-002], CC-4047-MM-003 [44] [hereafter referred to as MM-003], and IFM-2009-02) supporting the RRMM indication for pomalidomide in combination with dexamethasone. In addition, data for the total patient population exposed to pomalidomide in any MM indication are included. This includes patients exposed to pomalidomide in Studies MM-002, MM-003 and IFM-2009-02, as well as in Study CC-4047-MM-001 [45] (also known as Study CDC-407-00-001 [hereafter referred to as MM-001]). Data for pomalidomide in combination with bortezomib and dexamethasone from Study CC-4047-MM-007 [hereafter referred to as MM-007] are presented separately.

Details of the RRMM clinical studies included in this RMP are listed below:

- **MM-007:** A Phase 3, multicentre, randomised, 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 RRMM.
- **MM-002:** A Phase 1/2 multicentre, randomised, open-label, dose-escalation study to determine the maximum tolerated dose, safety, and efficacy of pomalidomide alone or in combination with low-dose dexamethasone in patients with RRMM who have received prior treatment that includes lenalidomide and bortezomib.
- **MM-003:** A Phase 3, multicentre, randomised, open-label study to compare the efficacy and safety of pomalidomide in combination with low-dose dexamethasone versus high-dose dexamethasone in subjects with RRMM.
- **IFM-2009-02:** A multicentre, randomised, open-label Phase 2 study of pomalidomide and dexamethasone in RRMM subjects with progressive disease who did not achieve at least a partial response to bortezomib and lenalidomide.
- **MM-001:** An open-label study of the safety and efficacy of pomalidomide treatment for patients with RRMM.

2.3.2 Patient Exposure

In total, 278 subjects have received pomalidomide (14/21 days) in combination with bortezomib and dexamethasone in RRMM Study MM-007. A total of 455 subjects have received pomalidomide (with dexamethasone [21/28 days]) in RRMM Studies MM-002, MM-003, and IFM-2009-02. In total, 686 subjects have received pomalidomide in combination with dexamethasone across 4 clinical studies (MM-001, MM-002, MM-003, and IFM-2009-02). Duration of exposure to pomalidomide is summarised in Table 2.3.2-1 for Study MM-007 and Table 2.3.2-2 for Studies MM-002, MM-003, and IFM-2009-02, with duration of pomalidomide exposure for Studies MM-001, MM-002, MM-003, and IFM-2009-02 summarised in Table 2.3.2-3.

Table 2.3.2-1: Duration of Exposure in Subjects Exposed to Pomalidomide in Combination with Bortezomib and Dexamethasone in RRMM Indication (Study MM 007)

Duration of Exposure (Weeks)	Persons (N [%])	Person-years
Relapsed and Refractory Multiple Myeloma		
< 1	3 (1.1)	0.0219
1 to < 3	12 (4.3)	0.4216
3 to < 6	19 (6.8)	1.5770
6 to < 9	17 (6.1)	2.3984
9 to < 12	22 (7.9)	4.4627
12 to < 15	19 (6.8)	4.6927
15 to < 18	20 (7.2)	6.2587

Table 2.3.2-1: Duration of Exposure in Subjects Exposed to Pomalidomide in Combination with Bortezomib and Dexamethasone in RRMM Indication (Study MM 007)

Duration of Exposure (Weeks)	Persons (N [%])	Person-years
18 to < 21	17 (6.1)	6.1492
21 to < 24	22 (7.9)	9.3689
24 to < 27	15 (5.4)	7.2608
27 to < 30	12 (4.3)	6.5462
30 to < 33	7 (2.5)	4.2382
33 to < 36	5 (1.8)	3.2991
36 to < 39	11 (4.0)	7.7481
39 to < 42	8 (2.9)	6.1684
42 to < 45	17 (6.1)	14.0589
45 to < 48	6 (2.2)	5.3744
48 to < 51	4 (1.4)	3.7728
51 to < 54	6 (2.2)	5.9877
54 to < 57	9 (3.2)	9.4976
57 to < 60	2 (0.7)	2.2313
60 to < 63	6 (2.2)	7.0828
63 to < 66	5 (1.8)	6.1985
66 to < 69	1 (0.4)	1.2649
69 to < 72	2 (0.7)	2.6831
72 to < 75	1 (0.4)	1.3799
75 to < 78	4 (1.4)	5.8836
78 to < 81	1 (0.4)	1.5113
81 to < 84	2 (0.7)	3.1239
84 to < 87	1 (0.4)	1.6646
87 to < 90	1 (0.4)	1.6756
≥ 108	1 (0.4)	2.1656
Total	278 (100.0)	146.1684
Cumulative Dose (mg)		
Mean (SD)	681.3 (543.36)	Mean (SD)
Median	521.0	Median
Range	4.0, 3164.0	Range

Data cutoff date: 26 Oct 2017.

Table 2.3.2-2: Duration of Exposure in Subjects Exposed to Pomalidomide in Combination with Dexamethasone in RRMM Indication (Studies MM 002, MM 003, and IFM 2009 02)

Duration of Exposure (Weeks)	Persons (N [%])	Person-years
Relapsed and Refractory Multiple Myeloma		
< 1	4 (0.9)	0.0465
1 to < 4	22 (4.8)	1.0319
4 to < 8	71 (15.6)	7.1759
8 to < 12	80 (17.6)	13.8081
12 to < 16	54 (11.9)	13.6665
16 to < 20	43 (9.5)	14.1279
20 to < 24	24 (5.3)	9.6531
24 to < 28	30 (6.6)	14.5881
28 to < 32	20 (4.4)	11.1696
32 to < 36	22 (4.8)	13.9491
36 to < 40	11 (2.4)	7.8984
40 to < 44	12 (2.6)	9.4535
44 to < 48	7 (1.5)	6.0917
48 to < 52	10 (2.2)	9.4174
52 to < 56	5 (1.1)	5.1472
56 to < 60	6 (1.3)	6.7452
60 to < 64	6 (1.3)	7.0174
≥ 64	28 (6.2)	47.8593
Total	455 (100.0)	198.8468
Cumulative Dose (mg)		
Mean (SD)	414.8 (410.92)	Mean (SD)
Median	252.0	Median
Range	8.0, 2267.0	Range

Data cutoff dates: Studies MM-002 (30 Mar 2012); MM-003 (07 Sep 2012); IFM-2009-02 (01 Feb 2012).

Table 2.3.2-3: Duration of Exposure in Subjects Exposed to Pomalidomide in Combination with Dexamethasone in All MM Indications (Studies MM 001, MM 002, MM 003, and IFM 2009 02)

Duration of Exposure (Weeks)	Persons (N [%])	Person-years
Total Patient Population		
< 1	9 (1.3)	0.0947
1 to < 4	50 (7.3)	2.4337
4 to < 8	126 (18.4)	12.1624
8 to < 12	100 (14.6)	17.5170
12 to < 16	69 (10.1)	17.4776
16 to < 20	49 (7.1)	16.2415
20 to < 24	39 (5.7)	15.7561
24 to < 28	42 (6.1)	20.3316
28 to < 32	26 (3.8)	14.6415
32 to < 36	30 (4.4)	19.0004
36 to < 40	17 (2.5)	12.1659
40 to < 44	17 (2.5)	13.4437
44 to < 48	9 (1.3)	7.8932
48 to < 52	19 (2.8)	18.0044
52 to < 56	10 (1.5)	10.2568
56 to < 60	9 (1.3)	10.0663
60 to < 64	9 (1.3)	10.5843
≥ 64	56 (8.2)	99.4472
Total	686 (100.0)	317.5181
Cumulative Dose (mg)		
Mean (SD)	452.1 (499.93)	Mean (SD)
Median	252.0	Median
Range	4.0, 3586.0	Range

Data cutoff dates: Studies MM-001 (Cohort I finalised on 04 Apr 2003; Cohort II finalised on 12 Jul 2004); MM-002 (30 Mar 2012); MM-003 (07 Sep 2012); IFM-2009-02 (01 Feb 2012).

Exposure to pomalidomide in combination with bortezomib and dexamethasone by dose is summarised in Table 2.3.2-4 for RRMM Study MM-007. Summaries of exposure to pomalidomide in combination with dexamethasone by dose are provided in Table 2.3.2-5 for RRMM Studies (MM-002, MM-003, and IFM-2009-02) and in Table 2.3.2-6 for the total MM subject population (Studies MM-001, MM-002, MM-003, and IFM-2009-02).

Table 2.3.2-4: Exposure by Dose in Subjects Exposed to Pomalidomide in Combination with Bortezomib and Dexamethasone in RRMM Indication (Study MM 007)

Planned Dose Level (mg/day)	Persons (N [%])	Person-years
Relapsed and Refractory Multiple Myeloma		
4	278 (100.0)	146.1684

Data cutoff date: 26 Oct 2017.

Table 2.3.2-5: Exposure by Dose in Subjects Exposed to Pomalidomide in Combination with Dexamethasone in RRMM Indication (Studies MM-002, MM-003, and IFM-2009-02)

Planned Dose Level (mg/day)	Persons (N [%])	Person-years
Relapsed and Refractory Multiple Myeloma		
4	455 (100.0)	198.8468

Data cutoff dates: Studies MM-002 (30 Mar 2012); MM-003 (07 Sep 2012); IFM-2009-02 (01 Feb 2012).

Table 2.3.2-6: Exposure by Dose in Subjects Exposed to Pomalidomide in Combination with Dexamethasone in All MM Indications (Studies MM 001, Studies MM 002, MM 003, and IFM 2009 02)

Planned Dose Level (mg/day)	Persons (N [%])	Person-years
Total Patient Population		
0.5	4 (0.6)	0.2710
1	10 (1.5)	0.7337
2	15 (2.2)	2.3299
2.5	10 (1.5)	0.8049
3	8 (1.2)	3.7673
4	617 (89.9)	298.7721
5	19 (2.8)	10.6256
10	3 (0.4)	0.2136

Data cutoff dates: Studies MM-001 (Cohort I finalised on 04 Apr 2003; Cohort II finalised on 12 Jul 2004); MM-002 (30 Mar 2012); MM-003 (07 Sep 2012); IFM-2009-02 (01 Feb 2012).

Exposure to pomalidomide in combination with bortezomib and dexamethasone by age is summarised in Table 2.3.2-7 for RRMM Study MM-007. Summaries of exposure to pomalidomide in combination with dexamethasone by age are provided in Table 2.3.2-8 for

RRMM Studies (MM-002, MM-003, and IFM-2009-02) and in Table 2.3.2-9 for the total MM subject population (Studies MM-001, MM-002, MM-003, and IFM-2009-02).

Table 2.3.2-7: Exposure by Age in Subjects Exposed to Pomalidomide in Combination with Bortezomib and Dexamethasone in RRMM Indication (Study MM 007)

Age Group (Years)	Persons (N [%])		Person-years	
	Male	Female	Male	Female
Total Patient Population				
≤ 65	65 (42.2)	55 (44.4)	37.6454	36.1588
> 65	89 (57.8)	69 (55.6)	39.8713	32.4928
≤ 75	128 (83.1)	104 (83.9)	67.4251	60.4627
> 75	26 (16.9)	20 (16.1)	10.0917	8.1889
Total	154 (100.0)	124 (100.0)	77.5168	68.6516

Data cutoff date: 26 Oct 2017.

Table 2.3.2-8: Exposure by Age in Subjects Exposed to Pomalidomide in Combination with Dexamethasone in RRMM Indication (Studies MM 002, MM 003, and IFM 2009 02)

Age Group (Years)	Persons (N [%])		Person-years	
	Male	Female	Male	Female
Relapsed and Refractory Multiple Myeloma				
≤ 65	155 (57.2)	106 (57.6)	76.0277	47.3454
> 65 to 75	89 (32.8)	63 (34.2)	30.7510	28.1489
> 75	27 (10.0)	15 (8.2)	12.6177	3.9562
Total	271 (100.0)	184 (100.0)	119.3963	79.4505

Data cutoff dates: Studies MM-002 (30 Mar 2012); MM-003 (07 Sep 2012); IFM-2009-02 (01 Feb 2012).

Table 2.3.2-9: Exposure by Age in Subjects Exposed to Pomalidomide in Combination with Dexamethasone in All MM Indications (Studies MM 001, MM 002, MM 003, and IFM 2009 02)

Age Group (Years)	Persons (N [%])		Person-years	
	Male	Female	Male	Female
Total Patient Population				
≤ 65	233 (59.0)	171 (58.8)	109.9058	79.4820
> 65 to 75	125 (31.6)	92 (31.6)	50.7756	43.2660
> 75	37 (9.4)	28 (9.6)	20.1859	13.9028
Total	395 (100.0)	291 (100.0)	180.8674	136.6508

Data cutoff dates: Studies MM-001 (Cohort I finalised on 04 Apr 2003; Cohort II finalised on 12 Jul 2004); MM-002 (30 Mar 2012); MM-003 (07 Sep 2012); IFM-2009-02 (01 Feb 2012).

Exposure to pomalidomide in combination with bortezomib and dexamethasone by ethnic or racial origin is summarised in Table 2.3.2-10 for RRMM Study MM-007. Summaries of exposure to pomalidomide in combination with dexamethasone by ethnic or racial origin are provided in Table 2.3.2-11 for RRMM Studies (MM-002, MM-003, and IFM-2009-02) and in Table 2.3.2-12 for the total MM subject population (Studies MM-001, MM-002, MM-003, and IFM-2009-02).

Table 2.3.2-10: Exposure by Racial/Ethnic Origin in Subjects Exposed to Pomalidomide in Combination with Bortezomib and Dexamethasone in RRMM Indication (Study MM 007)

Ethnic/Racial Origin	**Persons (N [%])**	**Person-years**
Relapsed and Refractory Multiple Myeloma		
Asian	14 (5.0)	10.0452
Black or African American	8 (2.9)	4.3422
Other	3 (1.1)	1.3580
White	234 (84.2)	120.3833
Missing	19 (6.8)	10.0397
Total	278 (100.0)	146.1684

Data cutoff date: 26 Oct 2017.

Table 2.3.2-11: Exposure by Racial/Ethnic Origin in Subjects Exposed to Pomalidomide in Combination with Dexamethasone in RRMM Indication (Studies MM 002, MM 003, and IFM 2009 02)

Ethnic/Racial Origin	Persons (N [%])	Person-years
Relapsed and Refractory Multiple Myeloma		
Asian	6 (1.3)	2.7789
Black or African American	21 (4.6)	14.2533
Other	4 (0.9)	1.4976
White	333 (73.2)	124.2738
Missing	91 (20.0)[a]	56.0433
Total	455 (100.0)	198.8468

[a] Race information was not collected in Study IFM-2009-02.

Data cutoff dates: Studies MM-002 (30 Mar 2012); MM-003 (07 Sep 2012); IFM-2009-02 (01 Feb 2012).

Table 2.3.2-12: Exposure by Racial/Ethnic Origin in Subjects Exposed to Pomalidomide in Combination with Dexamethasone in All MM Indications (Studies MM 001, Studies MM 002, MM 003, and IFM 2009 02)

Ethnic/Racial Origin	Persons (N [%])	Person-years
Total Patient Population		
Asian	13 (1.9)	4.4736
Black or African American	45 (6.6)	23.2909
Other	8 (1.2)	3.7125
White	488 (71.1)	203.4141
Missing	132 (19.2)[a]	82.6270
Total	686 (100.0)	317.5181

[a] Race information was not collected in Study IFM-2009-02.

Data cutoff dates: Studies MM-001 (Cohort I finalised on 04 Apr 2003; Cohort II finalised on 12 Jul 2004); MM-002 (30 Mar 2012); MM-003 (07 Sep 2012); IFM-2009-02 (01 Feb 2012).

Exposure to pomalidomide in special populations (ie, pregnant women lactating women, subjects with renal, hepatic or cardiac impairment, subpopulations with genetic polymorphisms and immunocompromised subjects) is not applicable as these subject populations were not included in the RRMM clinical studies (MM-007, MM-002, MM-003 and IFM-2009-02). Special populations were excluded from the clinical studies for safety reasons.

2.4 Populations Not Studied in Clinical Trials

2.4.1 Exclusion Criteria in Pivotal Clinical Studies within the Development Programme

Table 2.4.1-1: Important Exclusion Criteria in Pivotal Clinical Studies (MM-007, MM-001, MM-002, MM-003, and IFM-2009-02)

Exclusion Criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale (if not included as missing information)
Pregnancy	If pomalidomide is taken during pregnancy, a teratogenic effect of pomalidomide in humans is expected.	No.	Teratogenicity is included as an important identified risk in this RMP. Treatment with pomalidomide is contraindicated during pregnancy (SmPC, Section 4.3 and Section 4.4).
Women of childbearing potential, unless all the conditions of the PPP are met	If pomalidomide is taken during pregnancy, a teratogenic effect of pomalidomide in humans is expected.	No.	Teratogenicity is included as an important identified risk in this RMP. Pomalidomide is contraindicated in women of childbearing potential, except when all the conditions for pregnancy prevention have been met (SmPC, Section 4.3 and Section 4.4).
Male patients unable to follow or comply with the required contraceptive measures	If pomalidomide is taken during pregnancy, a teratogenic effect of pomalidomide in humans is expected.	No.	Teratogenicity is included as an important identified risk in this RMP. Pomalidomide is contraindicated in male patients who are unable to follow or comply with the required contraceptive measures (SmPC, Section 4.3).
Hypersensitivity to the active substance or to any of the excipients	To protect patient safety by ensuring that patients with known hypersensitivity to the medicinal product were not included in the clinical studies.	No.	Pomalidomide is contraindicated in patients with hypersensitivity to the active substance or to any of the excipients (SmPC, Section 4.3).
Hypersensitivity to the active substance or to any of the excipients	To protect patient safety by ensuring that patients with known hypersensitivity to the medicinal product were not	No.	Because of the potential for adverse reactions in breastfed infants from pomalidomide, a decision must be made whether to discontinue breastfeeding

Table 2.4.1-1: Important Exclusion Criteria in Pivotal Clinical Studies (MM-007, MM-001, MM-002, MM-003, and IFM-2009-02)

Exclusion Criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale (if not included as missing information)
	included in the clinical studies.		or to discontinue the medicinal product, taking into account the benefit of breastfeeding for the child and the benefit of the therapy for the woman (SmPC Section 4.6).
Prior history of malignancies, other than MM within 3 to 5 years prior to study.	Other malignancies (and their treatment) could influence the interpretation of safety, efficacy, and pharmacokinetic study data, in particular when assessing the incidence of SPM, and MDS/AML in particular.	No.	In this RMP, NMSC is included as an important identified risk and Other SPM is included as an important potential risk. These risks are adequately addressed through the risk minimisation and pharmacovigilance measures presented in Section 5 and Section 3 of this RMP, respectively.
Known positive for HIV or infectious hepatitis, type A, B or C	Such concomitant diseases could influence the interpretation of the study data.	No.	Severe infection due to neutropenia and pancytopenia is included as an important identified risk in this RMP. This risk is adequately addressed through the risk minimisation and pharmacovigilance measures presented in Section 5 and Section 3 of this RMP, respectively.
Peripheral neuropathy ≥ Grade 2	Many of the chemotherapies used to treat MM (vincristine, platinum containing agents, thalidomide, bortezomib) can cause or worsen existing peripheral neuropathy.[46,47] This could influence the interpretation of the study data.	No.	Section 4.4 of the SmPC indicates that patients with ongoing ≥ Grade 2 peripheral neuropathy were excluded from clinical studies with pomalidomide. Appropriate caution should be exercised when considering the treatment of such patients with pomalidomide. Peripheral sensory neuropathy is listed as an ADR in Section 4.8 of the SmPC.

Table 2.4.1-1: Important Exclusion Criteria in Pivotal Clinical Studies (MM-007, MM-001, MM-002, MM-003, and IFM-2009-02)

Exclusion Criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale (if not included as missing information)
Ongoing cardiac dysfunction such as CHF, unstable or poorly controlled angina pectoris or MI within 1 year before study treatment	Cardiac dysfunction not related to pomalidomide therapy could influence the interpretation of the study data, in particular that regarding the safety of pomalidomide.	No.	Cardiac failure is included as an important identified risk and Cardiac arrhythmia is included as an important potential risk in this RMP. These risks are adequately addressed through the risk minimisation and pharmacovigilance measures presented in Section 5 and Section 3 of this RMP, respectively. Section 4.4 of the SmPC indicates that patients with significant cardiac dysfunction (CHF [New York Heart Association Class III or IV]; MI within 12 months of starting study; unstable or poorly controlled angina pectoris) were excluded from clinical studies with pomalidomide. Cardiac events, including congestive cardiac failure, pulmonary oedema and atrial fibrillation have been reported, mainly in patients with pre-existing cardiac disease or cardiac risk factors. Appropriate caution should be exercised when considering the treatment of such patients with pomalidomide, including periodic monitoring for signs or symptoms of cardiac events.
Patients unable or unwilling to take anti-thrombotic prophylactic treatment	Recent or active cancer is a recognised prothrombotic risk factor for increasing the risk of venous thromboembolism. Prophylaxis with aspirin (and other anticoagulants in high	No.	Section 4.4 of the SmPC highlights the possibility of patients developing venous and arterial thromboembolism, and provides recommendations for the use of

Table 2.4.1-1: Important Exclusion Criteria in Pivotal Clinical Studies (MM-007, MM-001, MM-002, MM-003, and IFM-2009-02)

Exclusion Criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale (if not included as missing information)
	risk patients) was mandatory for all patients.		anticoagulation prophylaxis. Thromboembolic events are listed as ADRs and discussed in Section 4.8 of the SmPC.
Abnormal laboratory values including neutrophil and platelet count, creatinine clearance, corrected serum calcium, haemoglobin, serum glutamic oxaloacetic transaminase/aspartate aminotransferase or serum glutamic pyruvic transaminase/ ALT, serum total bilirubin	Prior clinical experience, reported dose-limiting toxicities of neutropenia. Abnormal laboratory values may result from an underlying medical condition that could influence the interpretation of the study data.	No.	In this RMP, severe infection due to neutropenia and pancytopenia, and thrombocytopenia and bleeding, are included as important identified risks. Section 4.2 of the SmPC includes dose modification advice for neutropenia and thrombocytopenia. Section 4.4 of the SmPC includes a warning on neutropenia and thrombocytopenia, and advice for monitoring complete blood counts at baseline, weekly for the first 8 weeks and then monthly thereafter. Neutropenia and thrombocytopenia are listed as ADRs and discussed in Section 4.8 of the SmPC.
Study IFM-2009-02			
Any > Grade 2 toxicity unresolved	Toxicity not related to pomalidomide therapy could influence the interpretation of the study data.	No.	In clinical practice, these patients may derive some benefit from treatment with pomalidomide. Section 4.2 of the SmPC includes dose modification advice for neutropenia and thrombocytopenia. Section 4.4 of the SmPC includes a warning on neutropenia and thrombocytopenia, and advice for monitoring

Table 2.4.1-1: Important Exclusion Criteria in Pivotal Clinical Studies (MM-007, MM-001, MM-002, MM-003, and IFM-2009-02)

Exclusion Criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale (if not included as missing information)
			complete blood counts at baseline, weekly for the first 8 weeks and monthly thereafter. Neutropenia and thrombocytopenia are listed as ADRs and discussed in Section 4.8 of the SmPC.
Ongoing active infection	Infection not related to pomalidomide therapy could influence the interpretation of the study data.	No.	Severe infection due to neutropenia and pancytopenia is included as an important identified risk in this RMP. This risk is adequately addressed through the risk minimisation and pharmacovigilance measures presented in Section 5 and Section 3 of this RMP, respectively.

2.4.2 Limitations to Detect Adverse Reactions in Clinical Trial Development Programmes

The clinical development programme is unlikely to detect rare adverse reactions. Patients with RRMM have a limited survival time meaning that the trial programme may be limited in its ability to assess cumulative effects, effects due to prolonged exposure, and effects with a long latency. Furthermore, these are, to a great extent, elderly patients with a limited natural life expectancy.

2.4.3 Limitations in Respect to Populations Typically Under-represented in Clinical Trial Development Programmes

Specific populations of patients were excluded from the clinical studies, thus experience in these populations is limited. Exposure of special populations is presented in Table 2.4.3-1.

Table 2.4.3-1: Exposure of Special Populations Included or Not in Clinical Trial Development Programmes

Type of special population	Exposure
Pregnant women	Not included in the clinical development programme.
Lactating women	Not included in the clinical development programme.

Table 2.4.3-1: Exposure of Special Populations Included or Not in Clinical Trial Development Programmes

Type of special population	Exposure
Patients with relevant comorbidities:	
Patients with renal impairment	In Study MM-007, 28.5% (80/281) versus 23.7% (66/278) of patients had moderate renal insufficiency (CrCl ≥ 30 and < 60 mL/min), and 3.9% (11/281) versus 3.6% (10/278) of patients had severe renal insufficiency (CrCl < 30 mL/min) in the pomalidomide in combination with bortezomib and dexamethasone and bortezomib and dexamethasone arms, respectively. Patients with severe renal impairment (CrCl < 30 mL/min) were eligible for the study as long as they were not requiring dialysis. Clinical studies in MM subjects with moderate and severe renal impairment are ongoing (CC-4047-MM-008 and CC-4047-MM-013). A meta-analysis combining pharmacokinetics data from both of these studies is complete (CC-4047-MPK-002). In CC-4047-MPK-002, in total 63 subjects have been exposed with the following renal functions (creatine clearance [CLcr] or estimated glomerular filtration rate [eGFR]): normal renal function (> 60 mL/min, n=8); moderate renal impairment (30 to 60 mL/min, n=15); severe renal impairment without dialysis (15 to 30 mL/min, n=30); severe renal impairment with dialysis (0 to 15 mL/min; n=10).
Patients with hepatic impairment	A clinical study in healthy subjects with varying degrees of hepatic impairment (CC-4047-CP-009) is complete with a final CSR (the synopsis for Study-CC-4047-CP-009 is included in Annex 9 of RMP Version 9.0). In total, 32 male subjects were included in this study.
Patients with cardiovascular impairment	Pomalidomide has been evaluated in a randomised, double-blind crossover study with four treatments, four periods and four sequences to investigate the effects of orally administered single doses of pomalidomide on the QT interval in healthy male subjects (CC-4047-CP-010). The study was designed according to International Conference on Harmonisation Guideline E14. It was shown that pomalidomide, when given as a single oral dose of up to 20 mg, is not associated with QT prolongation in healthy male subjects, and that this is a negative, thorough QT/QTc study. A single dose of 4 mg and 20 mg pomalidomide was safe and well tolerated by the healthy male subjects in this study.
Immunocompromised patients	The target population used in the clinical trial development programme were immunocompromised patients.
Patients with a disease severity different from inclusion criteria in clinical trials	No data are available at this time.
Population with relevant different ethnic origin	Of the subjects exposed to pomalidomide in combination with bortezomib and dexamethasone in Study MM-007, the majority of subjects were White (84.2%), with a small percentage of subjects Asian (5.0%) or Black or African American (2.9%). The majority of subjects in Studies MM-001, MM-002, and MM-003 were White (71.1%), with a small percentage of subjects Black or African American (6.6%) or Asian (1.9%). Information on race was not collected in Study IFM-2009-02; however, this study was conducted in France, representing a predominantly European population

Table 2.4.3-1: Exposure of Special Populations Included or Not in Clinical Trial Development Programmes

Type of special population	Exposure
	that also includes some patients of North African descent. Clinical trial exposure data are present by race and ethnic origin in Section 2.3. There are currently two completed BMS-sponsored studies that are specific to ethnic populations. • Japan: CC-4047-MM-004 (Completed [follow-up completed 08 Jul 2015]; CSR completed 23 May 2016).[48] The pomalidomide tolerated dose determined to be optimal for further development in Japan is the same dose used in development in non-Japanese studies (4 mg once per day on Days 1 to 21 of each 28-day cycle). • Japan: CC-4047-MM-011 (Completed [follow-up completed 25 Sep 2015, CSR completed 20 Jun 2016]).[49] There have been no unexpected safety findings in this study. The information received has not provided new safety findings with regard to the use of pomalidomide in patients of different racial origins. Based on the current information, no updates to risk minimisation are needed at this time.
Subpopulations carrying relevant genetic polymorphisms	Pomalidomide is partially metabolised by CYP450 enzymes (primarily CYP1A2). Genetic polymorphisms have not been studied in the pomalidomide clinical trial population.
Other	**Paediatric Population:** Pomalidomide is not authorised for use in children in the EU/EEA or elsewhere in the world. A class waiver for MM in paediatrics was granted by the PDCO at the EMA on 03 Dec 2007 due to the rareness of MM in the paediatric population (EMA/PDCO/920049/2011).[50] Children were not included in the clinical studies. **Elderly Population:** MM is a disease of the elderly. Of the 278 subjects exposed to pomalidomide in combination with bortezomib and dexamethasone in Study MM-007, 158 (56.8%) were aged > 65 years, with 46 (16.5%) aged > 75 years. Of the 686 subjects exposed to pomalidomide in combination with dexamethasone in Studies MM-001, MM-002, MM-003 and IFM-2009-02, 217 (31.6%) were aged > 65 to 75 years, and 65 (9.5%) were aged > 75 years. A clinical pharmacology study in healthy elderly subjects, aged 61 to 85 (CC-4047-CP-011) is complete with a final CSR.[51] The mean drug exposures were generally similar to younger subjects. No dose adjustment is required for pomalidomide. <u>Pomalidomide in combination with dexamethasone</u> For patients aged > 75 years, the starting dose of dexamethasone is 20 mg QD on Days 1, 8, 15 and 22 of each 28-day treatment cycle (SmPC, Section 4.2).

Table 2.4.3-1: Exposure of Special Populations Included or Not in Clinical Trial Development Programmes

Type of special population	Exposure
	Pomalidomide in combination therapy with bortezomib and dexamethasone For patients aged > 75 years, from Cycle 1 to 8, the starting dose of dexamethasone is 10 mg on Days 1, 2, 4, 5, 8, 9, 11, and 12 of each 21−day treatment cycle; from Cycle 9 and onwards, the dose of dexamethasone is 10 mg on Days 1, 2, 8, and 9 of each 21-day treatment cycle (SmPC, Section 4.2).

2.5 Post-Authorization Experience

2.5.1 Post-authorization Exposure

2.5.1.1 Method Used to Calculate Exposure

The cumulative value for exposure represents the estimated number of unique patients exposed to the product from 08-Feb-2013 through 07-Feb-2022.

The methodology for estimating commercial patient exposure utilizes up to 3 data sources:

1) BMS's Sales/Shipment Data – this data consist of all shipments of BMS product to all applicable countries and includes commercial and free-of-charge units for both branded and generic product (as applicable). The data are used to determine the units (eg, milligrams) of a product that was sold to a geography to estimate the number of patients who would have been exposed to that product, based on expected dosing in the geography. Shipment data are used to estimate the active patients for a period of time by dividing the total units sold by the average units per patient (note that average units per patient is derived from epidemiologic or market research).
2) Claims Data – this data consist of 2 distinct sources of electronic health care claims data in the USA: Optum Clinformatics Datamart and Symphony Claims for Hem/Onc. Claims data consisting of distinct patient IDs and prescription fill rates for each product are used to understand usage patterns. For newly approved products, until sufficient claims data are available, patterns are based on discontinuation rates derived from clinical trial experience.
3) Controlled Distribution Database – this data source provides detailed patient exposure including demographics, indication for use, and dosing information in the USA.

2.5.1.2 Exposure

Estimated cumulative commercial exposure to pomalidomide through 07-Feb-2022 is approximately 140,892 patients, which includes all non-BMS-sponsored study subjects from the USA and Canada, the NPP patients, and CU patients globally. The adjusted exposure (to avoid double counting of US and Canadian non-BMS-sponsored study, NPP, and CU subjects/patients) is 136,951 patients. Cumulative commercial exposure to pomalidomide by indication and patient

demographics is provided in Table 2.5.1.2-1, and cumulative commercial exposure by indication and region is provided in Table 2.5.1.2-2.

Table 2.5.1.2-1: Cumulative Pomalidomide Commercial Exposure by Indication and Demographics through 07-Feb-2022

Indication	Total	Sex			Age (Years)				FCBP	Dose		
		Male	Female	Unknown / Not Provided	0 to < 18	≥ 18 to < 65	≥ 65	Unknown / Not Provided	Yes	≤ 4 mg	> 4 mg	Unknown / Not Provided
Multiple Myeloma	66586	36992	29594	0	1	21103	45482	0	1200	66528	51	7
Kaposi's Sarcoma[a]	274	259	15	0	0	185	89	0	4	193	81	0
Other	1333	769	564	0	5	575	753	0	70	1297	36	0
Unknown/Not Provided	72699	N/A	N/A	72699	N/A	N/A	N/A	72699	N/A	N/A	N/A	72699
TOTAL	**140892**[b]	**38020**	**30173**	**72699**	**6**	**21863**	**46324**	**72699**	**1274**	**68018**	**168**	**72706**

Note: Details of the patient demographics, indication and dosing information were derived from the US REMS database.

[a] Kaposi's sarcoma is an approved indication in the US.

[b] This total includes subjects from non-BMS-sponsored studies in the USA and Canada and NPP and CU patients globally (unadjusted total). The adjusted total is 136,951 as indicated below in Table 2.5.1.2-2.

Table 2.5.1.2-2: Cumulative Pomalidomide Commercial Exposure by Indication and Region through 07-Feb-2022

Indication	Total	Region						
		EEA[a]	[redacted]	[redacted]	[redacted]	[redacted]	ROW[b]	[redacted]
Multiple Myeloma	66586	N/A	66586	N/A	N/A	N/A	N/A	N/A
Kaposi's Sarcoma[c]	274	N/A	274	N/A	N/A	N/A	N/A	N/A
Other	1333	N/A	1333	N/A	N/A	N/A	N/A	N/A
Unknown/Not Provided	72699	35960	0	11948	3496	2194	13228	5873
Subtotal	140892	35960	68193	11948	3496	2194	13228	5873
Non-BMS-sponsored Study/NPP/CU Exposure[d]	-3941	-879	-2598	N/A	-235	-192	N/A	-37
TOTAL	**136951**	**35081**	**65595**	**11948**	**3261**	**2002**	**13228**	**5836**

[a] Includes the 27 EU countries, Liechtenstein, Norway, and Iceland.

[b] Includes countries and regions not otherwise specified in the table.

[c] Kaposi's sarcoma is an approved indication in the US.

[d] Subjects from non-BMS sponsored studies in the USA and Canada and NPP and CU patients globally are subtracted to avoid double counting.

2.6 Additional EU Requirements for the Safety Specification

2.6.1 Potential for Misuse for Illegal Purposes

There are no specific risks or abuse or misuse of pomalidomide based on the pharmacological properties. The cumulative number of cases of drug misuse up to 07-Feb-2018 is 280.

2.7 Identified and Potential Risks

2.7.1 Identification of Safety Concerns in the Initial RMP Submission

The summary of the safety concerns in the initial RMP (Version 6.0) applicable at the time of authorisation (05-Aug-2013) is presented in Table 2.7.1-1. A description of the changes to the list of safety concerns in the approved RMPs is presented in Annex 8.

Table 2.7.1-1: Safety Concerns in the Initial RMP

Important identified risks	Teratogenicity
	Neutropenia
	Thromboembolic events
	Peripheral neuropathy
	Infection
	Thrombocytopenia and bleeding
	Tumour lysis syndrome
	Somnolence
Important potential risks	Second primary malignancies
	Thyroid disorders
	Renal failure
	QT interactions (prolongation)
	Severe skin reactions
	Cardiac failure
	Cardiac arrhythmia
	Off-label use
Missing information	Use in patients with renal impairment
	Use in patients with hepatic impairment
	Interactions with drugs affecting and metabolised by cytochrome P450 1A2, 3A4/5 and P-glycoprotein
	Interaction with oral contraceptives
	Use in patients of different racial origin
	Paediatric use
	Use during breastfeeding

2.7.1.1 Risks Not Considered Important for Inclusion in the List of Safety Concerns in the RMP

Adverse reactions with minimal clinical impact on patients and not associated with any relevant risk (in relation to the life-threatening haematologic disease being treated) include anaemia, bone pain, constipation, cough, decreased appetite, diarrhoea, dyspnoea, fatigue, leukopenia, muscle spasms, nausea, oedema peripheral, and pyrexia.

Identified adverse reactions not considered important for inclusion in the list of safety concerns include angioedema, hepatic disorders, interstitial lung disease (interstitial pneumonitis), peripheral neuropathy, severe skin reactions, somnolence (dizziness and confusion), thromboembolic events, and tumour lysis syndrome. Potential adverse reactions not considered important for inclusion in the list of safety concerns include gastrointestinal perforation, off-label use, renal failure, and thyroid disorders.

2.7.1.2 Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Table 2.7.1.2-1: Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Risk Type	Risk-Benefit Impact
Important identified risks	
Teratogenicity	Pomalidomide is structurally related to thalidomide, a known human teratogen that causes severe life threatening birth defects. Pomalidomide was found to be teratogenic in both rats and rabbits when administered during the period of major organogenesis (SmPC, Sections 4.4, 4.8 and 5.3). If pomalidomide is taken during pregnancy, a teratogenic effect of pomalidomide in humans is expected (SmPC, Sections 4.4, 4.6 and 4.8). Please see Section 2.7.3.1 for further details.
Severe Infection due to Neutropenia and Pancytopenia	Neutropenia is one of the most frequent adverse reactions of pomalidomide (Section 4.8 of the SmPC). Events of neutropenia may require local or non-invasive intervention, or limited invasive intervention (G-CSF). Pancytopenia is included as a common ADR following pomalidomide treatment in Section 4.8 of the SmPC. Local or non-invasive intervention, or limited invasive intervention may be required. Reactivation of hepatitis B has been reported rarely in patients receiving pomalidomide in combination with dexamethasone who have previously been infected with HBV. Some of these cases have progressed to acute hepatic failure (Section 4.4 of the SmPC). Infection was the most common nonhaematological toxicity, in clinical studies. Herpes zoster is listed as a common ADR in Section 4.8 of the SmPC. Infections may be moderate to severe or medically significant, life-threatening or fatal.

Table 2.7.1.2-1: Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Risk Type	Risk-Benefit Impact
	Please see Section 2.7.3.1 for further details.
Thrombocytopenia and Bleeding	Thrombocytopenia is one of the most common ADRs following treatment with pomalidomide (Section 4.8 of the SmPC). Haemorrhagic disorders have been reported with pomalidomide, especially in patients with risk factors such as concomitant medicinal products that increase susceptibility to bleeding. Local or non-invasive interventions, or a limited invasive intervention (platelet transfusion) may be required. Physicians should observe patients for signs of bleeding including epistaxis, especially with use of concomitant medicinal products known to increase the risk of bleeding.
	Please see Section 2.7.3.1 for further details.
Cardiac Failure	Cardiac failure is a common Grade 3/4 ADR of pomalidomide treatment and is included in Section 4.8 of the SmPC. Cardiac failure can have a mild to severe, life threatening, or fatal impact, which may require non-invasive to urgent continuous intervention.
	Please see Section 2.7.3.1 for further details.
Non-melanoma Skin Cancer	NMSC has been reported in patients receiving pomalidomide. BCC of the skin and SCC of the skin are listed as uncommon ADRs in Section 4.8 of the SmPC. NMSC may require hospitalisation for invasive intervention, but is not immediately life-threatening.
	Please see Section 2.7.3.1 for further details.
Important potential risks	
Other Second Primary Malignancies	Other SPM have been reported in patients receiving pomalidomide (Section 4.8 of the SmPC). Other SPM may require hospitalisation for invasive intervention, but are not immediately life-threatening.
	Please see Section 2.7.3.1 for further details.
Cardiac Arrhythmia	AF is listed as a common ADR of pomalidomide treatment in Section 4.8 of the SmPC. Events of AF may have a mild to severe to life threatening or fatal impact.
	Please see Section 2.7.3.1 for further details.

Missing Information

There is no missing information for the purpose of risk management planning.

2.7.2 New Safety Concerns and Reclassification with a Submission of an Updated RMP

There are no changes to the safety concerns proposed.

2.7.3 Details of Important Identified Risks, Important Potential Risks, and Missing Information

The important identified and potential safety risks of pomalidomide are summarised in the following tables, based on data from Study MM-007 and pooled data from Studies MM-002, MM-003, and IFM-2009-02. These are established as identified or potential safety risks based on the nonclinical and clinical development programme of the drug. Calculation of relative and excess risks is not applicable for these studies as the majority of subjects in Studies MM-002 and IFM-2009-02 received pomalidomide with low-dose dexamethasone. In Study MM-007, subjects received either pomalidomide in combination with bortezomib and low-dose dexamethasone, or bortezomib with low-dose dexamethasone. Of note, Study MM-002 had a pomalidomide only arm, which included 107 subjects. Of these subjects, 46 received pomalidomide only and did not have low-dose dexamethasone subsequently added to their regimen. In Study MM-003, subjects received either pomalidomide in combination with low-dose dexamethasone, or high-dose dexamethasone alone. For the following important identified and potential risks, data from the pomalidomide plus low-dose dexamethasone arm are pooled for Studies MM-002, IFM-2009-02 and MM-003. In addition, as Study MM-003 included a comparator arm, data for this study are presented for the pomalidomide plus low-dose dexamethasone versus high-dose dexamethasone arms. Data from Study MM-007 are presented by treatment arm.

Pooled data for frequency with 95% CIs only also included data from Study MM-001. Data from Study MM-007 were not pooled with the other studies in the RMP because the study regimen was a triplet regimen, which included bortezomib, meaning the results were not comparable. In addition, the study population and treatment duration in Study MM-007 were not comparable to that of the pooled Studies MM-002, MM-003, and IFM-2009-02 (Part II SVIII).

The RMP search criteria have been defined for each study based on the MedDRA version as noted in Table 2.7.3-1. Due to the different MedDRA versions used for each clinical study's database, the terms were used based on the MedDRA version used to code AEs in the clinical database.

Table 2.7.3-1: RMP Search Criteria

Study	RMP Search Criteria	MedDRA Version Used to Code AEs in Clinical Database
MM-007	20.0	20.0
MM-001	14.0[a]	14.0
MM-002	14.0a	14.0
MM-003	14.0a	14.0
IFM-2009-02	14.0a	14.0

[a] The search criteria for pancytopenia (included in the important identified risk of severe infection due to neutropenia and pancytopenia) and the important identified risk of cardiac failure were defined in MedDRA Version 17.0 and remapped back to MedDRA Version 14.0 in order to retrieve data from the clinical databases. The search criteria for the update of intracranial haemorrhage (included in the important identified risk of thrombocytopenia and bleeding) were defined in MedDRA Version 18.0 and remapped back to MedDRA Version 14.0 in order to retrieve data from the clinical databases. The search criteria for the important identified risk of NMSC, the important potential risk of other SPM, and the updates of viral reactivation (VZV and HBV; included in the important identified risk of severe

infection due to neutropenia and pancytopenia) and gastrointestinal haemorrhage (included in the important identified risk of thrombocytopenia and bleeding) were defined in MedDRA Version 18.1 and remapped back to MedDRA Version 14.0 in order to retrieve data from the clinical databases.

The data cutoff dates for more recently added data (for the important identified risks of severe infection due to neutropenia and pancytopenia, thrombocytopenia and bleeding, cardiac failure, and NMSC; and the important potential risk of other SPM) are as follows:

- MM-007: 26-Oct-2017.
- MM-001: Cohort I finalised on 04-Apr-2003; Cohort II finalised on 12-Jul-2004 (no change since previous data cutoff date).
- MM-002 Phase 1: 01-Mar-2013 (previous data cutoff date was 30-Mar-2012).
- MM-002 Phase 2: 14-May-2014 (previous data cutoff date was 30-Mar-2012).
- MM-003: 14-May-2014 (previous data cutoff date was 07-Sep-2012).
- IFM-2009-02: 01-Feb-2012 (no change since previous data cutoff date).

2.7.3.1 Presentation of Important Identified and Important Potential Risks

Important Identified Risk: Teratogenicity

Information concerning the risk of teratogenicity is summarized in Table 2.7.3.1-1.

Table 2.7.3.1-1: Important Identified Risk: Teratogenicity

Teratogenicity	
Potential mechanisms	No mechanism by which pomalidomide may cause teratogenicity has been fully established.
Evidence source and strength of evidence	Pomalidomide is structurally related to thalidomide, a known human teratogen that causes severe life-threatening birth defects. Pomalidomide was found to be teratogenic in both rats and rabbits when administered during the period of major organogenesis. If pomalidomide is taken during pregnancy, a teratogenic effect of pomalidomide in humans is expected. Although women of childbearing potential taking pomalidomide are particularly at risk, female partners of male patients taking pomalidomide are also at risk as pomalidomide may be present in semen.
Characterization of risk	There are no cases of pregnancy reported in female subjects on pomalidomide or female partners of male subjects on pomalidomide in studies MM-007, MM-001, MM-002, MM-003 and IFM-2009-02. A multiple ascending dose study that evaluated the transfer of pomalidomide (CC-4047-CP-006[52]) in semen in healthy volunteers after 4 doses of pomalidomide (4 mg QD) was completed in Quarter 4 (Q4) 2011.
Risk factors and risk groups	The 'at risk' group comprises female patients of childbearing potential or female partners of male patients treated with pomalidomide.

Table 2.7.3.1-1: Important Identified Risk: Teratogenicity

Teratogenicity	
Preventability	Pomalidomide is contraindicated during pregnancy and in women of childbearing potential, unless all the conditions of the PPP are met (SmPC, Sections 4.3, 4.4 and 4.6). Prescriptions for women of childbearing potential can be for a maximum duration of 4 weeks whereas prescriptions for all other patients can be for a maximum duration of 12 weeks (SmPC, Section 4.4). The teratogenic effect of pomalidomide in humans cannot be ruled out. Therefore, a PPP is in place, with details provided in the SmPC (Section 4.4). This includes the requirement for females of childbearing potential to use effective means of contraception for at least 4 weeks before therapy, during pomalidomide therapy and dose interruptions, and for 4 weeks following discontinuation of pomalidomide therapy, or continually abstain from reproductive heterosexual sexual intercourse. Females of childbearing potential must undergo regular pregnancy testing during treatment with pomalidomide and immediately discontinue pomalidomide therapy if pregnancy occurs. Furthermore, it is mandatory that women of childbearing potential receive counselling to be made aware of the risks of pomalidomide. A multiple ascending dose study that evaluated the transfer of pomalidomide (CC-4047-CP-006[52]) in semen in healthy volunteers after 4 doses of pomalidomide (4 mg QD) was completed in Q4 2011. The amount of pomalidomide recovered in semen at 4 hours post dose (on Day 4) ranged from 10.5 to 113 ng with a mean concentration of 16.4 ng/mL, which was approximately 67% of the pomalidomide plasma concentration observed at the same time point on Day 5 (ie, 24.5 ng/mL). Male patients taking pomalidomide must use effective contraception during therapy and for 7 days following discontinuation of pomalidomide therapy if their partner is of childbearing potential and not using effective contraception. As pomalidomide is distributed in semen, male patients taking pomalidomide must not donate sperm. Vasectomised males should wear a condom if engaged in sexual activity with a pregnant woman as seminal fluid may still contain pomalidomide in the absence of spermatozoa. All patients (males and females with or without childbearing potential) must agree to abstain from donating blood, semen and sperm while taking pomalidomide and for 7 days after the last dose. It is unknown whether pomalidomide is excreted in human milk. Pomalidomide was detected in milk of lactating rats following administration to the mother. Because of the potential for adverse reactions in breastfed infants from pomalidomide, a decision must be made whether to discontinue breastfeeding or to discontinue the medicinal product, taking into account the benefit of breastfeeding for the child and the benefit of the therapy for the woman (SmPC, Section 4.6). Further details of the risk minimisation measures for the risk of teratogenicity are outlined in Part V.
Impact on the risk-benefit balance of the product	Pomalidomide is structurally related to thalidomide, a known human teratogen, inducing a high frequency (about 30%) of severe and life-threatening birth defects such as: ectromelia (amelia, phocomelia, haemimelia) of the upper and/or lower extremities, microtia with abnormality of the external acoustic meatus (blind or absent), middle and

Table 2.7.3.1-1: Important Identified Risk: Teratogenicity

Teratogenicity	
	internal ear lesions (less frequent), ocular lesions (anophthalmia, microphthalmia), congenital heart disease and renal abnormalities. Potentially severe or life-threatening defects/disability, or foetal death.
Public health impact	Pomalidomide is structurally related to thalidomide, a known human teratogen that causes severe life-threatening birth defects. In 30% of pregnancies exposed to thalidomide in the 1960s, the children have had severe birth defects and mortality at or shortly after birth has been reported at a rate of approximately 40%.[53]
Data source	Studies MM-007, MM-001, MM-002, MM-003 and IFM-2009-02.
MedDRA terms	MM-007 MedDRA v20.0 PTs: pregnancy, pregnancy of partner, pregnancy test positive, abortion, abortion induced, abortion spontaneous, congenital anomaly, and human chorionic gonadotrophin positive. MM-001, MM-002, MM-003, and IFM-2009-02 MedDRA v14.0 PTs: pregnancy, pregnancy of partner, pregnancy test positive, abortion, abortion induced, abortion spontaneous, congenital anomaly, and blood human chorionic gonadotrophin positive.

Important Identified Risk: Severe Infection due to Neutropenia and Pancytopenia

Information concerning the risk of severe infection due to neutropenia and pancytopenia is summarised in Table 2.7.3.1-2.

Table 2.7.3.1-2: Important Identified Risk: Severe Infection due to Neutropenia and Pancytopenia

Severe Infection due to Neutropenia and Pancytopenia	
Potential mechanisms	No mechanism by which pomalidomide may directly cause infection has been established. Infection may be secondary to underlying disease and/or in some cases neutropenia. The pathogenesis of pomalidomide-induced neutropenia and pancytopenia has not been elucidated. Viral infection/reactivation in patients receiving pomalidomide is likely to be caused by many factors including underlying MM, cumulative immunosuppression and a generally older population.
Evidence source and strength of evidence	In non-clinical studies, decreased WBC counts (neutrophils, lymphocytes, and monocytes) were observed. In the clinical studies, infection was the most common non-haematological toxicity reported in patients who received pomalidomide, and approximately half of the events were Grade 3 or 4. The most commonly reported adverse reactions in clinical studies have been blood and lymphatic system disorders

Table 2.7.3.1-2: Important Identified Risk: Severe Infection due to Neutropenia and Pancytopenia

Severe Infection due to Neutropenia and Pancytopenia

including neutropenia, and it is one of the major dose-limiting toxicities of pomalidomide.

Pancytopenia has been identified from postmarketing data. In clinical studies, pancytopenia has been reported as a common ADR of pomalidomide treatment.

Characterization of risk

Frequency with 95% CI

Neutropenia

Study MM-007 (pomalidomide plus bortezomib and low-dose dexamethasone versus bortezomib and low-dose dexamethasone alone)

Study MM-007 (N = 548)		
Identified Risk	**Frequency (95% CI)**	
	Pomalidomide + Bortezomib + Dexamethasone	**Bortezomib + Dexamethasone**
Total neutropenia	47.1% (41.3 to 53.0)	10.7% (7.0 to 14.4)

The total frequency of neutropenia was higher in subjects receiving pomalidomide with bortezomib and low-dose dexamethasone (47.1%) compared to subjects receiving bortezomib and dexamethasone (10.7%).

Concurrent infection events (any grade) in subjects with neutropenia (≥ Grade 3 and ≥ Grade 4) in Study MM-007 are provided below:

Study MM-007 (N = 548)			
Identified Risk	**Statistic**	**Number (%) of Subjects**	
		Pomalidomide + Bortezomib + Dexamethasone	**Bortezomib + Dexamethasone**
Total neutropenia	P/N (%)	142/278 (51.1%)	36/270 (13.3%)
≥ Grade 3			
Total neutropenia ≥ Grade 3	M/N (%)	121/278 (43.5%)	28/270 (10.4%)
Neutropenia ≥ Grade 3 with concurrent infection (any grade)	n/M (%)	40/121 (33.1%)	6/28 (21.4%)

Table 2.7.3.1-2: Important Identified Risk: Severe Infection due to Neutropenia and Pancytopenia

Severe Infection due to Neutropenia and Pancytopenia

Neutropenia ≥ Grade 3 without concurrent infection (any grade)	n/M (%)	81/121 (66.9%)	22/28 (78.6%)
≥ Grade 4			
Total neutropenia ≥ Grade 4	M*/N (%)	38/278 (13.7%)	2/270 (0.7%)
Neutropenia ≥ Grade 4 with concurrent infection (any grade)	n*/M* (%)	16/38 (42.1%)	1/2 (50.0%)
Neutropenia ≥ Grade 4 without concurrent infection (any grade)	n*/M* (%)	22/38 (57.9%)	1/2 (50.0%)

P is the number of subjects with neutropenia AEs (all grades). N is the number of subjects in specific treatment group. M is the number of subjects with neutropenia AEs (≥ Grade 3). n is the number of subjects with neutropenia ≥ Grade 3 with or without concurrent infection (any grade). M* is the number of subjects with neutropenia AEs (≥ Grade 4). n* is the number of subjects with neutropenia ≥ Grade 4 with or without concurrent infection (any grade).

Definition of concurrent infection is infection within 1 week before/after the occurrence of neutropenia, and before or on the end date of infections (if any).

Studies MM-001, MM-002, MM-003, and IFM-2009-02 pooled (all pomalidomide-treated subjects)

Studies MM-001, MM-002, MM-003, and IFM-2009-02 (N = 686)	
Identified Risk	**Frequency (95% CI)**
Total neutropenia	55.1% (51.4 to 58.8)

Events of neutropenia were reported in 378/686 subjects (55.1%; 95% CI, 51.4-58.8). The frequency in all pomalidomide-treated subjects was comparable to the frequency in pomalidomide-treated subjects with RRMM (see below):

Studies MM-002, MM-003, and IFM-2009-02 pooled (pomalidomide-treated subjects with RRMM)

Studies MM-002, MM-003, and IFM-2009-02 (N = 455)	
Identified Risk	**Frequency (95% CI)**
Total neutropenia	55.6% (51.0 to 60.2)

Events of neutropenia were reported in 253/455 subjects (55.6%; 95% CI, 51.0-60.2). Neutropenia ≥ Grade 3 was reported by 234/455 (51.4%) subjects and neutropenia ≥ Grade 4 was reported by 99/455 (21.8%) subjects.

Concurrent infection events (any grade) in subjects with neutropenia (≥ Grade 3 and ≥ Grade 4) in the three studies are provided below:

Studies MM-002, MM-003, and IFM-2009-02 (N = 455)		
Identified Risk	**Statistic**[a]	**Number (%) of Subjects**
Total neutropenia	P/N (%)	253/455 (55.6%)
≥ Grade 3		
Total neutropenia ≥ Grade 3	M/N (%)	234/455 (51.4%)
Neutropenia ≥ Grade 3 with concurrent infection (any grade)	n/M (%)	101/234 (43.2%)
Neutropenia ≥ Grade 3 without concurrent infection (any grade)	n/M (%)	133/234 (56.8%)
≥ Grade 4		
Total neutropenia ≥ Grade 4	M*/N (%)	99/455 (21.8%)
Neutropenia ≥ Grade 4 with concurrent infection (any grade)	n*/M* (%)	34/99 (34.3%)
Neutropenia ≥ Grade 4 without concurrent infection (any grade)	n*/M* (%)	65/99 (65.7%)

[a] P is the number of subjects with neutropenia AEs (all grades). N is the number of subjects in treated with pomalidomide. M is the number of subjects with neutropenia AEs (≥ Grade 3). n is the number of subjects with neutropenia ≥ Grade 3 with or without concurrent infection (any grade). M* is the number of subjects with neutropenia AEs (≥ Grade 4). n* is the number of subjects with neutropenia ≥ Grade 4 with or without concurrent infection (any grade).

Definition of concurrent infection is any grade infection within 2 weeks before/after the occurrence of Grade ≥3 or Grade ≥ 4 neutropenia, and before or on the end date of Grade ≥ 3 or Grade ≥ 4 neutropenia.

Study MM-003 (pomalidomide plus low-dose dexamethasone versus high-dose dexamethasone)

MM-003 (N = 450)		
Identified Risk	**Frequency (95% CI)**	
	Pomalidomide + Dexamethasone	High-dose Dexamethasone

Total neutropenia	56.0% (50.4 to 61.6)	22.7% (16.0 to 29.4)

The total frequency of neutropenia was higher in subjects receiving pomalidomide with dexamethasone (56.0%, compared to 22.7% of subjects receiving high-dose dexamethasone). One subject (0.3%) receiving pomalidomide with dexamethasone discontinued study drug due to neutropenia. No subjects in the high-dose dexamethasone group discontinued study drug due to neutropenia.

Study MM-003 (N = 450)			
Identified Risk	**Statistic**[a]	**Number (%) of Subjects**	
		Pomalidomide + Dexamethasone	**High-dose Dexamethasone**
Total neutropenia	P/N (%)	168/300 (56.0%)	34/150 (22.7%)
≥ Grade 3			
Total neutropenia ≥ Grade 3	M/N (%)	159/300 (53.0%)	27/150 (18.0%)
Neutropenia ≥ Grade 3 with concurrent infection (any grade)	n/M (%)	67/159 (42.1%)	11/27 (40.7%)
Neutropenia ≥ Grade 3 without concurrent infection (any grade)	n/M (%)	92/159 (57.9%)	16/27 (59.3%)
≥ Grade 4			
Total neutropenia ≥ Grade 4	M*/N (%)	71/300 (23.7%)	12/150 (8.0%)
Neutropenia ≥ Grade 4 with concurrent infection (any grade)	n*/M* (%)	24/71 (33.8%)	6/12 (50.0%)
Neutropenia ≥ Grade 4 without concurrent infection (any grade)	n*/M* (%)	47/71 (66.2%)	6/12 (50.0%)

[a] P is the number of subjects with neutropenia AEs (all grades). N is the number of subjects treated with pomalidomide. M is the number of subjects with AEs (≥ Grade 3). n is the number of subjects with neutropenia ≥ Grade 3 with or without concurrent infection (any grade). M* is the number of subjects with neutropenia AEs (≥ Grade 4). n* is the number of subjects with neutropenia ≥ Grade 4 with or without concurrent infection (any grade).

Definition of concurrent infection is any grade infection within 2 weeks before/after the occurrence of Grade ≥ 3 or Grade ≥ 4 neutropenia, and before or on the end date of Grade ≥ 3 or Grade ≥ 4 neutropenia.

Pancytopenia

Study MM-007 (pomalidomide plus bortezomib and low-dose dexamethasone versus bortezomib and low-dose dexamethasone alone)

Table 2.7.3.1-2: Important Identified Risk: Severe Infection due to Neutropenia and Pancytopenia

Severe Infection due to Neutropenia and Pancytopenia

There were no events of pancytopenia in Study MM-007.

Studies MM-002, MM-003, and IFM-2009-02 pooled (pomalidomide-treated subjects with RRMM)

Studies MM-002, MM-003, and IFM-2009-02 (N = 455)	
Identified Risk	**Frequency (95% CI)**
Pancytopenia	1.8% (0.6 to 3.0)

Pancytopenia AEs were reported in 8/455 subjects (1.8%; 95% CI, 0.6-3.0). The frequency of pancytopenia AEs in subjects with RRMM was comparable to that in all pomalidomide-treated subjects from Studies MM-001, MM-002, MM-003 and IFM-2009-02 (1.5%).

Study MM-003 (pomalidomide plus low-dose dexamethasone versus high-dose dexamethasone)

MM-003 (N = 450)		
Identified Risk	**Frequency (95% CI)**	
	Pomalidomide + Dexamethasone	High-dose Dexamethasone
Pancytopenia	2.3% (0.6 to 4.0)	1.3% (0.0 to 3.2)

Pancytopenia AEs were reported at a low frequency in both study groups.

Infection

Study MM-007 (pomalidomide plus bortezomib and low-dose dexamethasone versus bortezomib and low-dose dexamethasone alone)

Study MM-007 (N = 548)		
Identified Risk	**Frequency (95% CI)**	
	Pomalidomide + Bortezomib + Dexamethasone	**Bortezomib + Dexamethasone**
Total infection	80.9% (76.3 to 85.6)	64.8 (59.1 to 70.5)
HBV reactivation	0	0.4 (0.0 to 1.1)
Viral reactivation	3.2% (1.2 to 5.3)	2.6% (0.7 to 4.5)
Cytomegalovirus infection	0	0.4 (0.0 to 1.1)
Herpes virus infection	0.4 (0.0 to 1.1)	0.4 (0.0 to 1.1)
Herpes zoster	2.9% (0.9 to 4.8)	1.5 (0.0 to 2.9)

Events of infection were reported in 225/278 subjects (80.9%; 95% CI, 76.3-85.6) treated with pomalidomide, bortezomib and low-dose

Table 2.7.3.1-2: Important Identified Risk: Severe Infection due to Neutropenia and Pancytopenia

Severe Infection due to Neutropenia and Pancytopenia

dexamethasone versus 175/270 subjects (64.8%; 95% CI 59.1-70.5) treated with bortezomib and low-dose dexamethasone alone. No AEs of HBV reactivation were reported in subjects treated with pomalidomide, bortezomib and low-dose dexamethasone. Events of HBV reactivation were reported in 1/270 subject (0.4%; 95% CI 0.0-1.1) treated with bortezomib and low-dose dexamethasone alone. Events of viral reactivation were reported in 9/278 subjects (3.2%; 95% CI, 1.2-5.3) treated with pomalidomide, bortezomib and low-dose dexamethasone versus 7/270 subjects (2.6%; 95% CI 0.7-4.5) treated with bortezomib and low-dose dexamethasone alone. Concurrent neutropenia events (any grade) in subjects with infection (≥ Grade 3 and ≥ Grade 4) in Study MM-007 are provided below:

Study MM-007 (N = 548)			
Identified Risk	**Statistic**	**Number (%) of Subjects**	
		Pomalidomide + Bortezomib + Dexamethasone	Bortezomib + Dexamethasone
Total infection	P/N (%)	223/278 (80.2%)	175/270 (64.8%)
≥ Grade 3			
Total infection ≥ Grade 3	M/N (%)	88/278 (31.7%)	48/270 (17.8%)
Infection ≥ Grade 3 with concurrent neutropenia (any grade)	n/M (%)	25/88 (28.4%)	4/48 (8.3%)
Infection ≥ Grade 3 without concurrent neutropenia (any grade)	n/M (%)	63/88 (71.6%)	44/48 (91.7%)
≥ Grade 4			
Total infection ≥ Grade 4	M*/N (%)	32/278 (11.5%)	10/270 (3.7%)
Infection ≥ Grade 4 with concurrent neutropenia (any grade)	n*/M* (%)	9/32 (28.1%)	3/10 (30.0%)
Infection ≥ Grade 4 without concurrent neutropenia (any grade)	n*/M* (%)	23/32 (71.9%)	7/10 (70.0%)

P is the number of subjects with infection AEs (all grades). N is the number of subjects in specific treatment group. M is the number of subjects with

Table 2.7.3.1-2: Important Identified Risk: Severe Infection due to Neutropenia and Pancytopenia

Severe Infection due to Neutropenia and Pancytopenia

infection AEs (≥ Grade 3). n is the number of subjects with infection ≥ Grade 3 with or without concurrent neutropenia (any grade). M* is the number of subjects with infection AEs (≥ Grade 4). n* is the number of subjects with infection ≥ Grade 4 with or without concurrent neutropenia (any grade).

Definition of concurrent neutropenia is neutropenia within 1 week before/after the occurrence of infections, and before or on the end date of infections (if any).

Studies MM-001, MM-002, MM-003, and IFM-2009-02 pooled (all pomalidomide-treated subjects)

Studies MM-001, MM-002, MM-003, and IFM-2009-02 (N = 686)	
Identified Risk	**Frequency (95% CI)**
Total infection	67.2% (63.7 to 70.7)
VZV reactivation	2.0% (1.0 to 3.1)
HBV reactivation	0

Events of infections and infestations were reported in 461/686 subjects (67.2%; 95% CI, 63.7-70.7). Events of varicella zoster virus (VZV) reactivation were reported in 14/686 subjects (2.0%; 95% CI, 1.0-3.1). No AEs of HBV reactivation were reported in these studies. The frequency in all pomalidomide-treated subjects was comparable to the frequency in pomalidomide-treated subjects with RRMM (see below):

Studies MM-002, MM-003, and IFM-2009-02 pooled (pomalidomide-treated subjects with RRMM)

Studies MM-002, MM-003, and IFM-2009-02 (N = 455)	
Identified Risk	**Frequency (95% CI)**
Total infection	70.3% (66.1 to 74.5)
VZV reactivation	2.2% (0.9 to 3.5)
HBV reactivation	0

Events of infection were reported in 320/455 subjects (70.3%; 95% CI, 66.1-74.5). Events of VZV reactivation were reported in 10/455 subjects (2.2%; 95% CI, 0.9-3.5). No AEs of HBV reactivation were reported in these studies. Infection ≥ Grade 3 was reported by 164/455 (36.0%) subjects and infection ≥ Grade 4 was reported by 40/455 (8.8%) subjects. Concurrent neutropenia events (any grade) in subjects with infection (≥ Grade 3 and ≥ Grade 4) in the two studies are provided below:

Studies MM-002, MM-003, and IFM-2009-02 (N = 455)		
Identified Risk	**Statistic**[a]	**Number (%) of Subjects**

Total infection	P/N (%)	320/455 (70.3%)
≥ Grade 3		
Total infection ≥ Grade 3	M/N (%)	164/455 (36.0%)
Infection ≥ Grade 3 with concurrent neutropenia (any grade)	n/M (%)	54/164 (32.9%)
Infection ≥ Grade 3 without concurrent neutropenia (any grade)	n/M (%)	110/164 (67.1%)
≥ Grade 4		
Total infection ≥ Grade 4	M*/N (%)	40/455 (8.8%)
Infection ≥ Grade 4 with concurrent neutropenia (any grade)	n*/M* (%)	9/40 (22.5%)
Infection ≥ Grade 4 without concurrent neutropenia (any grade)	n*/M* (%)	31/40 (77.5%)

[a] P is the number of subjects with infection AEs (all grades). N is the number of subjects treated with pomalidomide. M is the number of subjects with infection AEs (≥ Grade 3). n is the number of subjects with infection ≥ Grade 3 with or without concurrent neutropenia (any grade). M* is the number of subjects with infection AEs (≥ Grade 4). n* is the number of subjects with infection ≥ Grade 4 with or without concurrent neutropenia (any grade).

Definition of concurrent neutropenia is any grade neutropenia within 2 weeks before/after the occurrence of Grade ≥ 3 or Grade ≥ 4 infection, and before or on the end date of Grade ≥ 3 or Grade ≥ 4 infection.

Seriousness/Outcomes

Neutropenia

Study MM-007 (pomalidomide plus bortezomib and low-dose dexamethasone versus bortezomib and low-dose dexamethasone alone)

SAEs of neutropenia were reported in 7 (2.5%) subjects treated with pomalidomide, bortezomib and low-dose dexamethasone versus 0 subjects treated with bortezomib and low-dose dexamethasone alone. These were events of febrile neutropenia (5 [1.8%] subjects), neutropenia (1 [0.4%] subject), and neutropenic sepsis (1 [0.4%] subject). The outcomes of these SAEs are provided below:

Outcome	**Neutropenia**	
	Number (%) of Subjects	
	Pomalidomide + Bortezomib + Dexamethasone	**Bortezomib + Dexamethasone**
Recovered/resolved	6 (2.2)	0
Not recovered/not resolved	1 (0.4)	0

Total subjects with SAEs	7 (2.5%)	0

Note: only treatment-emergent SAEs are included in the table.

Studies MM-002, MM-003, and IFM-2009-02 pooled (pomalidomide-treated subjects with RRMM)

SAEs of neutropenia were reported in 35 (7.7%) subjects. These were events of febrile neutropenia (21 [4.6%] subjects), neutropenia (12 [2.6%] subjects), and neutropenic sepsis (3 [0.7%] subjects). The outcomes of these SAEs are provided below:

Outcome	**Neutropenia**
	Number (%) of Subjects
Ongoing at death	1 (0.2%)
Recovered/resolved	30 (6.6%)
Recovered with sequela	3 (0.7%)
Not recovered/not resolved	1 (0.2%)
Total subjects with SAEs	35 (7.7%)

Note: only treatment-emergent SAEs are included in the table.

Study MM-003 (pomalidomide plus low-dose dexamethasone versus high-dose dexamethasone)

SAEs of neutropenia were infrequent to frequent in the study groups (9.7% in subjects receiving pomalidomide with dexamethasone, 0.7% in subjects receiving high-dose dexamethasone).

Outcome	**Neutropenia**	
	Number (%) of Subjects	
	Pomalidomide + Dexamethasone	**High-dose Dexamethasone**
Recovered/resolved	25 (8.3%)	0
Recovered with sequela	3 (1.0%)	0
Not recovered/not resolved	1 (0.3%)	1 (0.7%)
Total subjects with SAEs	29 (9.7%)	1 (0.7%)

Note: only treatment-emergent SAEs are included in the table.

Pancytopenia

Study MM-007 (pomalidomide plus bortezomib and low-dose dexamethasone versus bortezomib and low-dose dexamethasone alone)

There were no events of pancytopenia in Study MM-007.

Studies MM-002, MM-003, and IFM-2009-02 pooled (pomalidomide-treated subjects with RRMM)

SAEs of pancytopenia were reported in 4 (0.9%) subjects. These were events of pancytopenia in 2 (0.4%) subjects, and blood disorder and febrile bone marrow aplasia in 1 (0.2%) subject each. The outcomes of these SAEs are provided below:

Outcome	Pancytopenia
	Number (%) of Subjects
Recovered/resolved	1 (0.2%)
Recovered with sequela	3 (0.7%)
Total subjects with SAEs	4 (0.9%)

Note: only treatment-emergent SAEs are included in the table.

Study MM-003 (pomalidomide plus low-dose dexamethasone versus high-dose dexamethasone)

SAEs of pancytopenia were reported in 3 (1.0%) and 2 (1.3%) subjects in the pomalidomide and dexamethasone and high-dose dexamethasone arms, respectively. In the pomalidomide and dexamethasone arm, these SAEs were events of pancytopenia and blood disorder in 2 (0.7%) and 1 (0.3%) subjects, respectively. In the high-dose dexamethasone arm, these SAEs were events of pancytopenia in 2 (1.3%) subjects.

Outcome	Pancytopenia	
	Number (%) of Subjects	
	Pomalidomide + Dexamethasone	**High-dose Dexamethasone**
Recovered/resolved	0	2 (1.3%)
Recovered with sequela	3 (1.0%)	0
Total subjects with SAEs	3 (1.0%)	2 (1.3%)

Note: only treatment-emergent SAEs are included in the table.

Infection

Study MM-007 (pomalidomide plus bortezomib and low-dose dexamethasone versus bortezomib and low-dose dexamethasone alone)

SAEs of infections were reported in 91 (32.7%) subjects treated with pomalidomide, bortezomib and low-dose dexamethasone versus 48 (17.8%) subjects treated with bortezomib and low-dose dexamethasone alone. The outcomes of these SAEs are provided below:

Outcome	Infection	
	Number (%) of Subjects	
	Pomalidomide + Bortezomib + Dexamethasone	**Bortezomib + Dexamethasone**
Death	11 (4.0%)[a]	3 (1.1%)[b]
Recovered/resolved	68 (24.5%)	36 (13.3%)
Recovering/resolving	5 (1.8%)	1 (0.4%)
Recovered with sequela	3 (1.1%)	1 (0.4%)

Table 2.7.3.1-2: Important Identified Risk: Severe Infection due to Neutropenia and Pancytopenia

Severe Infection due to Neutropenia and Pancytopenia

Not recovered/not resolved	4 (1.4%)	7 (2.6%)
Total subjects with SAEs	91 (32.7%)	48 (17.8%)

[a] Includes PTs of septic shock (2 [0.7%] subjects); Clostridium difficile colitis (1 [0.4%] subject); Escherichia sepsis (1 [0.4%] subject); H1N1 influenza (1 [0.4%] subject); infection (1 [0.4%] subject); influenza (1 [0.4%] subject); pneumonia (1 [0.4%] subject); Pneumonia staphylococcal (1 [0.4%] subject); Staphylococcal sepsis (1 [0.4%] subject); Streptococcal sepsis (1 [0.4%] subject).

[b] Includes PTs of Escherichia sepsis (1 [0.4%] subject); lower respiratory tract infection (1 [0.4%] subject); pneumonia (1 [0.4%] subject).

Note: only treatment-emergent SAEs are included in the table.

SAEs of HBV reactivation (PT: acute hepatitis B) were reported in 1 (0.4%) subject treated with bortezomib and low-dose dexamethasone alone. The outcome of this SAE was recovered/resolved. SAEs of viral reactivation were reported in 1 (0.4%) subject each treated with pomalidomide, bortezomib and low-dose dexamethasone (PT: herpes zoster) and with bortezomib and low-dose dexamethasone alone (PT: acute hepatitis B). The outcomes of SAEs in both subjects were recovered/resolved.

Studies MM-002, MM-003, and IFM-2009-02 pooled (pomalidomide-treated subjects with RRMM)

SAEs of infections and infestations were reported in 168 (36.9%) subjects. Events reported by > 1% of subjects were: pneumonia (81 [17.8%] subjects), sepsis (12 [2.6%] subjects), bronchitis (9 [2.0%] subjects), bronchopneumonia and upper respiratory tract infection (8 [1.8%] subjects each), lung infection and urinary tract infection (7 [1.5%] subjects each), lower respiratory tract infection (6 [1.3%] subjects), respiratory tract infection and septic shock (both 5 [1.1%] subjects). The outcomes of these SAEs are provided below:

Outcome	**Infection**
	Number (%) of Subjects
Death	19 (4.2%)[a]
Ongoing at death	4 (0.9%)
Recovered/resolved	115 (25.3%)
Recovered with sequela	10 (2.2%)
Not recovered/not resolved	16 (3.5%)
Unknown	1 (0.2%)
Not provided	3 (0.7%)

Table 2.7.3.1-2: Important Identified Risk: Severe Infection due to Neutropenia and Pancytopenia

Severe Infection due to Neutropenia and Pancytopenia

Total subjects with SAEs	168 (36.9%)

[a] A total of 9 (2.0%) subjects reported pneumonia. Events of sepsis, bronchopneumonia and lung infection were reported by 2 (0.4%) subjects each. Lower respiratory tract infection, septic shock, pneumonia pneumococcal and klebsiella sepsis were reported by 1 (0.2%) subject each.

Note: only treatment-emergent SAEs are included in the table.

SAEs of VZV reactivation were reported in 3 (0.7%) subjects. These were events of herpes zoster, herpes zoster disseminated and herpes zoster ophthalmic (1 [0.2%] subject each). The outcomes of these SAEs are provided below:

Outcome	**VZV Reactivation**
	Number (%) of Subjects
Recovered/resolved	2 (0.4%)
Not recovered/not resolved	1 (0.2%)
Total subjects with SAEs	3 (0.7%)

Note: only treatment-emergent SAEs are included in the table.

No SAEs of HBV reactivation were reported in these studies.

Study MM-003 (pomalidomide plus low-dose dexamethasone versus high-dose dexamethasone)

The frequency of SAEs of infections and infestations was comparable between the two study groups (36.0% and 28.0% in the pomalidomide with dexamethasone and high dose dexamethasone groups, respectively). The outcomes of these SAEs are provided below:

Outcome	**Infection**	
	Number (%) of Subjects	
	Pomalidomide + Dexamethasone	**High-dose Dexamethasone**
Death	12 (4.0%)[a]	13 (8.7%)[b]
Recovered/resolved	72 (24.0%)	22 (14.7%)
Recovered with sequela	8 (2.7%)	3 (2.0%)
Not recovered/not resolved	15 (5.0%)	4 (2.7%)
Unknown	1 (0.3%)	0
Total subjects with SAEs	108 (36.0%)	42 (28.0%)

Table 2.7.3.1-2: Important Identified Risk: Severe Infection due to Neutropenia and Pancytopenia

Severe Infection due to Neutropenia and Pancytopenia

[a] A total of 4 (1.3%) subjects reported pneumonia. Events of sepsis were reported by 2 (0.7%) subjects. Lower respiratory tract infection, septic shock, bronchopneumonia, lung infection, klebsiella sepsis and pneumonia pneumococcal were reported by 1 (0.3%) subject each.

[b] A total of 5 (3.3%) subjects reported septic shock. Pneumonia was reported by 3 (2.0%) subjects. Sepsis and lower respiratory tract infection were reported by 2 (1.3%) subjects each. Lung infection pseudomonal was reported by 1 (0.7%) subject.

Note: only treatment-emergent SAEs are included in the table.

SAEs of VZV reactivation were reported at a low frequency in subjects receiving pomalidomide with dexamethasone (1 [0.3%] subject) and in subjects receiving high-dose dexamethasone (2 [1.3%] subjects). The outcomes of these SAEs are provided below:

Outcome	**VZV Reactivation**	
	Number (%) of Subjects	
	Pomalidomide + Dexamethasone	**High-dose Dexamethasone**
Recovered/resolved	1 (0.3%)	1 (0.7%)
Recovered with sequela	0	1 (0.7%)
Total subjects with SAEs	1 (0.3%)	2 (1.3%)

Note: only treatment-emergent SAEs are included in the table.

No SAEs of HBV reactivation were reported in this study.

Severity and Nature of Risk

Neutropenia

Study MM-007 (pomalidomide plus bortezomib and low-dose dexamethasone versus bortezomib and low-dose dexamethasone alone)

The severity of SAEs of neutropenia are provided below:

Severity	**Neutropenia**	
	Number (%) of Subjects	
	Pomalidomide + Bortezomib + Dexamethasone	**Bortezomib + Dexamethasone**
Grade 3	5 (1.8%)	0
Grade 4	2 (0.7%)	0
Total	7 (2.5%)	0

No Grade 3 or Grade 4 SAEs of neutropenia were reported in the bortezomib and low-dose dexamethasone group. The SAEs of neutropenia in the pomalidomide plus bortezomib and low-dose dexamethasone group were

Table 2.7.3.1-2: Important Identified Risk: Severe Infection due to Neutropenia and Pancytopenia

Severe Infection due to Neutropenia and Pancytopenia

febrile neutropenia (Grade 3 in 4 [1.4%] subjects, Grade 4 in 1 [0.4%] subject); neutropenia (Grade 3 in 1 [0.4%] subject), and neutropenic sepsis (Grade 4 in 1 [0.4%] subject).

Studies MM-002, MM-003, and IFM-2009-02 pooled (pomalidomide-treated subjects with RRMM)

The severity of SAEs of neutropenia are provided below:

Severity	**Neutropenia**
	Number (%) of Subjects
Grade 3	20 (4.4%)
Grade 4	12 (2.6%)
Total	35 (7.7%)[a]

[a] Includes 3 subjects reporting Grade 2 SAEs.

The SAEs of neutropenia were febrile neutropenia (Grade 3 in 14 [3.1%] subjects, Grade 4 in 5 [1.1%] subjects), neutropenia (Grade 3 in 5 [1.1%] subjects, Grade 4 in 6 [1.3%] subjects), and neutropenic sepsis (Grade 3 in 2 [0.4%] subjects, Grade 4 in 1 [0.2%] subject).

Study MM-003 (pomalidomide plus low-dose dexamethasone versus high-dose dexamethasone)

The severity of SAEs of neutropenia are provided below:

Severity	**Neutropenia**	
	Number (%) of Subjects	
	Pomalidomide + Dexamethasone	**High-dose Dexamethasone**
Grade 3	17 (5.7%)	0
Grade 4	10 (3.3%)	1 (0.7%)
Total	29 (9.7%)[a]	1 (0.7%)

[a] Includes 2 subjects reporting Grade 2 SAEs.

There was a higher frequency of Grade 3 or 4 SAEs of neutropenia in the pomalidomide with dexamethasone group compared to the high-dose dexamethasone group.

Pancytopenia

Study MM-007 (pomalidomide plus bortezomib and low-dose dexamethasone versus bortezomib and low-dose dexamethasone alone)

There were no events of pancytopenia in Study MM-007.

Studies MM-002, MM-003, and IFM-2009-02 pooled (pomalidomide-treated subjects with RRMM)

Table 2.7.3.1-2: Important Identified Risk: Severe Infection due to Neutropenia and Pancytopenia

Severe Infection due to Neutropenia and Pancytopenia

The severity of SAEs of pancytopenia are provided below:

Severity	**Pancytopenia**
	Number (%) of Subjects
Grade 3	2 (0.4%)
Grade 4	2 (0.4%)
Total	4 (0.9%)

Study MM-003 (pomalidomide plus low-dose dexamethasone versus high-dose dexamethasone)

The severity of SAEs of pancytopenia are provided below:

Severity	**Pancytopenia**	
	Number (%) of Subjects	
	Pomalidomide + Dexamethasone	**High-dose Dexamethasone**
Grade 3	1 (0.3%)	2 (1.3%)
Grade 4	2 (0.7%)	0
Total	3 (1.0%)	2 (1.3%)

Two subjects experienced Grade 4 pancytopenia SAEs, both were in the pomalidomide plus dexamethasone arm.

Infection

Study MM-007 (pomalidomide plus bortezomib and low-dose dexamethasone versus bortezomib and low-dose dexamethasone alone)

The severity of SAEs of infection are provided below:

Severity	**Infection**	
	Number (%) of Subjects	
	Pomalidomide + Bortezomib + Dexamethasone	**Bortezomib + Dexamethasone**
Grade 3	49 (17.6%)	32 (11.9%)
Grade 4	19 (6.8%)	6 (2.2%)
Grade 5	11 (4.0%)	3 (1.1%)
Total	91 (32.7%)[a]	48 (17.8%)[b]

[a] Total includes Grade 1 (1 [0.4%] subject) and Grade 2 (11 [4.0%] subjects) SAEs.

[b] Total includes Grade 2 (7 [2.6%] subjects) SAEs.

The most frequently reported severe SAEs of infection were: pneumonia (Grade 3 in 20 [7.2%] subjects, Grade 4 in 6 [2.2%] subjects and Grade 5 in

Table 2.7.3.1-2: Important Identified Risk: Severe Infection due to Neutropenia and Pancytopenia

Severe Infection due to Neutropenia and Pancytopenia

1 [0.4%] subject in the pomalidomide plus bortezomib and low-dose dexamethasone arm versus Grade 3 in 13 [4.8%] subjects, Grade 4 in 1 [0.4%] subject and Grade 5 in 1 [0.4%] subject in the bortezomib and low-dose dexamethasone arm).

The severity of SAEs of HBV reactivation are provided below:

Severity	**HBV Reactivation**	
	Number (%) of Subjects	
	Pomalidomide + Bortezomib + Dexamethasone	**Bortezomib + Dexamethasone**
Grade 3	0	1 (0.4%)
Total	0	1 (0.4%)

The severity of SAEs of Viral Reactivation are provided below:

Severity	**Viral Reactivation**	
	Number (%) of Subjects	
	Pomalidomide + Bortezomib + Dexamethasone	**Bortezomib + Dexamethasone**
Grade 3	0	1 (0.4%)
Total	1 (0.4%)[a]	1 (0.4%)

[a] Total includes a Grade 2 SAE in 1 (0.4%) subject.

Studies MM-002, MM-003, and IFM-2009-02 pooled (pomalidomide-treated subjects with RRMM)

The severity of SAEs of infections and infestations are provided below:

Severity	**Infection**	**VZV Reactivation**	**HBV Reactivation**
	Number (%) of Subjects		
Grade 3	110 (24.2%)	3 (0.7%)	0
Grade 4	20 (4.4%)	0	0
Grade 5	18 (4.0%)	0	0
Total	168 (36.9%)[a]	3 (0.7%)	0

[a] Includes 19 subjects reporting Grade 2 SAEs and 1 subject reporting a Grade 1 SAE.

The most frequently reported severe SAEs of infections and infestations were: pneumonia (Grade 3 in 58 [12.7%] subjects, Grade 4 in 8 [1.8%] subjects and Grade 5 in 8 [1.8%] subjects), sepsis (Grade 3 in 8 [1.8%] subjects, Grade 4 in 1 [0.2%] subject, and Grade 5 in 2 [0.4%] subjects), bronchitis (Grade 3 in 7 [1.5%] subjects), bronchopneumonia (Grade 3 in 4 [0.9%] subjects, Grade 4 in 1 [0.2%] subject and Grade 5 in 2 [0.4%]

Table 2.7.3.1-2: Important Identified Risk: Severe Infection due to Neutropenia and Pancytopenia

Severe Infection due to Neutropenia and Pancytopenia

subjects) and urinary tract infection (Grade 3 in 7 [1.5%] subjects). The SAEs of VZV reactivation were herpes zoster, herpes zoster disseminated and herpes zoster ophthalmic (Grade 3 in 1 [0.2%] subject each). There were no reports of AEs of HBV reactivation in these studies.

Study MM-003 (pomalidomide plus low-dose dexamethasone versus high-dose dexamethasone)

The severity of SAEs of infections and infestations are provided below:

Severity	**Infection**	
	Number (%) of Subjects	
	Pomalidomide + Dexamethasone	**High-dose Dexamethasone**
Grade 3	69 (23.0%)	18 (12.0%)
Grade 4	16 (5.3%)	6 (4.0%)
Grade 5	12 (4.0%)	13 (8.7%)
Total	108 (36.0%)[a]	42 (28.0%)[b]

[a] Includes 11 subjects reporting Grade 2 SAEs.

[b] Includes 5 subjects reporting Grade 2 SAEs.

The severity of SAEs of VZV reactivation are provided below:

Severity	**VZV Reactivation**	
	Number (%) of Subjects	
	Pomalidomide + Dexamethasone	**High-dose Dexamethasone**
Grade 3	1 (0.3%)	1 (0.7%)
Total	1 (0.3%)	2 (1.3%)[a]

[a] Includes 1 subject reporting a Grade 2 SAE.

The severities of SAEs of infections and infestations and of VZV reactivation were comparable between the two study groups.

There were no reports of AEs of HBV reactivation in this study.

Risk factors and risk groups

Neutropenia

By far the most common cause of neutropenia in oncology practice is the myelosuppressive effects of cytotoxic chemotherapy and radiation treatment. Because of their relatively short life spans, neutrophils are particularly sensitive to the effects of recently administered chemotherapy, and nadirs of neutrophil counts are frequently observed 7 to 10 days following the administration of chemotherapy. Less commonly, antibodies to neutrophils, bone marrow infiltration with disruption of normal marrow stromal function, and splenic sequestration can play a role. Although there are several glycoproteins with effects on neutrophil precursor cells including interleukin

Table 2.7.3.1-2: Important Identified Risk: Severe Infection due to Neutropenia and Pancytopenia

Severe Infection due to Neutropenia and Pancytopenia	3, granulocyte macrophage colony stimulating factor, and macrophage colony stimulating factor, G CSF seems to be the primary regulator of basal and emergency neutrophil production as well as mature neutrophil function. There are also negative regulatory factors of neutrophil production that are less well understood, including neutrophil elastase and the src family kinases. Neutropenia can also result from decreased neutrophil survival associated with immune destruction, sequestration, consumption at sites of infection, and the effects of inflammatory cytokines such as tumour necrosis factor.[54] *Pancytopenia* The underlying aetiology and presentation for pancytopenia can include aplastic anaemia, megaloblastic anaemia, MDS, acute lymphoblastic leukaemia, hypersplenism, NHL, MM, acute myeloblastic leukaemia and chronic myelocytic leukaemia.[55] GvHD has also been described within the literature as contributory to the onset of pancytopenia.[56] A comprehensive review of 61 articles and 87 patients with pancytopenia onset after liver transplantation noted the most frequent presenting symptoms prior to the diagnosis of GVHD included rash (94.2%), fever (66.6%), diarrhoea (54%), and pancytopenia (54%). Diabetes mellitus type II may also contribute to the onset of pancytopenia. Several cross sectional studies and case reports have documented that an increased frequency of vitamin B12 deficiency among patients with diabetes mellitus type II is commonly related to inadequate dietary intake or malabsorption. Metformin use has been unequivocally demonstrated as the prime factor associated with vitamin B12 deficiency among patients with diabetes mellitus type II. Studies assessing type 2 diabetic patients on metformin have reported the prevalence of vitamin B12 deficiency to range from 5.8% to 33%. Patients enrolled in this study were those who were on high dose (> 2 g/day) and long-term (4 years) metformin treatment, both clinical factors known to be associated with vitamin B12 deficiency. In the absence of concurrent comorbidity like renal and hepatic dysfunction, recent guidelines advocate for the use of metformin as the first-line glucose lowering agent concurrently with life-style modification approaches. Despite its superior glycaemic lowering effect, metformin has long been shown to decrease vitamin B12 levels compounding the risk of megaloblastic anaemia. The risk of developing metformin associated vitamin B12 deficiency is greatly influenced by increasing age, metformin dose and duration of use.[57] Severe hepatocellular disease has also demonstrated a relative relationship to anaemia and pancytopenia. This may include acute or chronic gastrointestinal haemorrhage, and hypersplenism secondary to portal hypertension. Severe hepatocellular disease predisposes to haemorrhage because of impaired blood coagulation caused by deficiency of blood coagulation factors synthesised by hepatocytes. Aplastic anaemia, which is characterised by pancytopenia and hypocellular bone marrow may follow the development of hepatitis. In patients with chronic liver disease, anaemia may be exacerbated by deficiency of folic acid and/or vitamin B12.[58,59]

Table 2.7.3.1-2: Important Identified Risk: Severe Infection due to Neutropenia and Pancytopenia

Severe Infection due to Neutropenia and Pancytopenia

Without regard to underlying comorbidity, drug-induced pancytopenia is acknowledged with many drug classes. Many patients are on multiple concurrent therapies that may compound the risk of myelosuppressive effects and the induction of pancytopenia. These products, which may be used alone or in combination, include radiotherapy, busulfan, melphalan, cyclophosphamide, anthracyclines, nitrosoureas, amiodarone, chloramphenicol, sulfonamides, gold, anti-inflammatory, anti-thyroid, psychotropic, anticonvulsant and antidepressant drugs.

Infection

Numerous disease-related and chemotherapy-induced factors render the subject with cancer at increased risk for infection.[60] These include the type of cancer, depth and duration of neutropenia, and impairments in cellular function caused by cytotoxic or immunosuppressive drugs; breaches in the integument from surgical procedures, presence of indwelling plastic venous catheters, or mucositis of the gastrointestinal tract secondary to chemotherapy; and comorbid conditions such as malnutrition, deconditioning, or medical problems such as chronic obstructive lung disease or diabetes. In addition, steroid therapy induces a broad immunosuppressive effect, including impaired chemotaxis and killing by neutrophils, impaired T-cell function, and alterations in skin and mucosal barriers. Long-term or high-dose steroid therapy is a significant risk factor for invasive fungal infections in particular; such therapy also may predispose affected subjects to development of bacterial infections and Mycobacterium tuberculosis reactivation.

One US study that utilised the Surveillance, Epidemiology and End Results (SEER)-Medicare database reported that elderly cancer patients run a 1.2 to 2.4 times higher risk of developing VZV than those without cancer. Additional noted risk factors for developing VZV included age, gender, race, immunosuppressive conditions, and certain cancer therapies (eg, haematologic cancer patients: autologous and allogeneic stem cell transplants; solid cancer patients: radiotherapy). Haematologic or solid cancer patients with immunocompromising conditions ran a higher risk of developing VZV, as did haematologic cancer patients who received stem cell transplants (despite the routine use of prophylaxis post-transplant). Cancer patients aged 75 to 85 years old had a higher risk of developing VZV than patients 85 years and older which may be attributed to the different treatment approaches (ie, more aggressive chemotherapies used in younger patients, inducing greater immune suppression) and may lead to different VZV risks.[61] For patients with haematologic malignancies, the risk of developing shingles increases from 13% to 55% the year after a stem cell transplant (SCT).[62]

Risk factors for HBV reactivation include baseline HBV DNA > 105 copies/mL, baseline ALT levels, HBeAg seropositivity, corticosteroid therapy, anthracyclines, rituximab, male sex, younger age, and underlying disease of lymphoma or breast cancer.[63,64] The most common causes of HBV reactivation are the immunosuppression regimens adopted in solid organ transplantation, chemotherapy for onco-haematological diseases and

Table 2.7.3.1-2: Important Identified Risk: Severe Infection due to Neutropenia and Pancytopenia

Severe Infection due to Neutropenia and Pancytopenia	
	immunosuppressive drugs used in the treatment of autoimmune diseases. The immunosuppressive properties related to chemotherapy can cause flares of HBV in people who carry HBsAg in their serum. Flares can occur despite normal baseline serum ALT levels and can lead to HBV-related morbidity and mortality.[65] The rate of HBV reactivation after allogeneic BMT ranges 14% to 50%, with a lesser rate in autologous BMT; risk factors include corticosteroid use, donor HBsAg antibody sero-negativity, and GVHD.[64] The time-to-recovery of cellular immunity after peripheral blood stem cell transplantation is 3 to 5 months, which is the time course during which HBV reactivation has been documented.[66]
Preventability	The major dose-limiting toxicities of pomalidomide include neutropenia. Neutropenia can be managed with dose reduction. Dosing recommendations in the event of neutropenia can be found in Section 4.2 of the SmPC. Subjects may require use of blood product support and/or growth factors (SmPC, Sections 4.2 and 4.4). Monitoring of subjects, particularly in the initial weeks of treatment, is important to reduce the risk of myelosuppression-related complications like infection, fatigue, or weakness. A dose modification may be required (SmPC, Section 4.4). Complete blood cell counts should be monitored at baseline, weekly for the first 8 weeks of pomalidomide treatment and monthly thereafter (SmPC, Section 4.4) to monitor for haematologic adverse reactions, especially neutropenia. Infections and infestations is included in Section 4.8 of the SmPC, with herpes zoster listed as a common ADR and hepatitis B reactivation listed as unknown frequency. Infections text added to Section 4.4 of the SmPC, based on the PRAC Assessment Report for Periodic Safety Update Report (PSUR) 4 (reporting period 08-Feb-2015 to 07-Aug-2015) warns that HBV reactivation has been reported rarely in patients receiving pomalidomide in combination with dexamethasone and some cases led to acute hepatic failure and discontinuation of pomalidomide. This text also advises that HBV status should be established before initiating treatment with pomalidomide and recommends that patients who test positive for HBV infection consult with a physician with expertise in the treatment of hepatitis B. It advises caution when pomalidomide is used in combination with dexamethasone in patients previously infected with HBV. It also advises these patients should be closely monitored for signs and symptoms of active HBV infection throughout therapy. Appropriate statements regarding neutropenia and infections are included in the additional educational materials to be provided to healthcare professionals (HCPs) and subjects as part of the Risk Minimisation Plan. Further details of the risk minimisation measures for the risk of severe infection due to neutropenia and pancytopenia are outlined in Part V.

Table 2.7.3.1-2: Important Identified Risk: Severe Infection due to Neutropenia and Pancytopenia

Severe Infection due to Neutropenia and Pancytopenia	
Impact on the risk-benefit balance of the product	Moderate to severe or medically significant, life-threatening or fatal impact. Topical, oral or IV intervention (antibiotic, antifungal, or antiviral) indicated.
Public health impact	Disorders of blood cell production are frequently observed in subjects with cancer. Neutropenia is often associated with chemotherapeutic intervention. Neutropenia is one of the most frequent adverse reactions of lenalidomide, with a reported incidence of Grade 3 or 4 neutropenia with lenalidomide of approximately 35%, and approximately 11% and 1% with bortezomib and thalidomide, respectively. Analysing 3107 subjects with newly diagnosed MM entered into UK MRC trials from 1980 to 2002,[14] demonstrated that there was a significant correlation between early death and neutropenia ($P < 0.01$), and that death within 60 days of trial entry occurred in 299 subjects (10%). Forty-five percent of these deaths were directly attributable to bacterial infection: pneumonia in 89 (66%), generalised sepsis in 31 (23%) and other infections in 15 (11%). Neutropenia was present at diagnosis in only 11 of the 135 deaths attributed to infection. Neutropenia is a critically important problem in oncology practice for two reasons. First, neutropenia is the major factor driving the risk of life threatening infections, one of the most serious and costly toxicities of cancer treatment.[54] Second, neutropenia frequently results in substantial reductions in the delivered dose intensity of chemotherapy, causing even subjects with curable malignancies to receive less than the planned, optimal antitumour treatment. For both reasons, good neutropenia management is essential in oncology care.[54] Pancytopenia occurs frequently in subjects with malignancies who are receiving myelosuppressive or myeloablative therapies. A Safety Topic Review in which a cumulative search was performed in the BMS safety database through 24-Jul-2013 did not confirm an independent relationship between pomalidomide therapy and the appearance of pancytopenia. The risk minimisation activities put in place to control pancytopenia are considered adequate to prevent the risk of severe pancytopenia. A large study using population-based data from Sweden to estimate the risk of bacterial and viral infections among 9610 MM patients compared to 37,718 matched controls demonstrated that MM patients had a 6-fold (hazard ratio = 5.9; 95% CI = 5.7-6.1) risk of developing any infection compared to matched controls.[67] Infection is frequently associated with early mortality in subjects with MM. Herpes zoster virus-specific cell-mediated immunity keeps VZV in latency and prevents its reactivation.[68] Reviews have reported that the prevalence of latent VZV in the normal population ranges from 63% to 100%.[69] A retrospective analysis reported that in general, MM patients have shown a

Table 2.7.3.1-2: Important Identified Risk: Severe Infection due to Neutropenia and Pancytopenia

Severe Infection due to Neutropenia and Pancytopenia	
	risk of VZV infection of 1% to 4%, increasing with bortezomib treatment or transplants.[70] HBV persists for decades in patients following recovery from acute HBV infection during which it is controlled by the immune system. Therefore, situations that lead to immunosuppression in patients with chronic HBV infection may alter the natural history of this infection and give rise to reactivation.
Data source	Studies MM-007, MM-001, MM-002, MM-003, and IFM-2009-02.
MedDRA terms	MM-007 MedDRA v20.0 PTs: agranulocytosis, autoimmune neutropenia, cyclic neutropenia, febrile neutropenia, granulocyte count decreased, granulocytopenia, idiopathic neutropenia, leukopenia, myelocyte count decreased, myelocyte percentage decreased, neutropenia, neutrophil count decreased, neutrophil percentage decreased, white blood cell analysis abnormal, white blood cell count decreased are collectively referred to as neutropenia. MedDRA v20.0 PTs within the broad scope of sub-SMQ haematopoietic cytopenias affecting more than one type of blood cell and under the HLT marrow depression and hypoplastic anaemias are collectively referred to as pancytopenia. PTs listed within the MedDRA v20.0 system organ class of infections and infestations are collectively referred to as infection. For data regarding viral reactivation, the MedDRA v20.0 PTs of: acquired immunodeficiency syndrome, acute hepatitis B, acute hepatitis C, acute HIV infection, adenoviral hepatitis, AIDS cholangiopathy, AIDS related complex, AIDS related complication, AIDS retinopathy, asymptomatic HIV infection, asymptomatic viral hepatitis, BK virus infection, blood HCV RNA below assay limit, blood HIV RNA below assay limit, blood HIV RNA decreased, blood HIV RNA fluctuation, blood HIV RNA increased, chronic hepatitis B, chronic hepatitis C, congenital cytomegalovirus infection, congenital hepatitis B infection, congenital HIV infection, cytomegalovirus chorioretinitis, cytomegalovirus colitis, cytomegalovirus duodenitis, cytomegalovirus enteritis, cytomegalovirus enterocolitis, cytomegalovirus gastritis, cytomegalovirus gastroenteritis, cytomegalovirus gastrointestinal infection, cytomegalovirus gastrointestinal ulcer, cytomegalovirus hepatitis, cytomegalovirus infection, cytomegalovirus mononucleosis, cytomegalovirus mucocutaneous ulcer, cytomegalovirus myelomeningoradiculitis, cytomegalovirus myocarditis, cytomegalovirus nephritis, cytomegalovirus oesophagitis, cytomegalovirus pancreatitis, cytomegalovirus pericarditis, cytomegalovirus syndrome, cytomegalovirus test positive, cytomegalovirus urinary tract infection, cytomegalovirus viraemia, disseminated cytomegaloviral infection, disseminated varicella zoster vaccine virus infection, encephalitis cytomegalovirus, encephalitis post varicella, end stage AIDS, enterocolitis AIDS, Epstein-Barr virus positive mucocutaneous ulcer, Epstein-Barr viraemia, Epstein-Barr virus antibody, Epstein-Barr virus antibody positive, Epstein-Barr virus antigen positive, Epstein-Barr virus associated lymphoma, Epstein-Barr virus

Table 2.7.3.1-2: Important Identified Risk: Severe Infection due to Neutropenia and Pancytopenia

Severe Infection due to Neutropenia and Pancytopenia	associated lymphoproliferative disorder, Epstein-Barr virus infection, Epstein-Barr virus test positive, Gianotti-Crosti syndrome, HBV-DNA polymerase increased, hepatitis A, hepatitis A antibody, hepatitis A antibody abnormal, hepatitis A antibody normal, hepatitis A antibody positive, hepatitis A antigen, hepatitis A antigen positive, hepatitis A virus test positive, hepatitis B, hepatitis B antibody, hepatitis B antibody abnormal, hepatitis B antibody positive, hepatitis B antigen, hepatitis B antigen positive, hepatitis B core antibody, hepatitis B core antibody positive, hepatitis B core antigen, hepatitis B core antigen positive, hepatitis B DNA assay positive, hepatitis B DNA decreased, hepatitis B DNA increased, hepatitis B e antibody, hepatitis B e antibody positive, hepatitis B e antigen, hepatitis B e antigen positive, hepatitis B reactivation, hepatitis B surface antibody, hepatitis B surface antibody positive, hepatitis B surface antigen, hepatitis B surface antigen positive, hepatitis B virus test positive, hepatitis C, hepatitis C antibody, hepatitis C antibody positive, hepatitis C core antibody, hepatitis C core antibody positive, hepatitis C RNA, hepatitis C RNA decreased, hepatitis C RNA fluctuation, hepatitis C RNA increased, hepatitis C RNA positive, hepatitis C virus test positive, hepatitis D, hepatitis D antibody, hepatitis D antibody positive, hepatitis D antigen, hepatitis D antigen positive, hepatitis D RNA, hepatitis D RNA positive, hepatitis D virus test positive, hepatitis E, hepatitis E antibody, hepatitis E antibody abnormal, hepatitis E antibody positive, hepatitis E antigen, hepatitis E antigen positive, hepatitis E virus test positive, hepatitis F, hepatitis G, hepatitis H, hepatitis infectious, hepatitis infectious mononucleosis, hepatitis mumps, hepatitis non-A non-B, hepatitis non-A non-B non-C, hepatitis post transfusion, hepatitis viral, hepatitis viral test positive, hepatitis virus-associated nephropathy, herpes simplex encephalitis, herpes simplex hepatitis, herpes simplex test positive, herpes virus infection, herpes virus test, herpes virus test abnormal, herpes zoster, herpes zoster cutaneous disseminated, herpes zoster disseminated, herpes zoster infection neurological, herpes zoster oticus, HIV antibody, HIV antibody positive, HIV antigen, HIV antigen positive, HIV associated nephropathy, HIV cardiomyopathy, HIV enteropathy, HIV infection, HIV infection CDC category A, HIV infection CDC category B, HIV infection CDC category C, HIV infection CDC Group I, HIV infection CDC Group II, HIV infection CDC Group III, HIV infection CDC group IV, HIV infection CDC Group IV subgroup A, HIV infection CDC Group IV subgroup B, HIV infection CDC Group IV subgroup C1, HIV infection CDC Group IV subgroup C2, HIV infection CDC Group IV subgroup D, HIV infection CDC Group IV subgroup E, HIV infection WHO clinical stage I, HIV infection WHO clinical stage II, HIV infection WHO clinical stage III, HIV infection WHO clinical stage IV, HIV lipodystrophy, HIV peripheral neuropathy, HIV test positive, HIV viraemia, HIV wasting syndrome, HIV-associated neurocognitive disorder, human herpes virus 6 serology positive, human herpes virus 8 test positive, human herpesvirus 8 infection, human polyomavirus infection, immune reconstitution inflammatory syndrome associated Kaposi's sarcoma, infectious mononucleosis, JC virus infection, JC virus test positive, Kaposi's sarcoma, Kaposi's sarcoma AIDS related, lymphoma AIDS related, lymphoproliferative disorder, lymphoproliferative disorder in remission, meningitis herpes, meningoencephalitis herpetic, ophthalmic herpes simplex, ophthalmic herpes zoster, oral hairy leukoplakia,

Table 2.7.3.1-2: Important Identified Risk: Severe Infection due to Neutropenia and Pancytopenia

Severe Infection due to Neutropenia and Pancytopenia	perinatal HBV infection, perinatal HIV infection, persistent generalised lymphadenopathy, pneumonia cytomegaloviral, pneumonia herpes viral, polyomavirus test positive, polyomavirus-associated nephropathy, post transplant lymphoproliferative disorder, progressive multifocal leukoencephalopathy, retroviral infection, retroviral rebound syndrome, varicella, varicella virus test positive, viral hepatitis carrier, X-linked lymphoproliferative syndrome. For data regarding HBV reactivation, the MedDRA v20.0 PTs of: acute hepatitis B, adenoviral hepatitis, asymptomatic viral hepatitis, chronic hepatitis B, congenital hepatitis B infection, Gianotti-Crosti syndrome, hepatitis B, hepatitis B antibody, hepatitis B antibody abnormal, hepatitis B antibody negative, hepatitis B antibody normal, hepatitis B antibody positive, hepatitis B antigen, hepatitis B antigen positive, hepatitis B core antibody, hepatitis B core antibody negative, hepatitis B core antibody positive, hepatitis B core antigen, hepatitis B core antigen positive, hepatitis B DNA assay, hepatitis B DNA assay negative, hepatitis B DNA assay positive, hepatitis B DNA decreased, hepatitis B DNA increased, hepatitis B e antibody, hepatitis B e antibody negative, hepatitis B e antibody positive, hepatitis B e antigen, hepatitis B e antigen negative, hepatitis B e antigen positive, hepatitis B immunisation, hepatitis B reactivation, hepatitis B surface antibody, hepatitis B surface antibody negative, hepatitis B surface antibody positive, hepatitis B surface antigen, hepatitis B surface antigen negative, hepatitis B surface antigen positive, hepatitis B test negative, hepatitis B virus test, hepatitis B virus test positive, hepatitis infectious, hepatitis infectious mononucleosis, hepatitis post transfusion, hepatitis viral, hepatitis viral test, hepatitis viral test negative, hepatitis viral test positive, hepatitis virus-associated nephropathy, herpes simplex hepatitis, perinatal HBV infection, withdrawal hepatitis. MM-001, MM-002, MM-003, and IFM-2009-02 The MedDRA v14.0 PTs listed within the HLT for neutropenias are collectively referred to as neutropenia. The MedDRA v14.0 PTs within the broad scope of sub-SMQ haematopoietic cytopenias affecting more than one type of blood cell and under the HLT marrow depression and hypoplastic anaemias are collectively referred to as pancytopenia. PTs listed within the MedDRA v14.0 system organ class of infections and infestations are collectively referred to as infection. For the update of data regarding viral reactivation, the MedDRA v14.0 PTs of congenital varicella infection, herpes zoster, herpes zoster disseminated, herpes zoster infection neurological, herpes zoster multi-dermatomal, herpes zoster ophthalmic, herpes zoster oticus, varicella, varicella immunisation, varicella post vaccine and varicella virus test positive are collectively known as VZV reactivation. The MedDRA v14.0 PTs of adenoviral hepatitis, asymptomatic viral hepatitis, congenital hepatitis B infection, Gianotti-Crosti syndrome, hepatitis B, hepatitis B antibody, hepatitis B antibody abnormal, hepatitis B antibody negative, hepatitis B antibody normal, hepatitis B antibody

Table 2.7.3.1-2: Important Identified Risk: Severe Infection due to Neutropenia and Pancytopenia

Severe Infection due to Neutropenia and Pancytopenia	
	positive, hepatitis B antigen, hepatitis B antigen positive, hepatitis B core antigen, hepatitis B core antigen positive, hepatitis B DNA assay, hepatitis B DNA assay negative, hepatitis B DNA assay positive, hepatitis B DNA decreased, hepatitis B DNA increased, hepatitis B e antigen, hepatitis B e antigen negative, hepatitis B e antigen positive, hepatitis B immunisation, hepatitis B surface antigen, hepatitis B surface antigen negative, hepatitis B surface antigen positive, hepatitis B test negative, hepatitis B virus test, hepatitis B virus test positive, hepatitis infectious, hepatitis infectious mononucleosis, hepatitis post transfusion, hepatitis viral, hepatitis viral test, hepatitis virus-associated nephropathy, herpes simplex hepatitis, and withdrawal hepatitis are collectively known as HBV reactivation.

Important Identified Risk: Thrombocyopenia and Bleeding

Information concerning the risk of thrombocytopenia and bleeding is summarised in Table 2.7.3-3.

Table 2.7.3.1-3: Important Identified Risk: Thrombocytopenia and Bleeding

Thrombocytopenia and Bleeding	
Potential mechanisms	The pathogenesis of pomalidomide-induced thrombocytopenia has not been described.
Evidence source and strength of evidence	Decreased platelets in the blood and bleeding occur due to MM so may occur during treatment with pomalidomide in combination with dexamethasone. In addition, pomalidomide may cause reductions in platelet numbers which make patients more prone to bleeding.
Characterization of risk	**Frequency with 95% CI** *Study MM-007 (pomalidomide plus bortezomib and low-dose dexamethasone versus bortezomib and low-dose dexamethasone alone)*

Study MM-007 (N = 548)		
Identified Risk	**Frequency (95% CI)**	
	Pomalidomide + Bortezomib + Dexamethasone	**Bortezomib + Dexamethasone**
Total thrombocytopenias	36.7% (31.0 to 42.4)	39.3% (33.4 to 45.1)
Total bleeding	17.3% (12.8 to 21.7)	15.9% (11.6 to 20.3)
Intracranial haemorrhage	0.4% (0.0 to 1.1)	0
Gastrointestinal haemorrhage	1.4% (0.0 to 2.8)	3.0 (0.9 to 5.0)

The total frequencies of thrombocytopenia, bleeding, intracranial haemorrhage and gastrointestinal haemorrhage were comparable between

Table 2.7.3.1-3: Important Identified Risk: Thrombocytopenia and Bleeding

Thrombocytopenia and Bleeding

the two study groups. Concurrent bleeding events (any grade) in subjects with thrombocytopenia (≥ Grade 3 and ≥ Grade 4) in Study MM-007 are provided below:

Study MM-007 (N = 548)			
Identified Risk	**Statistic**	**Number (%) of Subjects**	
		Pomalidomide + Bortezomib + Dexamethasone	**Bortezomib + Dexamethasone**
Total thrombocytopenia	P/N (%)	102/278 (36.7%)	106/270 (39.3%)
≥ Grade 3			
Total thrombocytopenia ≥ Grade 3	M/N (%)	76/278 (27.3%)	80/270 (29.6%)
Thrombocytopenia ≥ Grade 3 with concurrent bleeding (any grade)	n/M (%)	10/76 (13.2%)	16/80 (20.0%)
Thrombocytopenia ≥ Grade 3 without concurrent bleeding (any grade)	n/M (%)	66/76 (86.8%)	64/80 (80.0%)
≥ Grade 4			
Total thrombocytopenia ≥ Grade 4	M*/N (%)	49/278 (17.6%)	31/270 (11.5%)
Thrombocytopenia ≥ Grade 4 with concurrent bleeding (any grade)	n*/M* (%)	8/49 (16.3%)	5/31 (16.1%)
Thrombocytopenia ≥ Grade 4 without concurrent bleeding (any grade)	n*/M* (%)	41/49 (83.7%)	26/31 (83.9%)

P is the number of subjects with thrombocytopenia AEs (all grades). N is the number of subjects in specific treatment group. M is the number of subjects with thrombocytopenia AEs (≥ Grade 3). n is the number of subjects with thrombocytopenia ≥ Grade 3 with or without concurrent bleeding (any grade). M* is the number of subjects with thrombocytopenia

Table 2.7.3.1-3: Important Identified Risk: Thrombocytopenia and Bleeding

Thrombocytopenia and Bleeding

AEs (≥ Grade 4). n* is the number of subjects with thrombocytopenia ≥ Grade 4 with or without concurrent bleeding (any grade).

Definition of concurrent bleeding is bleeding of any grade within 1 week before/after the occurrence of thrombocytopenia and before or on the end date of thrombocytopenia (if any).

Studies MM-001, MM-002, MM-003, and IFM-2009-02 pooled (all pomalidomide-treated subjects)

Studies MM-001, MM-002, MM-003, and IFM-2009-02 (N = 686)	
Identified Risk	**Frequency (95% CI)**
Total thrombocytopenias	29.7% (26.3 to 33.2)
Total bleeding	22.3% (19.2 to 25.4)
Intracranial haemorrhage	1.7% (0.8 to 2.7)
Gastrointestinal haemorrhage	2.8% (1.5 to 4.0)

Events of thrombocytopenia were reported in 204/686 subjects (29.7%; 95% CI, 26.3-33.2). Events of bleeding were reported in 153/686 subjects (22.3%; 95% CI, 19.2-25.4). Events of intracranial haemorrhage were reported in 12/686 subjects (1.7%; 95% CI, 0.8-2.7). Events of gastrointestinal haemorrhage were reported in 19/686 subjects (2.8%; 95% CI, 1.5-4.0). The frequency in all pomalidomide-treated subjects was comparable to the frequency in pomalidomide-treated subjects with RRMM (see below):

Studies MM-002, MM-003, and IFM-2009-02 pooled (pomalidomide-treated subjects with RRMM)

Studies MM-002, MM-003, and IFM-2009-02 (N = 455)	
Identified Risk	**Frequency (95% CI)**
Total thrombocytopenias	31.9% (27.6 to 36.1)
Total bleeding	21.3% (17.6 to 25.1)
Intracranial haemorrhage	2.0% (0.7 to 3.3)
Gastrointestinal haemorrhage	2.2% (0.9 to 3.5)

Events of thrombocytopenia were reported in 145/455 subjects (31.9%; 95% CI, 27.6-36.1). Events of bleeding were reported in 97/455 subjects (21.3%; 95% CI, 17.6-25.1). Events of intracranial haemorrhage were reported in 9/455 subjects (2.0%; 95% CI, 0.7-3.3). Events of gastrointestinal haemorrhage were reported in 10/455 subjects (2.2%; 95% CI, 0.9-3.5).

Events of thrombocytopenia were mostly Grade 3 to 4 events and rarely were the cause of discontinuing treatment (3 [0.7%] subjects). Thrombocytopenia ≥ Grade 3 was reported by 109/455 (24.0%) subjects and thrombocytopenia ≥ Grade 4 was reported by 66/455 (14.5%) subjects. Concurrent bleeding events (any grade) in subjects with thrombocytopenia (≥ Grade 3 and ≥ Grade 4) in the three studies are provided below:

Table 2.7.3.1-3: Important Identified Risk: Thrombocytopenia and Bleeding

Thrombocytopenia and Bleeding

Studies MM-002, MM-003, and IFM-2009-02 (N = 455)		
Identified Risk	**Statistic**[a]	**Number (%) of Subjects**
Total thrombocytopenias	P/N (%)	145/455 (31.9%)
≥ Grade 3		
Total thrombocytopenias ≥ Grade 3	M/N (%)	109/455 (24.0%)
Thrombocytopenias ≥ Grade 3 with concurrent bleeding (any grade)	n/M (%)	28/109 (25.7%)
Thrombocytopenias ≥ Grade 3 without concurrent bleeding (any grade)	n/M (%)	81/109 (74.3%)
≥ Grade 4		
Total thrombocytopenias ≥ Grade 4	M*/N (%)	66/455 (14.5%)
Thrombocytopenias ≥ Grade 4 with concurrent bleeding (any grade)	n*/M* (%)	19/66 (28.8%)
Thrombocytopenias ≥ Grade 4 without concurrent bleeding (any grade)	n*/M* (%)	47/66 (71.2%)

[a] P is the number of subjects with thrombocytopenia AEs (all grades). N is the number of subjects treated with pomalidomide. M is the number of subjects with thrombocytopenia AEs (≥ Grade 3). n is the number of subjects with thrombocytopenia ≥ Grade 3 with or without concurrent bleeding (any grade). M* is the number of subjects with thrombocytopenia AEs (≥ Grade 4). n* is the number of subjects with thrombocytopenia ≥ Grade 4 with or without concurrent bleeding (any grade).

Definition of concurrent bleeding is any grade bleeding within 2 weeks before/after the occurrence of Grade ≥ 3 or Grade ≥ 4 thrombocytopenia, and before or on the end date of Grade ≥ 3 or Grade ≥ 4 thrombocytopenia.

Note: all subjects were required to receive anticoagulants in these studies.

Study MM-003 (pomalidomide plus low-dose dexamethasone versus high-dose dexamethasone)

MM-003 (N = 450)		
Identified Risk	**Frequency (95% CI)**	
	Pomalidomide + Dexamethasone	**High-dose Dexamethasone**
Total thrombocytopenias	32.3% (27.0 to 37.6)	31.3% (23.9 to 38.8)
Total bleeding	21.3% (16.7 to 26.0)	24.0% (17.2 to 30.8)
Intracranial haemorrhage	1.7% (0.2 to 3.1)	0.7% (0.0 to 2.0)

Table 2.7.3.1-3: Important Identified Risk: Thrombocytopenia and Bleeding

Thrombocytopenia and Bleeding

Gastrointestinal haemorrhage	2.7% (0.8 to 4.5)	4.0% (0.9 to 7.1)

The total frequencies of thrombocytopenia, bleeding, intracranial haemorrhage and gastrointestinal haemorrhage were comparable between the two study groups.

Study MM-003 (N = 450)			
Identified Risk	**Statistic**[a]	**Number (%) of Subjects**	
		Pomalidomide + Dexamethasone	**High-dose Dexamethasone**
Total thrombocytopenias	P/N (%)	97/300 (32.3%)	47/150 (31.3%)
≥ Grade 3			
Total thrombocytopenias ≥ Grade 3	M/N (%)	74/300 (24.7%)	41/150 (27.3%)
Thrombocytopenias ≥ Grade 3 with concurrent bleeding (any grade)	n/M (%)	21/74 (28.4%)	11/41 (26.8%)
Thrombocytopenias ≥ Grade 3 without concurrent bleeding (any grade)	n/M (%)	53/74 (71.6%)	30/41 (73.2%)
≥ Grade 4			
Total thrombocytopenias ≥ Grade 4	M*/N (%)	45/300 (15.0%)	26/150 (17.3%)
Thrombocytopenias ≥ Grade 4 with concurrent bleeding (any grade)	n*/M* (%)	17/45 (37.8%)	9/26 (34.6%)
Thrombocytopenias ≥ Grade 4 without concurrent bleeding (any grade)	n*/M* (%)	28/45 (62.2%)	17/26 (65.4%)

[a] P is the number of subjects with thrombocytopenia AEs (all grades). N is the number of subjects treated with pomalidomide. M is the number of subjects with thrombocytopenia AEs (≥ Grade 3). n is the number of subjects with thrombocytopenia ≥ Grade 3 with or without concurrent bleeding (any grade). M* is the number of subjects with thrombocytopenia AEs (≥ Grade 4). n* is the number of subjects with thrombocytopenia ≥ Grade 4 with or without concurrent bleeding (any grade).

Definition of concurrent bleeding is any grade bleeding within 2 weeks before/after the occurrence of Grade ≥ 3 or Grade ≥ 4 thrombocytopenia, and before or on the end date of Grade ≥ 3 or Grade ≥ 4 thrombocytopenia.

Note: all subjects were required to receive anticoagulants in this study.

Table 2.7.3.1-3: Important Identified Risk: Thrombocytopenia and Bleeding

Thrombocytopenia and Bleeding

Based on the frequencies and 95% CIs reported with the pooled safety data, and comparator data from MM-003, thrombocytopenia and bleeding has been classified as an identified risk.

Seriousness/Outcomes

Study MM-007 (pomalidomide plus bortezomib and low-dose dexamethasone versus bortezomib and low-dose dexamethasone alone)

SAEs of thrombocytopenia (PT: thrombocytopenia) were reported in 1 (0.4%) subject treated with pomalidomide, bortezomib and low-dose dexamethasone versus 3 (1.1%) subjects treated with bortezomib and low-dose dexamethasone alone. The outcomes of these SAEs are provided below:

Outcome	**Total Thrombocytopenias**	
	Number (%) of Subjects	
	Pomalidomide + Bortezomib + Dexamethasone	**Bortezomib + Dexamethasone**
Recovered/resolved	1 (0.4%)	1 (0.4%)
Recovering/resolving	0	1 (0.4%)
Not recovered/not resolved	0	1 (0.4%)
Total subjects with SAEs	1 (0.4%)	3 (1.1%)

SAEs of bleeding were reported in 3 (1.1%) subjects treated with pomalidomide, bortezomib and low-dose dexamethasone versus 6 (2.2%) subjects treated with bortezomib and low-dose dexamethasone alone. These events were cerebral haemorrhage, gastric haemorrhage and urinary bladder haemorrhage, each reported in 1 (0.4%) subject treated with pomalidomide, bortezomib and low-dose dexamethasone; gastrointestinal haemorrhage, haemorrhoidal haemorrhage, haemothorax, lower gastrointestinal haemorrhage, osteorrhagia, post procedural haemorrhage, retroperitoneal haemorrhage and subcutaneous haematoma, each reported in 1 (0.4%) subject treated with bortezomib and low-dose dexamethasone alone. The outcomes of these SAEs are provided below:

Outcome	**Total Bleeding**	
	Number (%) of Subjects	
	Pomalidomide + Bortezomib + Dexamethasone	**Bortezomib + Dexamethasone**
Death	1 (0.4%)[a]	1 (0.4%)[b]
Recovered/resolved	1 (0.4%)	5 (1.9%)

Table 2.7.3.1-3: Important Identified Risk: Thrombocytopenia and Bleeding

Thrombocytopenia and Bleeding

Not recovered/not resolved	1 (0.4%)	0
Total subjects with SAEs	3 (1.1%)	6 (2.2%)

[a] PT: cerebral haemorrhage.

[b] osteorrhagia.

A fatal SAE of intracranial haemorrhage (PT: cerebral haemorrhage) was reported in 1 (0.4%) subject treated with pomalidomide, bortezomib and low-dose dexamethasone. There were no SAEs of intracranial haemorrhage in subjects treated with bortezomib and low-dose dexamethasone alone.

SAEs of gastrointestinal haemorrhage were reported in 1 (0.4%) subject treated with pomalidomide, bortezomib and low-dose dexamethasone (PT: gastric haemorrhage) versus 3 (1.1%) subjects treated with bortezomib and low-dose dexamethasone alone (PTs: gastrointestinal haemorrhage, haemorrhoidal haemorrhage and lower gastrointestinal haemorrhage, each reported in 1 [0.4%] subject). The outcomes of these SAEs are provided below:

Outcome	**Gastrointestinal Haemorrhage**	
	Number (%) of Subjects	
	Pomalidomide + Bortezomib + Dexamethasone	**Bortezomib + Dexamethasone**
Death	0	0
Recovered/resolved	0	3 (1.1%)
Not recovered/not resolved	1 (0.4%)	0
Total subjects with SAEs	1 (0.4%)	3 (1.1%)

Studies MM-002, MM-003, and IFM-2009-02 pooled (pomalidomide-treated subjects with RRMM)

SAEs of thrombocytopenia were reported in 9 (2.0%) subjects. These were events of thrombocytopenia (8 [1.8%] subjects) and platelet count decreased (1 [0.2%] subject). The outcomes of these SAEs are provided below:

Outcome	**Total Thrombocytopenias**
	Number (%) of Subjects
Recovered/resolved	4 (0.9%)
Not recovered/not resolved	5 (1.1%)
Total subjects with SAEs	9 (2.0%)

Note: only treatment-emergent SAEs are included in the table.

Table 2.7.3.1-3: Important Identified Risk: Thrombocytopenia and Bleeding

Thrombocytopenia and Bleeding

SAEs of bleeding were reported in 16 (3.5%) subjects. These included events of epistaxis which was reported by 3 (0.7%) subjects; cerebral haemorrhage, subarachnoid haemorrhage and subdural haematoma, which were reported by 2 (0.4%) subjects each; and catheter site haemorrhage, gastrointestinal haemorrhage, haemorrhage intracranial, haemorrhagic anaemia, haemorrhagic stroke, Mallory-Weiss syndrome, melaena, post procedural haematoma, retroperitoneal haemorrhage and upper gastrointestinal haemorrhage, which were reported by 1 (0.2%) subject each. The outcomes of these SAEs are provided below:

Outcome	**Total Bleeding**
	Number (%) of Subjects
Death	7 (1.5%)[a]
Recovered/resolved	6 (1.3%)
Recovered with sequela	1 (0.2%)
Not recovered/not resolved	2 (0.4%)
Total subjects with SAEs	16 (3.5%)

[a] A total of 2 (0.4%) subjects each reported cerebral haemorrhage and subarachnoid haemorrhage. Events of subdural haematoma, haemorrhage intracranial, and haemorrhagic stroke were reported by 1 (0.2%) subjects each.

Note: only treatment-emergent SAEs are included in the table.

SAEs of intracranial haemorrhage were reported in 8 (1.8%) subjects. These were events of cerebral haemorrhage, subarachnoid haemorrhage, and subdural haematoma (2 [0.4%] subjects each); and cerebrovascular accident (CVA), haemorrhage intracranial, and haemorrhagic stroke (1 [0.2%] subject each). The outcomes of these SAEs are provided below:

Outcome	**Intracranial Haemorrhage**
	Number (%) of Subjects
Death	7 (1.5%)
Recovered/resolved	1 (0.2%)
Total subjects with SAEs	8 (1.8%)

Note: only treatment-emergent SAEs are included in the table.

SAEs of gastrointestinal haemorrhage were reported in 3 (0.7%) subjects. These were events of gastrointestinal haemorrhage, Mallory-Weiss syndrome, Melaena and upper gastrointestinal haematoma (1 [0.2%] subjects each). The outcomes of these SAEs are provided below:

Outcome	**Gastrointestinal Haemorrhage**
	Number (%) of Subjects
Recovered/resolved	3 (0.7%)
Total subjects with SAEs	3 (0.7%)

Table 2.7.3.1-3: Important Identified Risk: Thrombocytopenia and Bleeding

Thrombocytopenia and Bleeding

Note: only treatment-emergent SAEs are included in the table.

Study MM-003 (pomalidomide plus low-dose dexamethasone versus high-dose dexamethasone)

The frequency of SAEs of thrombocytopenia was comparable between the two study groups (2.3% and 2.7% in the pomalidomide with dexamethasone and high-dose dexamethasone groups, respectively). The outcomes of these SAEs are provided below:

Outcome	**Total Thrombocytopenias**	
	Number (%) of Subjects	
	Pomalidomide + Dexamethasone	**High-dose Dexamethasone**
Recovered/resolved	2 (0.7%)	2 (1.3%)
Not recovered/not resolved	5 (1.7%)	2 (1.3%)
Total subjects with SAEs	7 (2.3%)	4 (2.7%)

Note: only treatment-emergent SAEs are included in the table.

The frequency of SAEs of bleeding was comparable between the two study groups (3.7% and 2.0% in the pomalidomide with dexamethasone and high-dose dexamethasone groups, respectively). The outcomes of these SAEs are provided below:

Outcome	**Total Bleeding**	
	Number (%) of Subjects	
	Pomalidomide + Dexamethasone	**High-dose Dexamethasone**
Death	3 (1.0%)[a]	1 (0.7%)[b]
Recovered/resolved	5 (1.7%)	1 (0.7%)
Recovered with sequela	1 (0.3%)	0
Not recovered/not resolved	2 (0.7%)	1 (0.7%)
Total subjects with SAEs	11 (3.7%)	3 (2.0%)

[a] Cerebral haemorrhage, subarachnoid haemrroage and subdural haematoma were reported by 1 (0.3%) subject each.

[b] One (0.7%) subject reported gastrointestinal haemorrhage.

The frequency of SAEs of intracranial haemorrhage was higher in the pomalidomide with dexamethasone group compared to the high-dose dexamethasone group (1.3% versus 0.7%). However, the median treatment duration in the pomalidomide with dexamethasone group (18.2 weeks) was longer than in the high-dose dexamethasone group (8.0 weeks), which means that those patients had a longer time in order to experience an event of intracranial haemorrhage.

The outcomes of these SAEs are provided below:

Table 2.7.3.1-3: Important Identified Risk: Thrombocytopenia and Bleeding

Thrombocytopenia and Bleeding

Outcome	Intracranial Haemorrhage	
	Number (%) of Subjects	
	Pomalidomide + Dexamethasone	High-dose Dexamethasone
Death	3 (1.0%)[a]	0
Recovered/resolved	1 (0.3%)	0
Not recovered/not resolved	0	1 (0.7%)
Total subjects with SAEs	4 (1.3%)	1 (0.7%)

[a] The SAEs with an outcome of death were cerebral haemorrhage, subarachnoid haemorrhage and subdural haematoma (1 [0.3%] subject each)

Note: only treatment-emergent SAEs are included in the table.

The frequency of SAEs of gastrointestinal haemorrhage was comparable between the two study groups (0.7% in both groups). The outcomes of these SAEs are provided below:

Outcome	Gastrointestinal Haemorrhage	
	Number (%) of Subjects	
	Pomalidomide + Dexamethasone	High-dose Dexamethasone
Death	0	1 (0.7%)[a]
Recovered/resolved	2 (0.7%)	0
Total subjects with SAEs	2 (0.7%)	1 (0.7%)

[a] The SAE with an outcome of death was gastrointestinal haemorrhage (1 [0.7%] subject).

Note: only treatment-emergent SAEs are included in the table.

Severity and Nature of Risk

Study MM-007 (pomalidomide plus bortezomib and low-dose dexamethasone versus bortezomib and low-dose dexamethasone alone)

The severity of SAEs of thrombocytopenia are provided below:

Severity	Total Thrombocytopenias	
	Number (%) of Subjects	
	Pomalidomide + Bortezomib + Dexamethasone	Bortezomib + Dexamethasone
Grade 3	1 (0.4%)	1 (0.4%)
Grade 4	0	2 (0.7%)
Total	1 (0.4%)	3 (1.1%)

Table 2.7.3.1-3: Important Identified Risk: Thrombocytopenia and Bleeding

Thrombocytopenia and Bleeding

The severity of SAEs of bleeding are provided below:

Severity	Total Bleeding	
	Number (%) of Subjects	
	Pomalidomide + Bortezomib + Dexamethasone	Bortezomib + Dexamethasone
Grade 3	1 (0.4%)	4 (1.5%)
Grade 4	0	0
Grade 5	1 (0.4%)	1 (0.4%)
Total	3 (1.1%)[a]	6 (2.2%)[b]

[a] Total includes a Grade 2 SAE in 1 (0.4%) subject.

[b] Total includes a Grade 2 SAE in 1 (0.4%) subject.

The severity of SAEs of intracranial haemorrhage are provided below:

Severity	Intracranial Haemorrhage	
	Number (%) of Subjects	
	Pomalidomide + Bortezomib + Dexamethasone	Bortezomib + Dexamethasone
Grade 3	0	0
Grade 4	0	0
Grade 5	1 (0.4%)	0
Total	1 (0.4%)	0

The severity of SAEs of gastrointestinal haemorrhage are provided below:

Severity	Gastrointestinal Haemorrhage	
	Number (%) of Subjects	
	Pomalidomide + Bortezomib + Dexamethasone	Bortezomib + Dexamethasone
Grade 3	1 (0.4%)	3 (1.1%)
Grade 4	0	0
Total	1 (0.4%)	3 (1.1%)

Studies MM-002, MM-003, and IFM-2009-02 pooled (pomalidomide-treated subjects with RRMM)

The severity of SAEs of thrombocytopenia are provided below:

Severity	Total Thrombocytopenias
	Number (%) of Subjects
Grade 3	4 (0.9%)

Grade 4	5 (1.1%)
Total	9 (2.0%)

The SAEs of thrombocytopenia were thrombocytopenia (Grade 3 in 4 [0.9%] subjects, Grade 4 in 4 [0.9%] subjects) and platelet count decreased (Grade 4 in 1 [0.2] subject).

The severity of SAEs of bleeding are provided below:

Severity	**Total Bleeding**
	Number (%) of Subjects
Grade 3	5 (1.1%)
Grade 4	2 (0.4%)
Grade 5	7 (1.5%)
Total	16 (3.5%)[a]

[a] Includes 2 subjects reporting Grade 2 SAEs.

The severity of SAEs of intracranial haemorrhage are provided below:

Severity	**Intracranial Haemorrhage**
	Number (%) of Subjects
Grade 5	7 (1.5%)
Total	8 (1.8%)[a]

[a] Includes 1 subject reporting a Grade 2 SAE.

The severity of SAEs of gastrointestinal haemorrhage are provided below:

Severity	**Gastrointestinal Haemorrhage**
	Number (%) of Subjects
Grade 3	1 (0.2%)
Grade 4	1 (0.2%)
Total	3 (0.7%)[a]

[a] Includes 1 subject reporting a Grade 2 SAE.

Study MM-003 (pomalidomide plus low-dose dexamethasone versus high-dose dexamethasone)

The severity of SAEs of thrombocytopenia are provided below:

Severity	**Total Thrombocytopenias**	
	Number (%) of Subjects	
	Pomalidomide + Dexamethasone	**High-dose Dexamethasone**
Grade 3	3 (1.0%)	1 (0.7%)
Grade 4	4 (1.3%)	3 (2.0%)
Total	7 (2.3%)	4 (2.7%)

Table 2.7.3.1-3: Important Identified Risk: Thrombocytopenia and Bleeding

Thrombocytopenia and Bleeding

The severity of SAEs of thrombocytopenia was comparable between the two study groups.

The severity of SAEs of bleeding are provided below:

Severity	**Total Bleeding**	
	Number (%) of Subjects	
	Pomalidomide + Dexamethasone	**High-dose Dexamethasone**
Grade 3	5 (1.7%)	0
Grade 4	2 (0.7%)	1 (0.7%)
Grade 5	3 (1.0%)	1 (0.7%)
Total	11 (3.7%)[a]	3 (2.0%)[b]

[a] Includes 1 subject reporting a Grade 2 SAE.

[b] Includes 1 subject reporting a Grade 2 SAE.

The severity of SAEs of haemorrhage was comparable between the two study groups.

The severity of SAEs of intracranial haemorrhage are provided below:

Severity	**Intracranial Haemorrhage**	
	Number (%) of Subjects	
	Pomalidomide + Dexamethasone	**High-dose Dexamethasone**
Grade 4	0	1 (0.7%)
Grade 5	3 (1.0%)	0
Total	4 (1.3%)[a]	1 (0.7%)

[a] Includes 1 subject reporting a Grade 2 SAE.

The severity of SAEs of gastrointestinal haemorrhage are provided below:

Severity	**Gastrointestinal Haemorrhage**	
	Number (%) of Subjects	
	Pomalidomide + Dexamethasone	**High-dose Dexamethasone**
Grade 3	1 (0.3%)	0
Grade 4	1 (0.3%)	0
Grade 5	0	1 (0.7%)
Total	2 (0.7%)	1 (0.7%)

Table 2.7.3.1-3: Important Identified Risk: Thrombocytopenia and Bleeding

Thrombocytopenia and Bleeding	
Risk factors and risk groups	The rate of blood cell production is both tightly regulated and highly variable. Under conditions of either increased destruction of cells, such as bleeding, haemolysis, or immune destruction of platelets, production rates of appropriate cells increase several fold. The regulation of this dynamic system is complex but for practical purposes can be conceived of as involving an interaction between a pool of pluripotent haematopoietic stem cells, capable of both infinite self-renewal and differentiation into mature blood cells and regulatory factors, including both a well-characterised set of glycoprotein haematopoietic growth factors and a less well-understood group of inhibitory factors.[54] The primary regulator of the platelet count in humans is thrombopoietin, a glycoprotein that is produced primarily in the liver and cleared primarily by platelets and their precursors. Thrombopoietin induces growth and development of megakaryocytes; levels fluctuate with changes in platelet count due to variations in clearance. Thrombocytopenia that is encountered in oncology practice may be due to the effects of chemotherapy, or after multiple cycles of treatment, liver disease with decreased thrombopoietin levels, immune destruction, particularly in subjects with lymphoid malignancies or infection with HIV, and sequestration. The incidence of gastrointestinal haemorrhage increases with advanced age.[71] Individuals aged60 years and older account for 35% to 45% of all cases of acute UGIB. A review of epidemiology studies of the complications of peptic ulcer disease reported annual incidence rates of haemorrhage ranging from 0.19 to 0.57 per 1000 persons in the general population and an annual incidence of 0.79 per 1000 persons older than 60 years of age.[72] A prospective study of patients undergoing upper gastrointestinal endoscopy at the National University Hospital of Iceland reported annual incidence rates of acute UGIB by age group as follows: 0.30 per 1000 individuals aged 18 to 24 years, 0.15 per 1000 individuals aged 25 to 39 years, 0.48 per 1000 individuals aged 40 to 59 years, 2.13 per 1000 individuals aged 60 to 79 years, and 5.70 per 1000 individuals aged 80 and older.[73] Relatively common medications in the elderly that may predispose individuals to gastrointestinal haemorrhage include aspirin and NSAIDs. A meta-analysis of 24 randomised controlled trials (almost 66,000 participants) revealed gastrointestinal haemorrhage in 2.47% of patients taking aspirin compared with 1.42% taking placebo.[74] A medical record review conducted in Japan reported incidence rates for UGIB of 2.65 and 1.29 per 1000 users of low-dose aspirin and NSAIDs, respectively.[75] A study using the UK General Practice Research Database (GPRD) reported a RR of 4.1 (95% CI: 3.5-4.7) of UGIB associated with current NSAID use (Hernández-Díaz, 2001a). Given previously published incidence rates of hospitalisation for peptic ulcer disease among nonusers of NSAIDs of 1 per 1000 person-years, Hernández-Díaz[76] reported that this risk translates to more than 3 additional cases per 1000 exposed persons per year. Also in the UK GPRD study, the risk of serious UGIB or perforation among current users of systemic steroids (85% of which was prednisolone) was RR = 1.8. The risk was greater (RR = 2.9) among users with steroid doses ≥ 30 mg prednisone, but the test

Table 2.7.3.1-3: Important Identified Risk: Thrombocytopenia and Bleeding

Thrombocytopenia and Bleeding	
	for dose-response was non-significant.[77] Steroids were similarly associated with bleeding OR = 1.8; 95% CI: 1.3-2.4) and perforations (OR = 1.6; 95% CI: 0.9-3.1). Simultaneous use of steroids with low-medium and high NSAID doses, respectively, produced ORs of 4.0 (95% CI: 1.3-12.0) and 12.7 (95% CI: 6.2-26.1), compared with users of none.[78]
Preventability	Thrombocytopenia can be managed with dose reduction. Dosing recommendations in the event of thrombocytopenia can be found in Section 4.2 of the SmPC. Subjects may require use of blood product support and/or growth factors (SmPC, Section 4.4). Monitoring of subjects, particularly in the initial weeks of treatment, is important to reduce the risk of myelosuppression related complications. A dose modification may be required. Complete blood cell counts should be monitored at baseline, weekly for the first 8 weeks of pomalidomide treatment and monthly thereafter (SmPC, Section 4.4) to monitor for haematologic adverse reactions. Physicians should observe patients for signs of bleeding including epistaxes, especially with use of concomitant medicinal products known to increase the risk of bleeding (SmPC, Section 4.4). Gastrointestinal haemorrhage is listed as a common ADR in Section 4.8 of the SmPC. Events of thrombocytopenia and bleeding leading to drug discontinuation in the RRMM clinical studies (Studies MM-002, MM-003and IFM-2009-02) were experienced by 3 (0.7%) and 1 (0.2%) subjects, respectively. Further details of the risk minimisation measures for the risk of thrombocytopenia and bleeding are outlined in Part V.
Impact on the risk-benefit balance of the product	Moderate impact - local or non-invasive intervention, or limited invasive intervention (platelet transfusion) needed.
Public health impact	Disorders of blood cell production are frequently observed in subjects with cancer. Under ordinary conditions in the healthy adult, blood cell production is extraordinarily prolific, with daily outputs in the range of 2 × 1011 erythrocytes, 5 × 1010 neutrophils, and 2.5 × 1011 platelets, as well as substantial numbers of lymphocytes, macrophages, antigen processing cells, eosinophils and basophils. With more than 5 million blood cells produced every second under ordinary conditions, the mitotic yield of normal bone marrow is greater than that of almost any malignancy. It is not surprising therefore that thrombocytopenia is a frequent unintended consequence of cancer treatments.[54] Haemorrhage is a very frequently observed AE in subjects with MM due to disorders of blood cell production. Approximately 15% of subjects with MM develop haemorrhage.[79] Thrombocytopenia is a common ADR associated with lenalidomide and thalidomide. In a retrospective case series of 2584 patients with MM, 24 (0.93%) patients had gastrointestinal involvement documented by tissue biopsy, with 2 (0.08%) patients experiencing gastrointestinal haemorrhage.[30] Gastrointestinal involvement was rarely seen at the time of initial diagnosis

Table 2.7.3.1-3: Important Identified Risk: Thrombocytopenia and Bleeding

Thrombocytopenia and Bleeding	
	(3/24 or 13%) and was more typically seen later in the course of disease (21/24 or 88%) often developing following SCT. In two reported case studies, MM patients experienced amyloidosis-induced gastrointestinal bleeding.[80,81] Approximately 10% to 15% of patients with MM have associated amyloidosis.[82,83] The cause of gastrointestinal haemorrhage during the course of MM is likely to be multifactorial. Other possible causes include mucosal changes attributable to bone marrow suppression, immunodeficiency, infections, and prior history of peptic ulcer disease.[31] Thrombocytopenia has been associated with pomalidomide treatment. Previous/concomitant anti-MM therapies and severity of the underlying disease are also important in the thrombocytopenia and subsequent bleeding risks. The risk minimisation activities put in place to control the thrombocytopenias are thus considered adequate to prevent the risk of severe thrombocytopenia and bleeding risks. In addition, the risk minimisation activities put in place to control gastrointestinal haemorrhage are considered adequate to prevent the risk of severe gastrointestinal haemorrhage. A Safety Topic Review of gastrointestinal haemorrhage in patients treated with pomalidomide in which a cumulative search was performed in the BMS safety database through 04-Jul-2014 noted that the causality of gastrointestinal haemorrhage in MM should be considered multifactorial. This is considering the well-described increased risk of gastrointestinal bleeding with dexamethasone use, the known bleeding risk associated with anticoagulant or antiplatelet therapy, and the known ADRs of thrombocytopenia, diarrhoea, and constipation with pomalidomide. Based on the PRAC Assessment Report for PSUR 2 (reporting period: 08-Feb-2014 to 07-Aug-2014), the PRAC Assessor agreed with the MAH that there is not enough evidence at the moment to include gastrointestinal haemorrhage in the product information; however, the MAH should keep this event under close review in the next PSUR and provide CIOMS forms for new cases. Based on the PRAC Assessment Report for PSUR 4 (reporting period 08-Feb-2015 to 07-Aug-2015), the PRAC requested the MAH to update the SmPC to include gastrointestinal haemorrhage in Section 4.8 (tabulated list of adverse reactions) and that haemorrhagic disorders is added to the description of selected AEs in Section 4.8. The PRAC also requested the addition of gastrointestinal haemorrhage to the important identified risk of thrombocytopenia and bleeding.
Data source	Studies MM-007, MM-001, MM-002, MM-003, and IFM-2009-02.
MedDRA terms	*MM-007* PTs listed within the MedDRA v20.0 sub-SMQ narrow scope of haematopoietic thrombocytopenia are collectively referred to as thrombocytopenia. PTs listed within the MedDRA v20.0 sub-SMQ narrow scope of haemorrhage terms (excluding laboratory terms) are collectively referred to as bleeding. *MM-001, MM-002, MM-003, and IFM-2009-02*

Table 2.7.3.1-3: Important Identified Risk: Thrombocytopenia and Bleeding

Thrombocytopenia and Bleeding	
	PTs listed within the MedDRA v14.0 sub-SMQ narrow scope of haematopoietic thrombocytopenia are collectively referred to as thrombocytopenia. PTs listed within the MedDRA v14.0 sub-SMQ narrow scope of haemorrhage terms (excluding laboratory terms) are collectively referred to as bleeding. For the update of data regarding intracranial haemorrhage, the MedDRA v14.0 sub-SMQ narrow scope of haemorrhagic cerebrovascular conditions and ad hoc PTs were used to match the more comprehensive v18.0 sub-SMQ narrow scope of haemorrhagic central nervous system vascular conditions. PTs listed within the MedDRA v14.0 sub-SMQ narrow scope of gastrointestinal haemorrhage are collectively referred to as gastrointestinal haemorrhage.

Important Identified Risk: Cardiac Failure

Information concerning the risk of cardiac failure is summarised in Table 2.7.3-4.

Table 2.7.3.1-4: Important Identified Risk: Cardiac Failure

Cardiac Failure	
Potential mechanisms	A mechanism by which pomalidomide could cause cardiac failure has not been identified.
Evidence source and strength of evidence	Cardiac failure has been identified from postmarketing data. In clinical studies, cardiac failure has been reported as a common ADR of pomalidomide treatment.
Characterization of risk	**Frequency with 95% CI** *Study MM-007 (pomalidomide plus bortezomib and low-dose dexamethasone versus bortezomib and low-dose dexamethasone alone)*

Study MM-007 (N = 548)		
Identified Risk	**Frequency (95% CI)**	
	Pomalidomide + Bortezomib + Dexamethasone	**Bortezomib + Dexamethasone**
Cardiac failure	4.3% (1.9 to 6.7)	1.5% (0.0 to 2.9)

The total frequency of cardiac failure was 4.3% in subjects receiving pomalidomide with bortezomib and low-dose dexamethasone versus 1.5% in subjects receiving bortezomib and dexamethasone.

Studies MM-002, MM-003, and IFM-2009-02 pooled (pomalidomide-treated subjects with RRMM)

Studies MM-002, MM-003, and IFM-2009-02 (N = 455)	
Identified Risk	**Frequency (95% CI)**

Cardiac failure	3.7% (2.0 to 5.5)

Cardiac failure AEs were reported in 17/455 subjects (3.7%; 95% CI, 2.0-5.5). The frequency of cardiac failure AEs in subjects with RRMM was comparable to that in all pomalidomide-treated subjects from Studies MM-001, MM-002, MM-003 and IFM-2009-02 (3.4%).

Study MM-003 (pomalidomide plus low-dose dexamethasone versus high-dose dexamethasone)

MM-003 (N = 450)		
Identified Risk	**Frequency (95% CI)**	
	Pomalidomide + Dexamethasone	**High-dose Dexamethasone**
Cardiac failure	3.7% (1.5 to 5.8)	4.0% (0.9 to 7.1)

Seriousness/Outcomes

Study MM-007 (pomalidomide plus bortezomib and low-dose dexamethasone versus bortezomib and low-dose dexamethasone alone)

SAEs of cardiac failure were reported in 6 (2.2%) subjects treated with pomalidomide, bortezomib and low-dose dexamethasone versus 4 (1.5%) subjects treated with bortezomib and low-dose dexamethasone alone. The outcomes of these SAEs are provided below:

Outcome	**Cardiac Failure**	
	Number (%) of Subjects	
	Pomalidomide + Bortezomib + Dexamethasone	**Bortezomib + Dexamethasone**
Death	1 (0.4%)[a]	0
Recovered/resolved	4 (1.4%)	3 (1.1%)
Recovering/resolving	1 (0.4%)	0
Recovered/resolved with sequelae	0	1 (0.4%)
Total subjects with SAEs	6 (2.2%)	4 (1.5%)

[a] PT: acute pulmonary oedema (1 [0.4%] subject).

Studies MM-002, MM-003, and IFM-2009-02 pooled (pomalidomide-treated subjects with RRMM)

SAEs of cardiac failure were reported in 10 (2.2%) subjects. These were events of cardiac failure congestive and cardiac failure (4 [0.9%] subjects each) and acute pulmonary oedema and cardiac failure acute (1 [0.2%] subject each). The outcomes of these SAEs are provided below:

Outcome	**Cardiac Failure**
	Number (%) of Subjects
Death	1 (0.2%)[a]

Recovered/resolved	9 (2.0%)
Total subjects with SAEs	10 (2.2%)

[a] A single (0.2%) subject reported cardiac failure congestive.

Note: only treatment-emergent SAEs are included in the table.

Study MM-003 (pomalidomide plus low-dose dexamethasone versus high-dose dexamethasone)

The frequency of SAEs of cardiac failure was comparable between study groups (2.3% and 2.0% in pomalidomide with dexamethasone and high-dose dexamethasone groups, respectively). The outcomes of these SAEs are provided below:

Outcome	**Cardiac Failure**	
	Number (%) of Subjects	
	Pomalidomide + Dexamethasone	**High-dose Dexamethasone**
Recovered/resolved	7 (2.3%)	2 (1.3%)
Not recovered/not resolved	0	1 (0.7%)
Total subjects with SAEs	7 (2.3%)	3 (2.0%)

Note: only treatment-emergent SAEs are included in the table.

Severity and Nature of Risk

Study MM-007 (pomalidomide plus bortezomib and low-dose dexamethasone versus bortezomib and low-dose dexamethasone alone)

The severity of SAEs of cardiac failure are provided below:

Severity	**Cardiac Failure**	
	Number (%) of Subjects	
	Pomalidomide + Bortezomib + Dexamethasone	**Bortezomib + Dexamethasone**
Grade 3	3 (1.1%)	3 (1.1%)
Grade 4	1 (0.4%)	1 (0.4%)
Grade 5	1 (0.4%)	0
Total	6 (2.2%)[a]	4 (1.5%)

[a] Total includes a Grade 2 SAE in 1 (0.4%) subject.

The frequency of SAEs of Grade 3, 4 or 5 was low in both treatment groups. The SAEs of cardiac failure in the pomalidomide plus bortezomib and low-dose dexamethasone group were acute pulmonary oedema (Grade 5 in 1 [0.4%] subject); cardiac failure (Grade 2, Grade 3 and Grade 4 in 1 [0.4%] subject each); and cardiac failure congestive (Grade 3 in 2 [0.7%] subjects). The SAEs of cardiac failure reported in the bortezomib and low-dose dexamethasone group were cardiac failure (Grade 3 in 1 [0.4%] subject,

Table 2.7.3.1-4: Important Identified Risk: Cardiac Failure

Cardiac Failure	

Grade 4 in 1 [0.4%] subject); cardiac failure congestive (Grade 3 in 2 [0.7%] subjects); and left ventricular failure (Grade 3 in 1 [0.4%] subject).

Studies MM-002, MM-003, and IFM-2009-02 pooled (pomalidomide-treated subjects with RRMM)

The severity of SAEs of cardiac failure are provided below:

Severity	**Cardiac Failure**
	Number (%) of Subjects
Grade 3	3 (0.7%)
Grade 4	3 (0.7%)
Grade 5	1 (0.2%)
Total	10 (2.2%)[a]

[a] Includes 3 (0.7%) subjects reporting Grade 2 SAEs.

The SAEs of cardiac failure were cardiac failure congestive (Grade 2 in 1 [0.2%] subject, Grade 4 in 2 [0.4%] subjects, Grade 5 in 1 [0.2%] subject), cardiac failure (Grade 2 in 1 [0.2%] subject, Grade 3 in 2 [0.4%] subjects, Grade 4 in 1 [0.2%] subject), acute pulmonary oedema (Grade 3 in 1 [0.2%] subject) and cardiac failure acute (Grade 2 in 1 [0.2%] subject).

Study MM-003 (pomalidomide plus low-dose dexamethasone versus high-dose dexamethasone)

The severity of SAEs of cardiac failure is provided below:

Severity	**Cardiac Failure**	
	Number (%) of Subjects	
	Pomalidomide + Dexamethasone	**High-dose Dexamethasone**
Grade 3	3 (1.0%)	1 (0.7%)
Grade 4	2 (0.7%)	2 (1.3%)
Total	7 (2.3%)[a]	3 (2.0%)

[a] Includes 2 (0.7%) subjects reporting a Grade 2 SAE.

The frequency of SAEs of Grade 3, 4 or 5 was low in both treatment groups.

Risk factors and risk groups

Cardiac symptoms in patients with MM can often be due to anaemia and may be due to iron overload and side effects of therapy[84] and possible fluid overload. General risk factors for CHF include increasing age, previous heart disease, diabetes, hypertension, amyloidosis, and previous anthracycline based chemotherapy treatment.[85] Cardiotoxicity of anthracyclines (eg, doxorubicin, daunorubicin and epirubicin) is usually cumulative and dose dependent. Risk factors include older age, pre-existing heart disease and hypertension.[86]

Table 2.7.3.1-4: Important Identified Risk: Cardiac Failure

Cardiac Failure	
Preventability	Possible monitoring of patients with known medical history that may be contributory to a cardiac failure event should be carried out by the treating physician. Additionally, if serious infection occurs in patients, they should be monitored/assessed/observed for cardiac failure symptoms/events. Section 4.4 of the SmPC states that patients with significant cardiac dysfunction (CHF [New York Heart Association Class III or IV]; MI within 12 months of starting study; unstable or poorly controlled angina pectoris) were excluded from clinical studies with pomalidomide. Cardiac events, including congestive cardiac failure, pulmonary oedema and atrial fibrillation have been reported, mainly in patients with pre-existing cardiac disease or cardiac risk factors. Appropriate caution should be exercised when considering the treatment of such patients with pomalidomide, including periodic monitoring for signs or symptoms of cardiac events. Further details of the risk minimisation measures for the risk of cardiac failure are outlined in Part V.
Impact on the risk-benefit balance of the product	Can have mild to severe to life-threatening or fatal impact. Symptoms can be mild with moderate activity or exertion to severe with minimal activity or at rest. Non-invasive intervention to urgent continuous intervention (eg, IV, mechanical haemodynamic support) indicated.
Public health impact	Heart failure is a disease of the elderly, and the prevalence increases dramatically with age.[87] Congestive heart failure is predominantly caused by cardiovascular diseases such as coronary artery disease, hypertension, and valvular heart disease. Chemotherapeutic drugs with potential ability to induce or exacerbate heart failure include anthracyclines, cyclophosphamide, paclitaxel, mitocantrone, 5-fluorouracil, and cytarabin. High-output cardiac failure is one of the known cardiovascular issues associated with MM and is frequently seen in patients with extensive bone lesions.[88] An association between cardiac failure and pomalidomide combined with dexamethasone or pomalidomide alone has not been established.
Data source	Studies MM-007, MM-001, MM-002, MM-003, and IFM-2009-02.
MedDRA terms	*MM-007* PTs listed within the MedDRA v20.0 SMQ narrow scope of cardiac failure are collectively referred to as cardiac failure. *MM-001, MM-002, MM-003, and IFM-2009-02* PTs listed within the MedDRA v14.0 SMQ narrow scope of cardiac failure are collectively referred to as cardiac failure.

Important Identified Risk: Non-melanoma Skin Cancer

Information concerning the risk of NMSC is summarised in Table 2.7.3-5.

Table 2.7.3.1-5: Important Identified Risk: Non-melanoma Skin Cancer

Non-melanoma Skin Cancer	
Potential mechanisms	No mechanism whereby pomalidomide may cause second malignancies has been identified. While none of the following may be exclusive there may be several explanations why patients with MM might develop secondary cancers, including: • Treatment-related Change of natural disease history as a result of improved survival in recent years. • As a consequence of the use of alkylating agents Prolonged immunosuppression (cytopenias). Use of G-CSF, especially in combination with high-dose chemotherapy. Increased surveillance of cancer patients. As a consequence of selective reporting. • Syndromic Cytogenetic factors associated with MM. Exposure to environmental agents (hypothetical).
Evidence source and strength of evidence	Patients treated with pomalidomide may be at an increased risk of developing new cancers (including skin cancers). In clinical studies, NMSC has been reported in patients receiving pomalidomide. Drug reaction with eosinophilia and systemic symptoms, toxic epidermal necrolysis and Stevens-Johnson syndrome have been observed in the postmarketing setting.
Characterization of risk	**Frequency with 95% CI** *Study MM-007 (pomalidomide plus bortezomib and low-dose dexamethasone versus bortezomib and low-dose dexamethasone alone)*

MM-007 (N = 548)		
Identified Risk	**Frequency (95% CI)**	
	Pomalidomide + Bortezomib + Dexamethasone	**Bortezomib + Dexamethasone**
NMSC	2.5% (0.7 to 4.4)	1.1% (0.0 to 2.4)

The total frequency of NMSC was comparable between the two study groups.

Studies MM-002, MM-003, and IFM-2009-02 pooled (pomalidomide-treated subjects with RRMM)

Studies MM-002, MM-003, and IFM-2009-02 (N = 455)	
Identified Risk	**Frequency (95% CI)**
NMSC	1.5% (0.4 to 2.7)

Table 2.7.3.1-5: Important Identified Risk: Non-melanoma Skin Cancer

Non-melanoma Skin Cancer

Events of NMSC were reported in 7/455 subjects (1.5%; 95% CI, 0.4-2.7). The frequency of NMSC AEs in subjects with RRMM was comparable to that in all pomalidomide-treated subjects from Studies MM-001, MM-002, MM-003 and IFM-2009-02 (1.6%).

Study MM-003 (pomalidomide plus low-dose dexamethasone versus high-dose dexamethasone)

MM-003 (N = 450)		
Identified Risk	**Frequency (95% CI)**	
	Pomalidomide + Dexamethasone	**High-dose Dexamethasone**
NMSC	1.7% (0.2 to 3.1)	0.7% (0.0 to 2.0)

The total frequency of NMSC was comparable between the two study groups.

Seriousness/Outcomes

Study MM-007 (pomalidomide plus bortezomib and low-dose dexamethasone versus bortezomib and low-dose dexamethasone alone)

SAEs of NMSC were reported in 7 (2.5%) subjects treated with pomalidomide, bortezomib and low-dose dexamethasone versus 3 (1.1%) subjects treated with bortezomib and low-dose dexamethasone alone. These were events of BCC in 4 (1.4%) subjects), Bowen's disease in 1 (0.4%) subject and squamous cell carcinoma of the skin in 2 (0.7%) subjects treated with pomalidomide, bortezomib and low-dose dexamethasone; BCC in 1 (0.4%) subject, and squamous cell carcinoma of the skin in 2 (0.7%) subjects treated with bortezomib and low-dose dexamethasone alone. The outcomes of these SAEs are provided below:

Outcome	**NMSC**	
	Number (%) of Subjects	
	Pomalidomide + Bortezomib + Dexamethasone	**Bortezomib + Dexamethasone**
Recovered/resolved	5 (1.8%)	3 (1.1%)
Not recovered/not resolved	2 (0.7%)	0
Total subjects with SAEs	7 (2.5%)	3 (1.1%)

Studies MM-002, MM-003, and IFM-2009-02 pooled (pomalidomide-treated subjects with RRMM)

SAEs of NMSC were reported in 7 (1.5%) subjects. These were events of BCC (5 [1.1%] subjects), head and neck cancer and SCC of skin (1 [0.2%] subject each). The outcomes of these SAEs are provided below:

Table 2.7.3.1-5: Important Identified Risk: Non-melanoma Skin Cancer

Non-melanoma Skin Cancer

Outcome	**NMSC**
	Number (%) of Subjects
Recovered/resolved	4 (0.9%)
Recovered with sequela	1 (0.2%)
Not recovered/not resolved	2 (0.4%)
Total subjects with SAEs	7 (1.5%)

Study MM-003 (pomalidomide plus low-dose dexamethasone versus high-dose dexamethasone)

SAEs of NMSC were reported at a low frequency both in subjects receiving pomalidomide with dexamethasone (5 [1.7%] subjects) and in subjects receiving high-dose dexamethasone (1 [0.7%] subjects). The outcomes of these SAEs are provided below:

Outcome	**NMSC**	
	Number (%) of Subjects	
	Pomalidomide + Dexamethasone	**High-dose Dexamethasone**
Recovered/resolved	2 (0.7%)	1 (0.7%)
Recovered with sequela	1 (0.3%)	0
Not recovered/not resolved	2 (0.7%)	0
Total subjects with SAEs	5 (1.7%)	1 (0.7%)

Severity and Nature of Risk

Study MM-007 (pomalidomide plus bortezomib and low-dose dexamethasone versus bortezomib and low-dose dexamethasone alone)

The severity of SAEs of NMSC are provided below:

Severity	**NMSC**	
	Number (%) of Subjects	
	Pomalidomide + Bortezomib + Dexamethasone	**Bortezomib + Dexamethasone**
Grade 3	0	1 (0.4%)
Grade 4	1 (0.4%)	0
Grade 5	0	0
Total	7 (2.5%)[a]	3 (1.1%)[b]

[a] Total includes Grade 2 SAEs in 6 (2.2%) subjects.

[b] Total includes Grade 2 SAEs in 2 (0.7%) subjects.

Table 2.7.3.1-5: Important Identified Risk: Non-melanoma Skin Cancer

Non-melanoma Skin Cancer	

The frequency of SAEs of NMSC of Grade 3, 4 or 5 was low in both treatment groups.

Studies MM-002, MM-003, and IFM-2009-02 pooled (pomalidomide-treated subjects with RRMM)

The severity of SAEs of NMSC are provided below:

Severity	**NMSC**
	Number (%) of Subjects
Grade 3	4 (0.9%)
Total	7 (1.5%)[a]

[a] Includes 1 (0.2%) subject reporting a Grade 1 SAE and 2 (0.4%) subjects reporting Grade 2 SAEs.

The severe SAEs of NMSC were BCC (Grade 3 in 2 [0.4%] subjects), head and neck cancer and SCC of skin (Grade 3 in 1 [0.2%] subject each).

Study MM-003 (pomalidomide plus low-dose dexamethasone versus high-dose dexamethasone)

The severity of SAEs of NMSC are provided below:

Severity	**NMSC**	
	Number (%) of Subjects	
	Pomalidomide + Dexamethasone	**High-dose Dexamethasone**
Grade 3	3 (1.0%)	0
Total	5 (1.7%)[a]	0[b]

[a] Includes 1 (0.3%) subject reporting a Grade 1 SAE and 1 (0.3%) subject reporting a Grade 2 SAE.

[b] Subject 1521005 from the high-dose dexamethasone arm of Study MM-003 had a missing toxicity grade for the event of BCC.

The frequency of SAEs of NMSC of Grade 3, 4 or 5 was low in both treatment groups.

Risk factors and risk groups

Skin colour and being exposed to sunlight are recognised risk factors for NMSC. NMSC is the most frequent malignancy mainly in fair-skinned populations.[89] However, other risk factors such as immune disorders, tobacco use, photosensitive drugs, and viral infections (human papilloma virus, HIV) have been reported to be associated with NMSC in rare instances.[90]

Rates of NMSC are higher in men as compared to women. NMSC rates are also higher in older age groups. One study based on the US insured population reported the mean age of NMSC was 69.[91]

Table 2.7.3.1-5: Important Identified Risk: Non-melanoma Skin Cancer

Non-melanoma Skin Cancer	
Preventability	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 (SmPC, Section 4.4). BCC of the skin and SCC of the skin and listed as uncommon ADRs in Section 4.8 of the SmPC. Further details of the risk minimisation measures for the risk of NMSC are outlined in Part V.
Impact on the risk-benefit balance of the product	Moderate to severe impact. Minimal, local intervention to medically significant but not immediately life-threatening with hospitalisation and invasive intervention indicated. Possibly disabling; limiting self-care ADL.
Public health impact	A comprehensive systematic review of the published literature reported that the global incidence of NMSC ranges from greater than 1000 per 100,000 person-years for BCC in Australia to less than 1 per 100,000 person-years in some areas of Africa.[89] In Europe, the incidence of BCC ranges from 33.6 per 100,000 person-years in Croatia to 115.6 per 100,000 person-years in the UK while SCC ranges from 8.9 per 100,000 person-years in Croatia to 31.7 per 100,000 person-years in Wales (Lomas, 2012). In North America, the incidence of BCC ranges from 147 per 100,000 person-years in Canada to 935.9 per 100,000 person-years in the US (Arizona) while SCC ranges from 60.2 per 100,000 person-years in Canada to 290 per 100,000 person-years in the US (New Mexico).[89] The highest rates of NMSC in the world have been reported in Australia. The incidence of BCC in Australia was 884 per 100,000 person-years while SCC was 387 per 100,000 person-years.[89] NMSC has also been observed as a second primary cancer among cancer patients in a few studies. In a study following a cohort of people who developed cancers in childhood and survived for 5 years or more, the incidence of BCC was 168.4 per 100,000 person-years in those less than 35, 1449.3 per 100,000 person-years for those 35 to 44 and 3785.9 per 100,000 person-years for those 45 to 54.[92] The highest proportion of reported cases was among those with Hodgkin's and leukaemia. In a pooled analysis of lenalidomide clinical trials, the incidence rate of NMSC in the placebo/dexamethasone arm was 0.91 per 100 person-years in MM patients.[93] An analysis of the Swedish Cancer Registry reported a SIR of 2.22 for second primary NMSC in MM patients as compared to the general population.[27] A Safety Topic Review of NMSC in patients treated with pomalidomide in which a cumulative search was performed in the BMS safety database through 15-Jul-2015 did not determine a causal association between NMSC and pomalidomide. Based on the PRAC Assessment Report for PSUR 4 (reporting period 08-Feb-2015 to 07-Aug-2015), the PRAC requested the MAH to update the SmPC to include NMSC in Sections 4.4 and 4.8. In addition, based on PRAC assessment NMSC was added to the RMP as an important identified risk.

Table 2.7.3.1-5: Important Identified Risk: Non-melanoma Skin Cancer

Non-melanoma Skin Cancer	
Data source	Studies MM-007, MM-001, MM-002, MM-003, and IFM-2009-02.
MedDRA terms	*MM-007* PTs within the MedDRA v14.0 HLT of skin neoplasms malignant and unspecified (excl melanoma) are collectively referred to as NMSC. *MM-001, MM-002, MM-003, and IFM-2009-02* PTs within the MedDRA v14.0 HLT of skin neoplasms malignant and unspecified (excl melanoma) are collectively referred to as NMSC.

Important Potential Risk: Other Second Primary Malignancies

Information concerning the risk of other SPM is summarised in Table 2.7.3.1-6.

Table 2.7.3.1-6: Important Potential Risk: Other Second Primary Malignancies

Other Second Primary Malignancies	
Potential mechanisms	No mechanism whereby pomalidomide may cause second malignancies has been identified. While none of the following may be exclusive there may be several explanations why patients with MM might develop secondary cancers, including: • Treatment-related Change of natural disease history as a result of improved survival in recent years. • As a consequence of the use of alkylating agents Prolonged immunosuppression (cytopenias). Use of G-CSF, especially in combination with high-dose chemotherapy. Increased surveillance of cancer patients. As a consequence of selective reporting. • Syndromic Cytogenetic factors associated with MM. **Exposure to environmental agents (hypothetical).**
Evidence source and strength of evidence	Patients treated with pomalidomide may be at an increased risk of developing new cancers. In clinical studies, SPM has been reported in patients receiving pomalidomide.
Characterization of risk	**Frequency with 95% CI** *Study MM-007 (pomalidomide plus bortezomib and low-dose dexamethasone versus bortezomib and low-dose dexamethasone alone)* **MM-007 (N = 548)**

Table 2.7.3.1-6: Important Potential Risk: Other Second Primary Malignancies

Other Second Primary Malignancies

Potential Risk	Frequency (95% CI)	
	Pomalidomide + Bortezomib + Dexamethasone	**Bortezomib + Dexamethasone**
Other SPM	0.7% (0.0 to 1.7)	0.7% (0.0 to 1.8)

Other SPM AEs were reported at a frequency of 0.7% in both study groups.

Studies MM-002, MM-003, and IFM-2009-02 pooled (pomalidomide-treated subjects with RRMM)

Studies MM-002, MM-003, and IFM-2009-02 (N = 455)	
Potential Risk	**Frequency (95% CI)**
Other SPM	1.1% (0.1 to 2.1)

Other SPM were reported in 5/455 subjects (1.1%; 95% CI, 0.1-2.1). The frequency of other SPM AEs in subjects with RRMM was comparable to that in all pomalidomide-treated subjects from Studies MM-001, MM-002, MM-003 and IFM-2009-02 (0.9%).

Study MM-003 (pomalidomide plus low-dose dexamethasone versus high-dose dexamethasone)

MM-003 (N = 450)		
Potential Risk	**Frequency (95% CI)**	
	Pomalidomide + Dexamethasone	**High-dose Dexamethasone**
Other SPM	0.7% (0.0 to 1.6)	0.7% (0.0 to 2.0)

Other SPM AEs were reported at a frequency of 0.7% in both study groups.

Seriousness/Outcomes

Study MM-007 (pomalidomide plus bortezomib and low-dose dexamethasone versus bortezomib and low-dose dexamethasone alone)

SAEs of other SPM were reported in 2 (0.7%) subjects treated with pomalidomide, bortezomib and low-dose dexamethasone and 2 (0.7%) subjects treated with bortezomib and low-dose dexamethasone alone. The other SPM SAEs were events of scrotal cancer and squamous cell carcinoma, each reported in 1 (0.4%) subject treated with pomalidomide, bortezomib and low-dose dexamethasone and bronchial carcinoma and squamous cell carcinoma, each reported in 1 (0.4%) subject treated with bortezomib and low-dose dexamethasone alone. The outcomes of these SAEs are provided below:

Outcome	**Other SPM**
	Number (%) of Subjects

Table 2.7.3.1-6: Important Potential Risk: Other Second Primary Malignancies

Other Second Primary Malignancies

	Pomalidomide + Bortezomib + Dexamethasone	**Bortezomib + Dexamethasone**
Recovered/resolved	1 (0.4%)	1 (0.4%)
Not recovered/not resolved	1 (0.4%)	1 (0.4%)
Total subjects with SAEs	2 (0.7%)	2 (0.7%)

Studies MM-002, MM-003, and IFM-2009-02 pooled (pomalidomide-treated subjects with RRMM)

SAEs of other SPM were reported in 5 (1.1%) subjects. The other SPM SAEs were events of AML, colon cancer, lung adenocarcinoma stage IV, meningioma benign and tumour invasion (1 [0.2%] subject each). The outcomes of the other SPM SAEs are provided below:

Outcome	**Other SPM**
	Number (%) of Subjects
Death	1 (0.2%)[a]
Recovered/resolved	1 (0.2%)
Not recovered/not resolved	3 (0.7%)
Total subjects with SAEs	5 (1.1%)

[a] Lung adenocarcinoma stage IV was reported by 1 (0.2%) subject.

Study MM-003 (pomalidomide plus low-dose dexamethasone versus high-dose dexamethasone)

SAEs of other SPM were reported in 2 (0.7%) subjects receiving pomalidomide with dexamethasone and 1 (0.7%) subject receiving high-dose dexamethasone. These SAEs were lung adenocarcinoma stage IV and meningioma benign (1 [0.3%] subject each) in the pomalidomide with dexamethasone group and prostate cancer (1 [0.7%] subject) in the high-dose dexamethasone group. The outcomes of the other SPM SAEs are provided below:

Outcome	**Other SPM**	
	Number (%) of Subjects	
	Pomalidomide + Dexamethasone	**High-dose Dexamethasone**
Death	1 (0.3%)[a]	0
Not recovered/not resolved	1 (0.3%)	1 (0.7%)

Table 2.7.3.1-6: Important Potential Risk: Other Second Primary Malignancies

Other Second Primary Malignancies

Total subjects with SAEs	2 (0.7%)	1 (0.7%)

[a] Lung adenocarcinoma stage IV was reported by 1 (0.2%) subject.

Severity and Nature of Risk

Study MM-007 (pomalidomide plus bortezomib and low-dose dexamethasone versus bortezomib and low-dose dexamethasone alone)

The severity of SAEs of other SPM are provided below:

Severity	**Other SPM**	
	Number (%) of Subjects	
	Pomalidomide + Bortezomib + Dexamethasone	**Bortezomib + Dexamethasone**
Grade 3	0	1 (0.4%)
Grade 4	2 (0.7%)	0
Grade 5	0	0
Total	2 (0.7%)	2 (0.7%)[a]

[a] Total includes a Grade 2 SAE in 1 (0.4%) subject.

The frequency of SAEs of other SPM of Grade 3, 4 or 5 was low in both treatment groups.

Studies MM-002, MM-003, and IFM-2009-02 pooled (pomalidomide-treated subjects with RRMM)

The severity of SAEs of other SPM are provided below:

Severity	**Other SPM**
	Number (%) of Subjects
Grade 3	1 (0.2%)
Grade 4	1 (0.2%)
Grade 5	1 (0.2%)
Total	5 (1.1%)[a]

[a] Includes 1 (0.2%) subject reporting a Grade 1 SAE and 1 (0.2%) subject reporting a Grade 2 SAE.

The severe SAEs of other SPM were lung adenocarcinoma stage IV (Grade 5 in 1 [0.2%] subject), colon cancer (Grade 4 in 1 [0.2%] subject) and AML (Grade 3 in 1 [0.2%] subject).

Study MM-003 (pomalidomide plus low-dose dexamethasone versus high-dose dexamethasone)

Table 2.7.3.1-6: Important Potential Risk: Other Second Primary Malignancies

Other Second Primary Malignancies

The severity of SAEs of other SPM are provided below:

Severity	Other SPM	
	Number (%) of Subjects	
	Pomalidomide + Dexamethasone	High-dose Dexamethasone
Grade 5	1 (0.3%)	0
Total	2 (0.7%)[a]	1 (0.7%)[b]

[a] Includes 1 (0.3%) subject reporting a Grade 1 SAE.

[b] Includes 1 (0.7%) subject reporting a Grade 2 SAE.

The frequency of SAEs of other SPM of Grade 3, 4 or 5 was low in both treatment groups.

Risk factors and risk groups

Travis[29] has grouped second primary cancers into three major groups based on the predominant etiologic factors ie, treatment related, syndromic, and those due to shared etiologic factors, while emphasising the non-exclusivity of these groups. In the following, possible explanations for the epidemiologic findings presented in the previous section will be discussed.

- **Prolonged survival as a result of improved therapies**

Due to improvements in the care of patients with cancer, the number of cancer survivors has been increasing in recent years. Increased longevity increases the risk of developing a second malignancy, whether due to the late sequelae of treatment, lifestyle factors, environmental exposures, or host factors (eg, aging, genetic factors, gene-environment interactions), or a combination of these factors. Second solid tumours are a leading cause of mortality among several populations of long-term survivors.

As reported from the SEER Cancer Statistics Review 1975 to 2009, the 5-year relative survival among MM patients has increased from 25.1% among patients first diagnosed in 1975 to 1977 to 42.6% among patients first diagnosed between 2002 and 2008 ($p < 0.05$). Among patients aged less than 65 years at first diagnosis between 2002 and 2008, 5-year relative survival is 54.4%; among those aged 65 years and older, survivorship is 31.3%.[94]

- **Heredity**

Additional insight has also been obtained in elucidating the risk of malignancies in close family members of patients affected by MM. The available data show an increased risk of more than one malignancy in MM patients and first-degree relatives compared to the general population. The reason for this finding is still unclear but may clearly involve risk conferred by shared genetic factors.[95,96]

Preventability

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 (SmPC, Section 4.4).

Table 2.7.3.1-6: Important Potential Risk: Other Second Primary Malignancies

Other Second Primary Malignancies	
	Further details of the risk minimisation measures for the risk of other SPM are outlined in Part V.
Impact on the risk-benefit balance of the product	Moderate to severe impact. Minimal, local intervention to medically significant but not immediately life-threatening with hospitalisation and invasive intervention indicated. Possibly disabling; limiting self-care ADL.
Public health impact	Dores[25] undertook an analysis of all second primary cancers among 23,838 MM patients in the SEER-9 Cancer Registries from 1973 to 2000. Non-melanoma skin cancers are not reportable to the SEER programme and therefore are not included in these data. The authors reported that among patients of all ages, the overall risk of second primary cancer was not increased (SIR = 0.98; 95% CI 0.93-1.04). Despite these findings, research has identified an elevated risk of specific forms, in particular MDS, AML, NHL and Kaposi sarcoma in North American and European populations. Increased risk of second cancer was shown in the SEER analysis by Dores[25] for patients less than 70 years of age (SIR = 1.09). Within this age group, increased risks were associated with AML (SIR = 13.43), Kaposi sarcoma (SIR = 4.89), melanoma of skin (SIR = 1.67) and cancer of the urinary bladder (SIR = 1.62). Among subjects aged ≥ 70 years, significantly increased risks were observed for AML (SIR = 4.62) and for chronic myeloid leukaemia (SIR = 2.79). In this study, the risk for NHL was not significantly elevated over the entire time period, but was noted to be significantly elevated at 5 to 9 years (SIR = 2.02) and most of these may be assumed to be B-cell malignancies. Among patients of all ages in the SEER analysis, the risk of AML in MM patients was highly elevated overall (SIR = 8.32) and followed an inverted-U curve by duration of follow-up, with statistically significant risk increases noted at 1 to 4 years of follow-up (SIR = 7.21), 5 to 9 years of follow-up (SIR = 18.53) and > 10 years of follow-up (SIR = 11.52). Cannon,[97] looking at SEER data for MM and Kaposi sarcoma during the period 1973 to 1995, found significant associations between MM and Kaposi sarcoma (SIR = 5.42), NHL (SIR = 1.51), cancer of the urinary bladder (SIR = 1.42), the colon (SIR = 1.25) and of the prostate (SIR = 1.13), including synchronous cases diagnosed at the same time as MM that were excluded from the previous study. Dong[24] summarised the risk of second primary neoplasms among 8656 myeloma patients in the Swedish Family Cancer Database 1958 to 1996. Overall, 475 subsequent malignancies were observed. Again, the overall risk of a second malignancy was not increased (SIR = 0.94). However, the aggregate risk of haematolymphoproliferative disorders was significantly elevated (SIR = 2.19), driven primarily by a significantly increased risk for myeloid leukaemia (SIR = 8.19) and NHL (SIR = 1.74). The risk of developing myeloid leukaemia was greatest 1 to 9 years after the initial diagnosis (SIR = 9.50). In a large systematic evaluation of population-based data from Sweden, Mailankody[27] found that compared to the general population, MM patients had a 1.26-fold increased risk of developing any secondary malignancy and

Table 2.7.3.1-6: Important Potential Risk: Other Second Primary Malignancies

Other Second Primary Malignancies	
	an 11-fold increased risk of developing AML/MDS. In exploratory analyses, the authors demonstrated that the risk of AML/MDS among MM patients diagnosed prior to the introduction of immunomodulatory drugs (IMiDs; pre 2000 in Sweden; SIR = 13.51 [95% CI 8.83-19.80]) was not significantly different to patients diagnosed after IMiDs introduction (follow-up until 2006, ie, when thalidomide was the only IMiD in use; SIR = 8.35 [95% CI 4.17-14.94]). However, as the actual usage of IMiD therapy in Sweden during the study period was relatively low and the follow-up time restricted, these analyses should be interpreted with caution. One large clinical case series by Hasskarl[26] described the occurrence of metachronous malignancy among 589 myeloma patients identified during 1997 to 2008 at one large university centre in Germany. Of interest, 41/589 patients (7%) had a malignancy other than MM diagnosed either prior to or at the same time as MM. These prior or synchronous neoplasms were composed of colorectal (7), gynaecologic (7), skin including melanoma (6), renal-urothelial (6), prostate (4), and others. There were 7 lymphomas diagnosed, of which 6 were mature B-cell neoplasms which occurred prior to or synchronously. Fewer patients experienced second cancer after an MM diagnosis (18/589; 3%). Among the latter, haematologic malignancies, specifically AML/MDS, were the most common, being identified at the same time in one patient and after the MM diagnosis in 5 patients. As survival after a diagnosis of cancer improves, identification and quantification of the late effects of cancer and its therapy have become critical. Generally, new cancer is considered to be one of the most serious events experienced by cancer survivors. The number of patients with multiple primary cancers is growing rapidly, with independent second malignancies now comprising about 16% of incident cancers reported to the National Cancer Institute (NCI) SEER Programme in 2003. Moreover, second tumours may be a cause of mortality among several populations of long-term survivors.[29] It should be noted, however, that the risk of dying from MM is considerably higher than the risk of developing a second cancer.[98] Based on the PRAC Assessment Report for PSUR 4 (reporting period 08-Feb-2015 to 07-Aug-2015), NMSC was added to the RMP as an important identified risk and the important potential risk of SPM was redefined as other SPM.
Data source	Studies MM-007, MM-001, MM-002, MM-003, and IFM-2009-02.
MedDRA terms	*MM-007* MedDRA v14.0 HLGTs of haematopoietic neoplasms (excl leukaemias and lymphomas), leukaemias, lymphomas Hodgkin's disease, lymphomas NEC, lymphomas non-Hodgkin's B-cell, lymphomas non-Hodgkin's T-cell, lymphomas non-Hodgkin's unspecified histology, breast neoplasms malignant and unspecified (incl nipple), endocrine neoplasms malignant and unspecified, gastrointestinal neoplasms malignant and unspecified, hepatobiliary neoplasms malignant and unspecified, miscellaneous and site unspecified neoplasms malignant and unspecified, nervous system neoplasms malignant and unspecified NEC, renal and urinary tract

Table 2.7.3.1-6: Important Potential Risk: Other Second Primary Malignancies

Other Second Primary Malignancies	
	neoplasms malignant and unspecified, reproductive and genitourinary neoplasms gender unspecified NEC, reproductive neoplasms female malignant and unspecified, reproductive neoplasms male malignant and unspecified, respiratory and mediastinal neoplasms malignant and unspecified, skeletal neoplasms malignant and unspecified, soft tissue neoplasms malignant and unspecified (excl sarcomas), and soft tissue sarcomas. MedDRA v14.0 HLTs of mesotheliomas malignant and unspecified, ocular melanomas, ocular neoplasms malignancy unspecified, ocular neoplasms malignant (excl melanomas), and skin melanomas (excl ocular). *MM-001, MM-002, MM-003, and IFM-2009-02* MedDRA v14.0 HLGTs/HLTs of haematopoietic neoplasms (excl leukaemias and lymphomas); leukaemias; lymphomas Hodgkin's disease; lymphomas NEC; lymphomas non-Hodgkin's B-cell; lymphomas non-Hodgkin's T-cell; lymphomas non-Hodgkin's unspecified histology; breast neoplasms malignant and unspecified; endocrine neoplasms malignant and unspecified; gastrointestinal neoplasms malignant and unspecified; hepatobiliary neoplasms malignant and unspecified; mesotheliomas; miscellaneous and site unspecified neoplasms malignant and unspecified; ocular neoplasms; renal and urinary tract neoplasms malignant and unspecified; reproductive and genitourinary neoplasms gender unspecified NEC; reproductive neoplasms female malignant and unspecified; reproductive neoplasms male malignant and unspecified; respiratory and mediastinal neoplasms malignant and unspecified; skeletal neoplasms malignant and unspecified; skin melanomas (excluding ocular); soft tissue neoplasms malignant and unspecified (excl sarcomas); soft tissue sarcomas.

Important Potential Risk: Cardiac Arrhythmia

Information concerning the risk of cardiac arrhythmia is summarised in Table 2.7.3-7.

Table 2.7.3.1-7: Important Potential Risk: Cardiac Arrhythmia

Cardiac Arrhythmia	
Potential mechanisms	No mechanisms by which pomalidomide may cause cardiac arrhythmias have been identified.
Evidence source and strength of evidence	Patients treated with pomalidomide in combination with dexamethasone may be at increased risk of cardiac arrhythmias. It is unclear whether pomalidomide can cause cardiac arrhythmias. In clinical studies, a greater proportion of patients treated with pomalidomide in combination with dexamethasone reported cardiac arrhythmias compared to patients who were treated with high-dose dexamethasone.

Table 2.7.3.1-7: Important Potential Risk: Cardiac Arrhythmia

Cardiac Arrhythmia	
Characterization of risk	**Frequency with 95% CI** *Study MM-007 (pomalidomide plus bortezomib and low-dose dexamethasone versus bortezomib and low-dose dexamethasone alone)*

Study MM-007 (N = 548)		
Potential Risk	**Frequency (95% CI)**	
	Pomalidomide + Bortezomib + Dexamethasone	**Bortezomib + Dexamethasone**
Cardiac arrhythmia	15.8% (11.5 to 20.1)	5.9% (3.1 to 8.7)

The total frequency of cardiac arrhythmia was higher in subjects receiving pomalidomide with bortezomib and low-dose dexamethasone (15.8%) compared to subjects receiving bortezomib and dexamethasone (5.9%). With the exception of AF (26 [9.4%] subjects), all PTs were reported for < 1.5% of subjects treated with pomalidomide plus bortezomib and low-dose dexamethasone, including electrocardiogram QT prolonged (4 [1.4%] subjects), sinus bradycardia (2 [0.7%] subjects), sinus tachycardia (3 [1.1%] subjects), supraventricular tachycardia (1 [0.4%] subject), and ventricular tachycardia (2 [0.7%] subjects). Of note, sinus tachycardia was reported for 4 (1.5%) subjects, supraventricular tachycardia for 2 (0.7%) subjects, and ventricular tachycardia for 1 (0.4%) subject receiving bortezomib and low-dose dexamethasone.

Studies MM-002, MM-003, and IFM-2009-02 pooled (pomalidomide-treated subjects with RRMM)

Studies MM-002, MM-003, and IFM-2009-02 (N = 455)	
Potential Risk	**Frequency (95% CI)**
Cardiac arrhythmia	15.8% (12.5 to 19.2)

Cardiac arrhythmia AEs were reported in 72/455 subjects (15.8%; 95% CI, 12.5-19.2). The frequency of cardiac arrhythmia AEs in subjects with RRMM was comparable to that in all pomalidomide-treated subjects from Studies MM-001, MM-002, MM-003 and IFM-2009-02 (15.6%). The most frequently reported PTs were AF (22 [4.8%] subjects), syncope (12 [2.6%] subjects), palpitations (8 [1.8%] subjects), and tachycardia (7 [1.5%] subjects). All other PTs were reported for < 1% of subjects, including bradycardia, which was reported for 3 (0.7%) subjects.

Study MM-003 (pomalidomide plus low-dose dexamethasone versus high-dose dexamethasone)

MM-003 (N = 449)		
Potential Risk	**Frequency (95% CI)**	
	Pomalidomide + Dexamethasone	**High-dose Dexamethasone**
Cardiac arrhythmia	14.7% (10.7 to 18.7)	10.7% (5.8 to 15.7)

Table 2.7.3.1-7: Important Potential Risk: Cardiac Arrhythmia

Cardiac Arrhythmia

Cardiac arrhythmia AEs were reported at generally comparable frequencies in the pomalidomide plus dexamethasone and high-dose dexamethasone arms (14.7% versus 10.7%). Based on the frequencies and 95% CIs reported with the pooled safety data, and comparator data from MM-003, cardiac arrhythmia has been classified as a potential risk. With the exception of AF (10 [3.3%] subjects), all PTs were reported for < 2.5% of subjects treated with pomalidomide plus dexamethasone. Of note, bradycardia was reported for 2 (0.7%) pomalidomide plus dexamethasone-treated subjects and no high-dose dexamethasone-treated subjects.

Seriousness/Outcomes

Study MM-007 (pomalidomide plus bortezomib and low-dose dexamethasone versus bortezomib and low-dose dexamethasone alone)

SAEs of cardiac arrhythmia were reported in 13 (4.7%) subjects treated with pomalidomide, bortezomib and low-dose dexamethasone versus 4 (1.5%) subjects treated with bortezomib and low-dose dexamethasone alone. The outcomes of these SAEs are provided below:

Outcome	**Cardiac Arrhythmia**	
	Number (%) of Subjects	
	Pomalidomide + Bortezomib + Dexamethasone	**Bortezomib + Dexamethasone**
Death	0	0
Recovered/resolved	10 (3.6%)	3 (1.1%)
Recovered/resolved with sequelae	1 (0.4%)	0
Recovering/resolving	1 (0.4%)	1 (0.4%)
Not recovered/not resolved	1 (0.4%)	0
Total subjects with SAEs	13 (4.7%)	4 (1.5%)

Studies MM-002, MM-003, and IFM-2009-02 pooled (pomalidomide-treated subjects with RRMM)

SAEs of cardiac arrhythmia were reported in 16 (3.5%) subjects. The most common events were AF (7 [1.5%] subjects), and syncope (2 [0.4%] subjects). The outcomes of these SAEs are provided below:

Outcome	**Cardiac Arrhythmia**
	Number (%) of Subjects
Death	3 (0.7%)[a]
Ongoing at death	2 (0.4%)

Table 2.7.3.1-7: Important Potential Risk: Cardiac Arrhythmia

Cardiac Arrhythmia

Recovered/resolved	9 (2.0%)
Not recovered/not resolved	2 (0.4%)
Total subjects with SAEs	16 (3.5%)

[a] Events of cardiac arrest, cardio-respiratory arrest and sudden death were reported by 1 (0.2%) subject each.

Note: only treatment-emergent SAEs are included in the table.

Study MM-003 (pomalidomide plus low-dose dexamethasone versus high-dose dexamethasone)

The frequency of SAEs of cardiac arrhythmia was comparable between study groups (4.0% and 3.4% in the pomalidomide with dexamethasone and high-dose dexamethasone groups, respectively). The outcomes of these SAEs are provided below:

Outcome	**Cardiac Arrhythmia**	
	Number (%) of Subjects	
	Pomalidomide + Dexamethasone	**High-dose Dexamethasone**
Death	3 (1.0%)[a]	1 (0.7%)[b]
Recovered/resolved	7 (2.3%)	4 (2.7%)
Not recovered/not resolved	2 (0.7%)	0
Total subjects with SAEs	12 (4.0%)	5 (3.4%)

[a] Events of cardiac arrest, cardio-respiratory arrest and sudden death were reported by 1 (0.3%) subject each.

[b] A single (0.7%) subject reported cardiac arrest.

Note: only treatment-emergent SAEs are included in the table.

Severity and Nature of Risk

Study MM-007 (pomalidomide plus bortezomib and low-dose dexamethasone versus bortezomib and low-dose dexamethasone alone)

The severity of SAEs of cardiac arrhythmia are provided below:

Severity	**Cardiac Arrhythmia**	
	Number (%) of Subjects	
	Pomalidomide + Bortezomib + Dexamethasone	**Bortezomib + Dexamethasone**

Table 2.7.3.1-7: Important Potential Risk: Cardiac Arrhythmia

Cardiac Arrhythmia

Grade 3	7 (2.5%)	3 (1.1%)
Grade 4	1 (0.4%)	0
Grade 5	0	0
Total	13 (4.7%)[a]	4 (1.5%)[b]

[a] Total includes Grade 2 SAEs in 5 (1.8%) subjects.

[b] Total includes a Grade 2 SAE in 1 (0.4%) subject.

The most common severe SAE of cardiac arrhythmia was AF (Grade 3 in 4 [1.4%] subjects and Grade 4 in 1 [0.4%] subject treated with pomalidomide, bortezomib and low-dose dexamethasone and Grade 3 in 2 [0.7%] subjects treated with bortezomib and low-dose dexamethasone alone).

Studies MM-002, MM-003, and IFM-2009-02 pooled (pomalidomide-treated subjects with RRMM)

The severity of SAEs of cardiac arrhythmia are provided below:

Severity	**Cardiac Arrhythmia**
	Number (%) of Subjects
Grade 3	8 (1.8%)
Grade 4	1 (0.2%)
Grade 5	3 (0.7%)
Total	16 (3.5%)[a]

[a] Includes 4 (0.9%) subjects reporting Grade 2 SAEs.

The most common severe SAE of cardiac arrhythmia was AF (Grade 3 in 5 [1.1%] subjects).

Study MM-003 (pomalidomide plus low-dose dexamethasone versus high-dose dexamethasone)

The severity of SAEs of cardiac arrhythmia are provided below:

Severity	**Cardiac Arrhythmia**	
	Number (%) of Subjects	
	Pomalidomide + Dexamethasone	**High-dose Dexamethasone**
Grade 3	5 (1.7%)	2 (1.3%)
Grade 4	1 (0.3%)	0
Grade 5	3 (1.0%)	1 (0.7%)
Total	12 (4.0%)[a]	5 (3.4%)[b]

[a] Includes 3 (1.0%) subjects reporting Grade 2 SAEs.

Table 2.7.3.1-7: Important Potential Risk: Cardiac Arrhythmia

Cardiac Arrhythmia	
	[b] Includes 2 (1.3%) subjects reporting Grade 2 SAEs. The frequency of SAEs of Grade 3, 4 or 5 was low in both treatment groups.
Risk factors and risk groups	The AnTicoagulation and Risk Factors in Atrial Fibrillation (ATRIA) study showed that AF occurred more often in men than in women and the prevalence rates were 0.1% in people < 55 years of age to 3.8% in those ≥ 60 years of age to 9% in people ≥ 80 years of age.[99]
Preventability	No mechanisms by which pomalidomide may cause cardiac arrhythmias have been identified. Section 4.4 of the SmPC states that patients with significant cardiac dysfunction (CHF [New York Heart Association Class III or IV]; MI within 12 months of starting study; unstable or poorly controlled angina pectoris) were excluded from clinical studies with pomalidomide. Cardiac events, including congestive cardiac failure, pulmonary oedema and atrial fibrillation have been reported, mainly in patients with pre-existing cardiac disease or cardiac risk factors. Appropriate caution should be exercised when considering the treatment of such patients with pomalidomide, including periodic monitoring for signs or symptoms of cardiac events. Further details of the risk minimisation measures for the risk of cardiac arrhythmia are outlined in Part V.
Impact on the risk-benefit balance of the product	Can have mild to severe to life-threatening or fatal impact. Symptoms can be mild or moderate with no or minimal non-invasive medical intervention indicated. Severe or life-threatening symptoms may warrant urgent invasive intervention (eg, pacemaker, ablation).
Public health impact	AF is the most prevalent major arrhythmia in the elderly.[100] In the US, 80% of AF occurs in patients over the age of 65 years. In the Framingham Heart Study, 2.2% of men had AF and women had a slightly lower prevalence of 1.7%.[100] Drug-induced cardiotoxicity may present as drug-induced arrhythmia.[101] Patients who develop AF are at increased risk of serious cardiovascular complications, such as heart failure and ischaemic stroke.[101] However, an association between cardiac arrhythmias and pomalidomide in combination with dexamethasone or pomalidomide alone cannot be established.
Data source	Studies MM-007, MM-001, MM-002, MM-003, and IFM-2009-02.
MedDRA terms	*MM-007* PTs listed within the MedDRA v20.0 narrow scope of all sub-SMQs of cardiac arrhythmias (except for the sub-SMQ of congenital and neonatal arrhythmias). *MM-001, MM-002, MM-003, and IFM-2009-02* PTs listed within the MedDRA v14.0 SMQs narrow scope of arrhythmia related investigations, signs and symptoms; bradyarrhythmia terms, nonspecific; conduction defects; disorders of sinus node function; cardiac arrhythmia terms, nonspecific; supraventricular tachyarrhythmias;

Table 2.7.3.1-7: Important Potential Risk: Cardiac Arrhythmia

Cardiac Arrhythmia	
	tachyarrhythmia terms, nonspecific; and ventricular tachyarrhythmias are collectively referred to as cardiac arrhythmia.

2.7.3.2 Presentation of the Missing Information

Not applicable.

2.8 Summary of the Safety Concerns

Safety concerns are summarized in Table 2.8-1.

Table 2.8-1: 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

3 PART III: PHARMACOVIGILANCE PLAN

3.1 Routine Pharmacovigilance Activities

Routine Pharmacovigilance activities in BMS as described in the BMS Pharmacovigilance System Master File and Drug Safety's Standard Operating Procedures are in accordance with "Good Pharmacovigilance Practices in the EU".

In addition to expedited reporting, BMS vigilantly undertakes follow-up on all ADRs, including serious ADRs that are provided to health authorities to ensure that all details of the case are captured for optimal clinical evaluation. This includes efforts to obtain all relevant information and to establish the final outcome of the ADRs.

3.1.1 An Analysis of Adverse Drug Reactions of Special Interest within the Required PSURs

Emerging potential safety signals can be detected by periodic and if appropriate, cumulative evaluation of the ADRs. The results are compiled in the PSUR with summaries and conclusions submitted to the health authorities. PSURs are submitted in accordance with "Guidelines on Good

Pharmacovigilance Practices in the EU". Periodicity of the PSUR submissions is defined by the most current EURD list.

In addition, data regarding pregnancy exposure to pomalidomide are targeted for review and specifically discussed in the PSUR document. These data include all pregnancy case reports collected during the specified period together with cumulative data. Non-medically confirmed case reports of suspected foetal exposure are also provided, whenever applicable. Non-patient exposure in pregnant females (eg, a nurse opening the capsules, laboratory technician, or carer) is also provided with the corresponding outcome in each PSUR.

3.1.2 Routine Pharmacovigilance Activities Beyond Adverse Reactions Reporting and Signal Detection

3.1.2.1 Specific Adverse Reaction Follow-up Questionnaire

For events of special interest, materials and tools (such as event-specific questions) have been developed to ensure that consistent and good quality follow-up information can be obtained.

Event-specific questionnaires are used to collect adverse reaction and follow-up information for all of the important identified and potential risks (see Section 2.7.3). These forms are provided in Annex 4 of the RMP.

3.1.2.2 Other Forms of Routine Pharmacovigilance Activities

Expedited Reporting and Follow-up of Pregnancy

The pregnancy capture and follow-up procedure is detailed below.

The PPP aims to minimise the risks of teratogenicity by ensuring HCPs and patients are fully informed of and understand the risks of teratogenicity prior to starting their pomalidomide treatment. Like thalidomide and lenalidomide, pomalidomide is an immunomodulatory agent with expected teratogenic effects in humans. Therefore, the core PPP for pomalidomide is based on the EU and EEA approved core PPP for lenalidomide and thalidomide. It reflects advice, guidance and direction obtained from the Member States during the implementation process for lenalidomide and thalidomide. Where possible and with the agreement of the NCA, BMS harmonised the pomalidomide PPP with the already implemented lenalidomide PPP and/or thalidomide PPP in each Member State. In order to ensure there is a consistent approach with the ability to capture all information globally, the same principles on obtaining follow-up data on pregnancies are implemented in all territories where pomalidomide is marketed whilst taking into account the legal and healthcare differences in those territories worldwide.

The objectives of the system are:

- To obtain information on all reported pregnancies of females exposed to pomalidomide.
- To obtain information on all reported pregnancies of female partners of male patients exposed to pomalidomide.
- To determine the root cause of all pregnancies and hence failures of the PPP.

In the EU, BMS uses the following method to enhance the capture of reports of pregnancy over and above reliance upon spontaneous reporting:

- Standard Initial Pregnancy Reporting Forms, which are included with each HCP Kit.
- The Educational Materials in the Educational HCP's Kit make reference to the requirement to report all suspected pregnancies to the local BMS office and where applicable to the NCA. The Patient Brochure also advises the patient to immediately seek medical advice if there is any risk or suspicion of possible pregnancy. Similar advice is also provided with reference to female partners of male patients.

Database of Pregnancy Reports

All reports of pregnancies received by BMS are entered into BMS's Global Safety Database. This includes all Consumer reports in addition to HCP reports. Any abnormal pregnancy test result (eg, β-hCG elevated and positive urine pregnancy test) is immediately processed. EU Health Authorities are notified of these reports.

Follow-up

All reports of pregnancies are followed up. Follow-up is via the physician/obstetrician/neonatologist/paediatrician as appropriate. In each country office, any report of pregnancy is followed up by the Drug Safety staff. All reports of pregnancy are also immediately notified to the QPPV and QPPV deputies.

All reports of abnormal pregnancy test results are followed up with the prescriber and follow-up information sent to Health Authorities.

Frequency/Duration of Follow-up

Upon receipt of a notification of pregnancy, the HCP is asked to complete the Initial Pregnancy Report Form. The Initial Pregnancy Report Form includes a field for Estimated Date of Delivery. Upon receipt of this information by BMS, dates for further follow-up actions are tracked.

The HCP/Obstetrician is also sent a Follow-Up and Outcome Form to be completed at the outcome of the Pregnancy.

An Infant follow-up form is available for use in the event that a birth defect is detected as an outcome.

Corresponding standard forms are available on request.

Root Cause of Failure of Pregnancy Prevention Programme

The Pregnancy Background Form includes questions to determine why the PPP was unsuccessful for the case in question.

Regulatory Reporting of Pregnancies

All initial pregnancy reports and follow-up information are reported on an expedited basis within 15 days.

Should any suspected teratogenic effect be reported following treatment with pomalidomide, this is expedited immediately.

Compliance with the PPP is monitored in each member state. Examples of methods to monitor compliance include keeping a record of counselling patients prior to prescription, a record of a negative pregnancy test within 3 days of prescription and a record of dispensing within 7 days of the prescription date, etc. The maximum interval of consecutive PPP compliance studies is agreed on between BMS and individual NCAs.

3.2 Additional Pharmacovigilance Activities and Action Plans

3.2.1 Pregnancy Prevention Programme Implementation

The pregnancy capture and follow-up procedure is detailed above.

Physicians are encouraged or required as by local legislation to report pregnancies to BMS or in accordance to local legislation to the NCA.

Additional monitoring of the implementation of the BMS PPP is carried out on a country basis in agreement with relevant NCA (Table 3.2.1-1).

A postmarketing surveillance study (Study CC-4047-MM-015, described in Table 3.2.1.1-1) is also being performed in Member States where this is feasible and active reporting of pregnancies is encouraged through this study.

Table 3.2.1-1: Pregnancy Prevention Programme Implementation

Study Short Name and Title	Rationale and Study Objectives	Study Design	Study Population	Milestones
Monitoring of PPP implementation.	Monitoring of implementation of PPP.	Additional monitoring of implementation of BMS PPP on a country-specific basis in accordance with local legal framework and with agreement of the relevant NCA (see Annex 6)	Patients in the EU receiving pomalidomide.	Ongoing. In line with the PSUR.

3.2.1.1 Additional Studies

Study CC-4047-MM-015:[102] A noninterventional postauthorisation registry of patients treated with pomalidomide for RRMM is ongoing. This will monitor the incidence of ADRs in the "real world" situation and monitor the implementation and compliance of the BMS PPP and controlled access system on a country basis in agreement with the relevant NCA (ie, monitoring of Patient Card completion). The draft registry protocol was submitted to PRAC in Sep 2013. PRAC approval of the registry protocol occurred on 05-Dec-2013 (endorsement). Following PRAC approval of the CC-4047-MM-015 protocol in Dec 2013, a revised protocol incorporating the PRAC comments was finalised as Version 2.0 on 08-Jan-2014 and sent to PRAC on 21-Jan-2014 without need for further approval. On 22-Mar-2017, a revised proposed protocol for

CC-4047-MM-015 was submitted to the EMA, in response to the points raised in the PRAC Outcome (EMEA/H/C/PSA/S/0012) dated 12-Jan-2017. These revisions reflected updated timelines for the end of recruitment and submission of the final study report as well as the sample size, research question and objectives and research methods. On 09-Jun-2017, the PRAC endorsed the pomalidomide PASS protocol revisions (CC-4047-MM-015 Version 3.0 finalised as Version 4.0) proposed by the MAH. On 29-Sep-2022, the PRAC endorsed the PASS protocol amendment (CC-4047-MM-015, Version 5.0). As of 10-Oct-2022, 761 subjects have been enrolled in 111 active sites (Table 3.2.1.1-1).

Table 3.2.1.1-1: Study CC-4047-MM-015

Study Short Name and Title	Rationale and Study Objectives	Study Design	Study Population	Milestones
CC-4047-MM-015 A noninterventional postauthorisation registry of patients treated with pomalidomide for RRMM who have received at least two prior treatment regimens, including both lenalidomide and bortezomib, and have demonstrated disease progression on the last therapy.	Monitor incidence of ADRs in "real world situation" and implementation and compliance of BMS PPP.	Noninterventional postauthorisation registry.	Patients treated with pomalidomide for RRMM who have received at least two prior treatment regimens, including both lenalidomide and bortezomib, and have demonstrated disease progression on the last therapy.	Ongoing Submission of draft registry protocol to PRAC: Sep 2013 First review by PRAC completed: 05-Dec-2013 Submission of updated registry protocol (based on initial PRAC comments) to PRAC: 14-Jan-2014 (inclusion of minor adjustments after PRAC endorsement) Revised proposed protocol submitted to the EMA on 22-Mar-2017, in response to the points raised in the PRAC Outcome (EMEA/H/C/PSA/S/0012) dated 12-Jan-2017. Protocol revisions endorsed by PRAC on 09-Jun-2017. Start patient recruitment: 26-Jun-2014 Final CSR expected Q1-2025

3.2.1.2 Second Primary Malignancies Monitoring in Ongoing Studies

Invasive SPM will be considered important medical events. Monitoring of SPM in clinical trials is described in Table 3.2.1.2-1.

Table 3.2.1.2-1: Solicited Reporting and Long-term Follow-up of SPM

Study Short Name and Title	Rationale and Study Objectives	Study Design	Study Population	Milestones
SPM monitoring	Long-term safety evaluation and monitoring in the context of clinical trials. Monitor incidence of SPM in the clinical trial setting. Long-term follow-up of SPM in the clinical trial setting.	Solicited reporting and long-term follow-up of SPM in all BMS-sponsored clinical studies. Long-term (at least 5 years from the date of the randomisation of the last patient in the study) follow-up in all BMS-sponsored clinical studies	Patients receiving pomalidomide in clinical trials.	Start with approval Analysis on ongoing basis PSUR/ Development Safety Update Report (DSUR) cycle

3.3 Summary Table of Additional Pharmacovigilance Activities

Table 3.3-1: On-going and Planned Additional Pharmacovigilance Activities

Study / Status	Summary of objectives	Safety concerns addressed	Milestone(s)	Due Date(s)
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 BMS 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	Q1-2025 (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 BMS-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
Long-term follow-up of SPM in all BMS-sponsored clinical studies Started	• Long-term follow-up of SPM in all BMS-sponsored clinical studies	NMSC, other SPM	Please note: Ongoing. Safety updates to be submitted with future PSURs.	PSUR/DSUR cycle

4 PART IV: PLANS FOR POST-AUTHORIZATION EFFICACY STUDIES

There are no planned or ongoing postauthorisation efficacy studies for pomalidomide

5 PART V: RISK MINIMISATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMISATION ACTIVITIES)

The core requirements of the PPP, other additional risk minimisation measures and controlled access apply across all Member States, however, the local implementation may differ between Member States taking into account the local differences in healthcare delivery, legal framework, and culture. Therefore, consultations will take place with NCAs to determine the appropriate method of delivery of the PPP, other additional risk minimisation measures, and controlled access system in each Member State. The MAH has a number of years' experience running such risk minimisation measures for both thalidomide and lenalidomide, and the pomalidomide programme is similar to existing thalidomide and lenalidomide programmes. However, in some countries, the more than 5 years implemented controlled access system differs between products according to NCA agreement within one country.

In countries where pomalidomide is already marketed, DHPC has provided the most important information on the safety and the risk minimisation measures to be taken in a non-promotional, clear and consistent way across the EU. The DHPC mentioned:

- That a PPP has been implemented in conjunction with the NCAs and the importance that the PPP should be adhered to.
- That educational HCP kits are available and will be provided to them and that they are not promotional material.
- The approved indication to reduce "off-label" use with a different target population with a higher rate of women of childbearing potential impacted and the risk of teratogenicity.

It must also be noted that other activities aimed at minimising the risk of other safety concerns, such as myelosuppression are also included in the additional risk minimisation activities.

5.1 Routine Risk Minimisation Measures

Summaries of the risk minimisation measures for the identified and potential risks and missing information requiring additional risk minimisation activities are provided in Table 5.1-1.

Table 5.1-1: Description of Routine Risk Minimisation Measures by Safety Concern

Safety concern	Routine risk minimisation activities
Important Identified Risks	
Teratogenicity	**Routine risk communication:** The risk of teratogenicity is discussed in Section 4.8 of the SmPC. The PL warns of the potential teratogenic effects of pomalidomide and the need to avoid pregnancy.

Table 5.1-1: Description of Routine Risk Minimisation Measures by Safety Concern

Safety concern	Routine risk minimisation activities
Important Identified Risks	
	Routine risk minimisation activities recommending specific clinical measures to address the risk: Pomalidomide is 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 (SmPC Section 4.3). Stringent controls are required to ensure exposure of an unborn child to pomalidomide does not occur (SmPC Section 4.4). These include: • Counselling • Contraception • Pregnancy testing • Precautions for men • Additional precautions • Prescription duration Further information is provided in Sections 4.6 and 5.3 of the SmPC. **Other routine risk minimisation measures beyond the Product Information:** Pomalidomide is subject to restricted medical prescription.
Severe Infection due to Neutropenia and Pancytopenia	**Routine risk communication:** Neutropenia, pancytopenia, and infections and infestations are listed as ADRs and neutropenia and infection are discussed in Section 4.8 of the SmPC. The PL warns that pomalidomide may cause a fall in the number of RBCs, WBCs, and platelets at the same time (pancytopenia), and describes possible symptoms. It also warns that if a patient has had HBV infection pomalidomide may cause the virus to become active again; therefore, the doctor is advised to check if the patient has ever had hepatitis B infection prior to pomalidomide treatment. Infections, including shingles and recurrence of hepatitis B infection, are listed as possible side effects. **Routine risk minimisation activities recommending specific clinical measures to address the risk:** Dose modification advice for neutropenia is included in Section 4.2 of the SmPC. A warning of neutropenia and advice for blood tests at baseline, weekly for the first 8 weeks and monthly thereafter, is included in Section 4.4 of the SmPC. Section 4.4 of the SmPC also provides a warning regarding HBV reactivation and advises that HBV status should be established before initiating treatment with pomalidomide. Patients should be closely monitored for signs and symptoms of active HBV infection throughout therapy.

Table 5.1-1: Description of Routine Risk Minimisation Measures by Safety Concern

Safety concern	Routine risk minimisation activities
Important Identified Risks	
	Other routine risk minimisation measures beyond the Product Information: Pomalidomide is subject to restricted medical prescription.
Thrombocytopenia and Bleeding	**Routine risk communication:** Thrombocytopenia, intracranial haemorrhage and gastrointestinal haemorrhage are discussed and listed as ADRs in Section 4.8 of the SmPC. The PL warns that pomalidomide may cause bleeding or bruising without a cause. This document lists bleeding within the skull, nosebleeds and bleeding from the bowels or stomach as possible side effects. **Routine risk minimisation activities recommending specific clinical measures to address the risk:** Dose modification advice for thrombocytopenia is included in Section 4.2 of the SmPC. A warning of thrombocytopenia and advice for blood tests at baseline, weekly for the first 8 weeks and monthly thereafter, is included in Section 4.4 of the SmPC. Advice for physicians to observe patients for signs of bleeding including epistaxes, especially with use of concomitant medicinal products known to increase the risk of bleeding, is also included. **Other routine risk minimisation measures beyond the Product Information:** Pomalidomide is subject to restricted medical prescription.
Cardiac Failure	**Routine risk communication:** Cardiac failure is listed as an ADR in Section 4.8 of the SmPC. A warning regarding heart failure is included in the PL. **Routine risk minimisation activities recommending specific clinical measures to address the risk:** 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 events. **Other routine risk minimisation measures beyond the Product Information:** Pomalidomide is subject to restricted medical prescription.
Non-melanoma Skin Cancer	**Routine risk communication:** BCC of the skin and SCC of the skin are listed as ADRs in Section 4.8 of the SmPC. A warning regarding BCC and SCC is included in the PL. **Routine risk minimisation activities recommending specific clinical measures to address the risk:** Section 4.4 of the SmPC provides a warning that physicians should carefully evaluate patients before and during treatment using standard cancer screening for occurrence of SPM and institute treatment as indicated.

Table 5.1-1: Description of Routine Risk Minimisation Measures by Safety Concern

Safety concern	Routine risk minimisation activities
Important Identified Risks	
	Other routine risk minimisation measures beyond the Product Information: Pomalidomide is subject to restricted medical prescription.
Important Potential Risks	
Other Second Primary Malignancies	**Routine risk communication:** Section 4.4 of the SmPC states that SPM have been reported in patients receiving pomalidomide. **Routine risk minimisation activities recommending specific clinical measures to address the risk:** Section 4.4 of the SmPC provides a warning that physicians should carefully evaluate patients before and during treatment using standard cancer screening for occurrence of SPM and institute treatment as indicated. **Other routine risk minimisation measures beyond the Product Information:** Pomalidomide is subject to restricted medical prescription.
Cardiac Arrhythmias	**Routine risk communication:** AF is listed as an ADR in Section 4.8 of the SmPC. AF is listed in the PL. **Routine risk minimisation activities recommending specific clinical measures to address the risk:** None proposed. **Other routine risk minimisation measures beyond the Product Information:** Pomalidomide is subject to restricted medical prescription.
Missing Information	
None	

5.2 Additional Risk Minimisation Measures

Additional risk minimisation measures are summarised in Table 5.2-1 and Annex 6.

Table 5.2-1: Additional Risk Minimisation Measures

Pregnancy Prevention Programme	**Objectives:** The BMS PPP is designed to minimise the risk of teratogenicity by: • Ensuring that exposure of an unborn child to pomalidomide does not occur • Ensuring early alert to the physician of any pregnancies • Educating patients and HCPs on the safe use of pomalidomide • Pregnancy testing and contraceptive requirements • A system to ensure that all appropriate measures have been performed prior to the drug being dispensed

Table 5.2-1: Additional Risk Minimisation Measures

- Managing and monitoring the distribution of pomalidomide
- Follow-up on the effectiveness of the PPP
- Compliance monitoring and assessment (examples include record of counselling patients prior to prescription, record of negative pregnancy test within 3 days of prescription and record of dispensing within 7 days of prescription date).

This controlled access is designed to minimise the risk of exposure to paediatric patients or non-target populations and provide education on the risk and the necessary steps to prevent foetal exposure.

Rationale for the additional risk minimisation activity:

To minimise the risk of teratogenicity and provide education on the risk and necessary steps to prevent foetal exposure to pomalidomide.

Target audience and planned distribution path:
The target audience is HCPs who will prescribe pomalidomide and patients.

Proposed Actions

The key elements of the BMS PPP are:

- Direct communication with the HCP prior to launch ('Dear HCP' letter).
- Educational Programme:
  - Educational HCP's kit to include educational healthcare professional brochure, educational brochures for patients, patient card, risk awareness forms, and information on where to find latest SmPC.
- Therapy management
- Prescribing controls
- Dispensing controls
- Assessment

The Patient Card and/or an equivalent tool is used to manage the controlled access within the national territory as agreed with the NCA.

- **Plans to evaluate the effectiveness of the interventions and criteria for success:**
- Compliance with the PPP will be monitored in each member state in agreement with the relevant NCA (eg, record of counselling patients prior to prescription, record of a negative pregnancy test within 3 days of prescription and a record of dispensing within 7 days of the prescription date, etc).
- 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 the implementation and compliance of BMS PPP and controlled access system on a country basis in agreement with the relevant NCA (ie, monitoring of Patient Card completion).

Proposed Review Period

The BMS PPP will be analysed on an ongoing basis and summarised at the time of the PSUR with respect to any pregnancy exposures. Additional information to be provided in the updates include:

- Status of the implementation in each Member State.
- Any adaptations to the PPP will be included as an update.

Table 5.2-1: Additional Risk Minimisation Measures

	• The results of any compliance measurements as process indicators undertaken in individual countries according to country specific agreements with NCAs. • Reports of pregnancy exposure to be reviewed on an ongoing basis and summarised at the time of the PSUR overall and by country. • Root causes for pregnancy exposure. • Outcome of pregnancy. • Modifications and corrective action will be taken accordingly. Criteria for Success Outcome indicator: pregnancy exposures
Additional HCP Educational Materials • Educational healthcare professional brochure • Information on where to find latest SmPC	**Objectives:** Provision of information to HCPs for the risks of: • Thrombocytopenia and bleeding • Cardiac failure **Rationale for the additional risk minimisation activity:** HCPs to understand the risks specified above and the appropriate management of these risks. **Target audience and planned distribution path:** Pomalidomide HCP additional educational materials to be provided to prescribing physicians and pharmacists. • **Plans to evaluate the effectiveness of the interventions and criteria for success:** • Study CC-4047-MM-015: Noninterventional postauthorisation registry of patients treated with pomalidomide for RRMM to monitor incidence of ADRs in "real world" situation. • Expedited reporting (evaluation plus reporting [E+R]) as per EU guidance, GVP • PSUR as per EU guidance, GVP (E+R) Criteria for Success No significant increase in frequency of reports in the postmarketing setting as presented in the SmPC. Planned Dates for Assessment Next PSUR update with next data-lock point covered.
Direct HCP Communication Prior to Launch ('Dear HCP' Letter)	**Objectives:** Provision of information to HCPs for the risk of teratogenicity. 'Dear HCP' Letter to be provided to prescribing physicians and pharmacists to inform on the risk of teratogenicity and the implemented PPP. **Rationale for the additional risk minimisation activity:** Healthcare professionals to understand the risk specified above and the appropriate management of this risk. **Target audience and planned distribution path:** The target audience is HCPs who will prescribe pomalidomide.

Table 5.2-1: Additional Risk Minimisation Measures

	Plans to evaluate the effectiveness of the interventions and criteria for success: Compliance with the PPP will be monitored in each member state (eg, record of counselling patients prior to prescription, record of a negative pregnancy test within 3 days of prescription and a record of dispensing within 7 days of the prescription date, etc). • 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 the implementation and compliance of the BMS PPP and controlled access system on a country basis in agreement with the relevant NCA (ie, monitoring of Patient Card completion). • Reports of pregnancy exposure to be reviewed on an ongoing basis and summarised at the time of the PSUR.
Additional Patient Educational Materials • Educational brochures for patients	**Objectives:** Provision of a Pomalidomide Patient brochure to patients for the risk of Thrombocytopenia and bleeding. **Rationale for the additional risk minimisation activity:** A Pomalidomide Patient brochure is provided as additional educational material to advise that pomalidomide may cause thrombocytopenia and the need for regular blood tests. **Target audience and planned distribution path:** The target audience is patients who are prescribed pomalidomide. **Plans to evaluate the effectiveness of the interventions and criteria for success:** • Study CC-4047-MM-015: Noninterventional postauthorisation registry of patients treated with pomalidomide for RRMM to monitor incidence of ADRs in "real world" situation. • Expedited reporting (E+R) as per EU guidance, GVP • PSUR as per EU guidance, GVP (E+R) Criteria for Success No significant increase in frequency of reports in the postmarketing setting as presented in the SmPC. Planned Dates for Assessment Next PSUR update with next data-lock point covered.

5.3 Summary of Risk Minimization Measures

A summary of risk minimization measures and pharmacovigilance activities by safety concern is provided in Table 5.3-1.

Table 5.3-1: Summary of Risk Minimization Measures and Pharmacovigilance Activities

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Important Identified Risks		
Teratogenicity	**Routine risk minimisation measures:** 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.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • Expedited reporting of all pregnancies and abnormal pregnancy test results. • Pregnancy specific questionnaires for collection of detailed initial and follow-up information for pregnancies (see Annex 4). • 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 BMS PPP as part of standard follow-up.
	Additional risk minimisation measures: BMS PPP • Educational Programme – DHPC prior to launch (‘Dear HCP’ Letter). – Educational HCP’s kit to include educational healthcare professional brochure, educational brochures for patients, patient card, risk awareness forms, and information on where to find latest SmPC. • Therapy management – Criteria for determining women of childbearing potential, contraceptive measures and pregnancy testing for women of childbearing potential.	**Additional pharmacovigilance activities:** 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 BMS PPP on a country basis in agreement with the relevant NCA (ie, monitoring of Patient Card completion).

Table 5.3-1: Summary of Risk Minimization Measures and Pharmacovigilance Activities

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
	– Advice in SmPC, DHPC and educational materials. • System to ensure appropriate measures have been completed – Patient Card to document childbearing status, counselling and pregnancy testing.	
Severe Infection due to Neutropenia and Pancytopenia	**Routine risk minimisation measures:** 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 fall in the number of RBCs, WBCs, and platelets at the same time (pancytopenia), and describes possible symptoms.	**Routine pharmacovigilance activities 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 risk minimisation measures: None proposed.	**Additional pharmacovigilance activities:** 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 measures:** 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	**Routine pharmacovigilance activities 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

Table 5.3-1: Summary of Risk Minimization Measures and Pharmacovigilance Activities

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
	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 bleeding or bruising without a cause, and lists bleeding within the skull, nosebleeds and bleeding from the bowels or stomach as possible side effects.	• Additional information from ongoing clinical trials • Event specific questionnaire for the collection of the AE and follow-up.
	Additional risk minimisation measures: • Educational HCP brochure. • Educational brochure for patients.	**Additional pharmacovigilance activities:** Study CC-4047-MM-015: Noninterventional postauthorisation registry of patients treated with pomalidomide for RRMM to monitor incidence of ADRs in "real world" situation.
Cardiac Failure	**Routine risk minimisation measures:** 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 events. • Listed as an ADR in Section 4.8. PL • A warning regarding heart failure is included in the PL.	**Routine pharmacovigilance activities 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 risk minimisation measures: • Educational HCP brochure.	**Additional pharmacovigilance activities:** 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 measures:** 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.	**Routine pharmacovigilance activities 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.

Table 5.3-1: Summary of Risk Minimization Measures and Pharmacovigilance Activities

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
	• 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 measures:** • None proposed.	• **Additional pharmacovigilance activities:** • 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 BMS-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 BMS-sponsored clinical studies
Important Potential Risks		
Other Second Primary Malignancies	**Routine risk minimisation measures:** 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 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 measures:** None proposed.	**Routine pharmacovigilance activities 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 activities:** • 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 BMS-sponsored clinical studies (status

Table 5.3-1: Summary of Risk Minimization Measures and Pharmacovigilance Activities

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
		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 BMS-sponsored clinical studies • Invasive SPM will be considered important medical events.
Cardiac Arrhythmia	**Routine risk minimisation measures:** SmPC • AF listed as an ADR in Section 4.8. PL • AF listed in PL.	**Routine pharmacovigilance activities 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 risk minimisation measures: None proposed.	**Additional pharmacovigilance activities:** 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.		

6 SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of risk management plan for IMNOVID (POMALIDOMIDE)

This is a summary of the risk management plan (RMP) for Imnovid. The RMP details important risks of Imnovid, how these risks can be minimised, and how more information will be obtained about Imnovid 's risks and uncertainties (missing information).

Imnovid 's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Imnovid should be used.

This summary of the RMP for Imnovid should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Imnovid's RMP.

I. The medicine and what it is used for

Imnovid in combination with dexamethasone is indicated for the treatment of adult patients with relapsed and refractory multiple myeloma (RRMM) who have received at least two prior treatment regimens, including both lenalidomide and bortezomib, and have demonstrated disease progression on the last therapy (see SmPC for the full indication). Imnovid contains pomalidomide as the active substance and it is given by oral route of administration.

Imnovid in combination with bortezomib and dexamethasone is indicated for the treatment of adult patients with MM who have received at least one prior treatment regimen including lenalidomide.

Further information about the evaluation of Imnovid's benefits can be found in Imnovid's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpagehttp://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/002682/human_med_001669.jsp&mid=WC0b01ac058001d124.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Imnovid, together with measures to minimise such risks and the proposed studies for learning more about Imnovid's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals
- Important advice on the medicine's packaging
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly

- The medicine's legal status — the way a medicine is supplied to the patient (eg, with or without prescription) can help to minimise its risks

Together, these measures constitute *routine risk minimisation* measures.

In the case of Imnovid, these measures are supplemented with *additional risk minimisation measures* mentioned under relevant important risks, below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment, so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

II.A List of important risks and missing information

Important risks of Imnovid are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Imnovid. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected.

List of important risks and missing information

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

II.B Summary of important risks

Important identified risks

Teratogenicity	
Evidence for linking the risk to the medicine	Pomalidomide is structurally related to thalidomide, a known human teratogen that causes severe life-threatening birth defects. Pomalidomide was found to be teratogenic in both rats and rabbits when administered during the period of major organogenesis. If pomalidomide is taken during pregnancy, a teratogenic effect of pomalidomide in humans is expected. Although women of childbearing potential taking pomalidomide are particularly at risk, female partners of male patients taking pomalidomide are also at risk as pomalidomide may be present in semen.
Risk factors and risk groups	The 'at risk' group comprises female patients of childbearing potential or female partners of male patients treated with pomalidomide.
Risk minimization measures	Routine risk minimization activities: SmPC • Contraindicated in pregnant women and in women of childbearing potential, unless all the conditions of the Pregnancy Prevention Programme (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 minimization measures: BMS PPP • Educational Programme – Direct Healthcare Professional Communication (DHPC) prior to launch ('Dear HCP' Letter). – Educational HCP's kit to include educational healthcare professional brochure, educational brochures for patients, patient card, risk awareness forms, and information on where to find latest SmPC. • Therapy management – Criteria for determining women of childbearing potential, contraceptive measures and pregnancy testing for women of childbearing potential. – Advice in SmPC, DHPC and educational materials. • Controlled access system to ensure appropriate measures have been completed

Important identified risks

	– Patient Card to document childbearing status, counselling and pregnancy testing.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Study CC-4047-MM-015: Noninterventional postauthorisation registry of patients treated with pomalidomide for RRMM to monitor the incidence of ADRs in the "real world" situation and to monitor the implementation and compliance of the BMS PPP and controlled access system on a country basis in agreement with the relevant National Competent Authority (NCA; ie, monitoring of Patient Card completion).
Severe Infection due to Neutropenia and Pancytopenia	
Evidence for linking the risk to the medicine	In non-clinical studies, decreased WBC counts (neutrophils, lymphocytes, and monocytes) were observed. In the clinical studies, infection was the most common non-haematological toxicity reported in patients who received pomalidomide, and approximately half of the events were Grade 3 or 4. The most commonly reported adverse reactions in clinical studies have been blood and lymphatic system disorders including neutropenia, and it is one of the major dose-limiting toxicities of pomalidomide. Pancytopenia has been identified from postmarketing data. In clinical studies, pancytopenia has been reported as a common ADR of pomalidomide treatment.
Risk factors and risk groups	*Neutropenia* By far the most common cause of neutropenia in oncology practice is the myelosuppressive effects of cytotoxic chemotherapy and radiation treatment. Because of their relatively short life spans, neutrophils are particularly sensitive to the effects of recently administered chemotherapy, and nadirs of neutrophil counts are frequently observed 7 to 10 days following the administration of chemotherapy. Less commonly, antibodies to neutrophils, bone marrow infiltration with disruption of normal marrow stromal function, and splenic sequestration can play a role. Although there are several glycoproteins with effects on neutrophil precursor cells including interleukin 3, granulocyte macrophage colony stimulating factor, and macrophage colony stimulating factor, G CSF seems to be the primary regulator of basal and emergency neutrophil production as well as mature neutrophil function. There are also negative regulatory factors of neutrophil production that are less well understood, including neutrophil elastase and the src family kinases. Neutropenia can also result from decreased neutrophil survival associated with immune destruction, sequestration, consumption at sites of infection, and the effects of inflammatory cytokines such as tumour necrosis factor. *Pancytopenia* The underlying aetiology and presentation for pancytopenia can include aplastic anaemia, megaloblastic anaemia, MDS, acute lymphoblastic leukaemia, hypersplenism, NHL, MM, acute myeloblastic leukaemia and chronic myelocytic leukaemia. Graft versus host disease has also been described within the literature as contributory to the onset of pancytopenia. A comprehensive review of 61 articles and 87 patients with pancytopenia onset after liver transplantation noted the most frequent presenting symptoms prior to the diagnosis of GvHD included rash (94.2%), fever (66.6%), diarrhoea (54%), and pancytopenia (54%). Diabetes mellitus type II may also contribute to the onset of pancytopenia. Several cross sectional studies and case reports have documented that an

increased frequency of vitamin B12 deficiency among patients with diabetes mellitus type II is commonly related to inadequate dietary intake or malabsorption. Metformin use has been unequivocally demonstrated as the prime factor associated with vitamin B12 deficiency among patients with diabetes mellitus type II. Studies assessing type 2 diabetic patients on metformin have reported the prevalence of vitamin B12 deficiency to range from 5.8% to 33%. Patients enrolled in this study were those who were on high dose (> 2 g/day) and long-term (4 years) metformin treatment, both clinical factors known to be associated with vitamin B12 deficiency. In the absence of concurrent comorbidity like renal and hepatic dysfunction, recent guidelines advocate for the use of metformin as the first-line glucose lowering agent concurrently with life-style modification approaches. Despite its superior glycaemic lowering effect, metformin has long been shown to decrease vitamin B12 levels compounding the risk of megaloblastic anaemia. The risk of developing metformin-associated vitamin B12 deficiency is greatly influenced by increasing age, metformin dose and duration of use.

Severe hepatocellular disease has also demonstrated a relative relationship to anaemia and pancytopenia. This may include acute or chronic gastrointestinal haemorrhage, and hypersplenism secondary to portal hypertension. Severe hepatocellular disease predisposes to haemorrhage because of impaired blood coagulation caused by deficiency of blood coagulation factors synthesised by hepatocytes. Aplastic anaemia, which is characterised by pancytopenia and hypocellular bone marrow may follow the development of hepatitis. In patients with chronic liver disease, anaemia may be exacerbated by deficiency of folic acid and/or vitamin B12.

Without regard to underlying comorbidity, drug-induced pancytopenia is acknowledged with many drug classes. Many patients are on multiple concurrent therapies that may compound the risk of myelosuppressive effects and the induction of pancytopenia. These products, which may be used alone or in combination, include radiotherapy, busulfan, melphalan, cyclophosphamide, anthracyclines, nitrosoureas, amiodarone, chloramphenicol, sulfonamides, gold, anti-inflammatory, anti-thyroid, psychotropic, anticonvulsant and antidepressant drugs.

Infection

Numerous disease-related and chemotherapy-induced factors render the subject with cancer at increased risk for infection. These include the type of cancer, depth and duration of neutropenia, and impairments in cellular function caused by cytotoxic or immunosuppressive drugs; breaches in the integument from surgical procedures, presence of indwelling plastic venous catheters, or mucositis of the gastrointestinal tract secondary to chemotherapy; and comorbid conditions such as malnutrition, deconditioning, or medical problems such as chronic obstructive lung disease or diabetes. In addition, steroid therapy induces a broad immunosuppressive effect, including impaired chemotaxis and killing by neutrophils, impaired T-cell function, and alterations in skin and mucosal barriers. Long-term or high-dose steroid therapy is a significant risk factor for invasive fungal infections in particular; such therapy also may predispose affected subjects to development of bacterial infections and Mycobacterium tuberculosis reactivation.

One US study that utilised the SEER-Medicare database reported that elderly cancer patients run a 1.2 to 2.4 times higher risk of developing VZV than those without cancer. Additional noted risk factors for developing VZV included age, gender, race, immunosuppressive conditions, and certain cancer therapies (eg, haematologic cancer patients: autologous and allogeneic stem cell

Important identified risks

	transplants; solid cancer patients: radiotherapy). Haematologic or solid cancer patients with immunocompromising conditions ran a higher risk of developing VZV, as did haematologic cancer patients who received stem cell transplants (despite the routine use of prophylaxis post-transplant). Cancer patients aged 75 to 85 years old had a higher risk of developing VZV than patients 85 years and older which may be attributed to the different treatment approaches (ie, more aggressive chemotherapies used in younger patients, inducing greater immune suppression) and may lead to different VZV risks. For patients with haematologic malignancies, the risk of developing shingles increases from 13% to 55% the year after a SCT. Risk factors for HBV reactivation include baseline HBV DNA > 105 copies/mL, baseline ALT levels, hepatitis B e antigen seropositivity, corticosteroid therapy, anthracyclines, rituximab, male sex, younger age, and underlying disease of lymphoma or breast cancer. The most common causes of HBV reactivation are the immunosuppression regimens adopted in solid organ transplantation, chemotherapy for onco-haematological diseases and immunosuppressive drugs used in the treatment of autoimmune diseases. The immunosuppressive properties related to chemotherapy can cause flares of HBV in people who carry HBsAg in their serum. Flares can occur despite normal baseline serum ALT levels and can lead to HBV-related morbidity and mortality. The rate of HBV reactivation after allogeneic BMT ranges 14% to 50%, with a lesser rate in autologous BMT; risk factors include corticosteroid use, donor HBsAg antibody sero-negativity, and GvHD. The time-to-recovery of cellular immunity after peripheral blood stem cell transplantation is 3 to 5 months, which is the time course during which HBV reactivation has been documented.
Risk minimization measures	Routine risk minimization measures: SmPC • Dose modification advice for neutropenia (Section 4.2). • Warning regarding hepatitis B virus (HBV) reactivation and advice that HBV status should be established before treatment (Section 4.4). • Warning of neutropenia, and advice for blood tests at baseline, weekly for the first 8 weeks and monthly thereafter (Section 4.4). • Neutropenia, pancytopenia and infections and infestations are listed as adverse drug reactions (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. • The PL warns that pomalidomide may cause a fall in the number of red blood cells, white blood cells (WBCs), and platelets at the same time (pancytopenia), and describes possible symptoms. Additional risk minimization measures: None proposed.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Study CC-4047-MM-015: Noninterventional postauthorisation registry of patients treated with pomalidomide for RRMM to monitor incidence of ADRs in “real world” situation.

Important identified risks

Thrombocytopenia and Bleeding	
Evidence for linking the risk to the medicine	Decreased platelets in the blood and bleeding occur due to MM so may occur during treatment with pomalidomide in combination with dexamethasone. In addition, pomalidomide may cause reductions in platelet numbers which make patients more prone to bleeding.
Risk factors and risk groups	The rate of blood cell production is both tightly regulated and highly variable. Under conditions of either increased destruction of cells, such as bleeding, haemolysis, or immune destruction of platelets, production rates of appropriate cells increase several fold. The regulation of this dynamic system is complex but for practical purposes can be conceived of as involving an interaction between a pool of pluripotent haematopoietic stem cells, capable of both infinite self-renewal and differentiation into mature blood cells and regulatory factors, including both a well-characterised set of glycoprotein haematopoietic growth factors and a less well-understood group of inhibitory factors. The primary regulator of the platelet count in humans is thrombopoietin, a glycoprotein that is produced primarily in the liver and cleared primarily by platelets and their precursors. Thrombopoietin induces growth and development of megakaryocytes; levels fluctuate with changes in platelet count due to variations in clearance. Thrombocytopenia that is encountered in oncology practice may be due to the effects of chemotherapy, or after multiple cycles of treatment, liver disease with decreased thrombopoietin levels, immune destruction, particularly in subjects with lymphoid malignancies or infection with HIV, and sequestration. The incidence of gastrointestinal haemorrhage increases with advanced age. Individuals aged 60 years and older account for 35% to 45% of all cases of UGIB. A review of epidemiology studies of the complications of peptic ulcer disease reported annual incidence rates of haemorrhage ranging from 0.19 to 0.57 per 1000 persons in the general population and an annual incidence of 0.79 per 1000 persons older than 60 years of age. A prospective study of patients undergoing upper gastrointestinal endoscopy at the National University Hospital of Iceland reported annual incidence rates of acute UGIB by age group as follows: 0.30 per 1000 individuals aged 18 to 24 years, 0.15 per 1000 individuals aged 25 to 39 years, 0.48 per 1000 individuals aged 40 to 59 years, 2.13 per 1000 individuals aged 60 to 79 years, and 5.70 per 1000 individuals aged 80 and older. Relatively common medications in the elderly that may predispose individuals to gastrointestinal haemorrhage include aspirin and NSAIDs. A meta-analysis of 24 randomised controlled trials (almost 66,000 participants) revealed gastrointestinal haemorrhage in 2.47% of patients taking aspirin compared with 1.42% taking placebo. A medical record review conducted in Japan reported incidence rates for UGIB of 2.65 and 1.29 per 1000 users of low-dose aspirin and NSAIDs, respectively. A study using the UK GPRD reported a RR of 4.1 (95% CI: 3.5-4.7) of UGIB associated with current NSAID use. Given previously published incidence rates of hospitalisation for peptic ulcer disease among nonusers of NSAIDs of 1 per 1000 person-years, Hernández-Díaz reported that this risk translates to more than 3 additional cases per 1000 exposed persons per year. Also in the UK GPRD study, the risk of serious UGIB or perforation among current users of systemic steroids (85% of which was prednisolone) was RR = 1.8. The risk was greater (RR = 2.9) among users with steroid doses ≥ 30 mg prednisone, but the test for dose-response was non-significant. Steroids were similarly associated with bleeding (OR = 1.8; 95% CI: 1.3-2.4) and perforations (OR = 1.6; 95% CI: 0.9-3.1). Simultaneous

Important identified risks

	use of steroids with low-medium and high NSAID doses, respectively, produced ORs of 4.0 (95% CI: 1.3-12.0) and 12.7 (95% CI: 6.2-26.1), compared with users of none.
Risk minimization measures	Routine risk minimization measures: 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 bleeding or bruising without a cause, and lists bleeding within the skull, nosebleeds and bleeding from the bowels or stomach as possible side effects. Additional risk minimization measures: • HCP additional educational materials. • Patient brochure.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Study CC-4047-MM-015: Noninterventional postauthorisation registry of patients treated with pomalidomide for RRMM to monitor incidence of ADRs in "real world" situation.
Cardiac Failure	
Evidence for linking the risk to the medicine	Cardiac failure has been identified from postmarketing data. In clinical studies, cardiac failure has been reported as a common ADR of pomalidomide treatment.
Risk factors and risk groups	Cardiac symptoms in patients with MM can often be due to anaemia and may be due to iron overload and side effects of therapy and possible fluid overload. General risk factors for CHF include increasing age, previous heart disease, diabetes, hypertension, amyloidosis, and previous anthracycline based chemotherapy treatment. Cardiotoxicity of anthracyclines (eg, doxorubicin, daunorubicin and epirubicin) is usually cumulative and dose dependent. Risk factors include older age, pre-existing heart disease and hypertension.
Risk minimization measures	Routine risk minimization measures: 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 events. • Listed as an ADR in Section 4.8. PL • A warning regarding heart failure is included in the PL. Additional risk minimization measures: HCP additional educational materials.
Additional pharmacovigilance activities	Additional pharmacovigilance activities:

Important identified risks

	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	
Evidence for linking the risk to the medicine	Patients treated with pomalidomide may be at an increased risk of developing new cancers (including skin cancers). In clinical studies, NMSC has been reported in patients receiving pomalidomide. Drug reaction with eosinophilia and systemic symptoms, toxic epidermal necrolysis and Stevens-Johnson syndrome have been observed in the postmarketing setting.
Risk factors and risk groups	Skin colour and being exposed to sunlight are recognised risk factors for NMSC. NMSC is the most frequent malignancy mainly in fair-skinned populations. However other risk factors such as immune disorders, tobacco use, photosensitive drugs, and viral infections (human papilloma virus, HIV) have been reported to be associated with NMSC in rare instances. Rates of NMSC are higher in men as compared to women. NMSC rates are also higher in older age groups. One study based on the US insured population reported the mean age of NMSC was 69 years.
Risk minimization measures	Routine risk minimization measures: SmPC • Section 4.4 contains a warning that secondary primary malignancies (SPM), such as non-melanoma skin cancer (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. • Basal cell carcinoma (BCC) of the skin and squamous cell carcinoma (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 minimization measures: None proposed.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • 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 BMS-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 BMS-sponsored clinical studies

Important potential risks

Other Second Primary Malignancies	
Evidence for linking the risk to the medicine	Patients treated with pomalidomide may be at an increased risk of developing new cancers. In clinical studies, SPM has been reported in patients receiving pomalidomide.
Risk factors and risk groups	Travis has grouped second primary cancers into three major groups based on the predominant etiologic factors ie, treatment related, syndromic, and those due to shared etiologic factors, while emphasising the non-exclusivity of these

Important potential risks

	groups. In the following, possible explanations for the epidemiologic findings presented in the previous section will be discussed. • **Prolonged survival as a result of improved therapies** Due to improvements in the care of patients with cancer, the number of cancer survivors has been increasing in recent years. Increased longevity increases the risk of developing a second malignancy, whether due to the late sequelae of treatment, lifestyle factors, environmental exposures, or host factors (eg, aging, genetic factors, gene-environment interactions), or a combination of these factors. Second solid tumours are a leading cause of mortality among several populations of long-term survivors. As reported from the SEER Cancer Statistics Review 1975 to 2009, the 5-year relative survival among MM patients has increased from 25.1% among patients first diagnosed in 1975 to 1977 to 42.6% among patients first diagnosed between 2002 and 2008 ($p < 0.05$). Among patients aged less than 65 years at first diagnosis between 2002 and 2008, 5-year relative survival is 54.4%; among those aged 65 years and older, survivorship is 31.3%. • **Heredity** Additional insight has also been obtained in elucidating the risk of malignancies in close family members of patients affected by MM. The available data show an increased risk of more than one malignancy in MM patients and first-degree relatives compared to the general population. The reason for this finding is still unclear but may clearly involve risk conferred by shared genetic factors.
Risk minimization measures	Routine risk minimization measures: 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 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 minimization measures: None proposed.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • 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 BMS-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 BMS-sponsored clinical studies Invasive SPM will be considered important medical events.
Cardiac Arrhythmia	
Evidence for linking the risk to the medicine	Patients treated with pomalidomide in combination with dexamethasone may be at increased risk of cardiac arrhythmias. It is unclear whether pomalidomide can cause cardiac arrhythmias. In clinical studies, a greater proportion of patients treated with pomalidomide in combination with dexamethasone

Important potential risks

	reported cardiac arrhythmias compared to patients who were treated with high-dose dexamethasone.
Risk factors and risk groups	The ATRIA study showed that AF occurred more often in men than in women and the prevalence rates were 0.1% in people < 55 years of age to 3.8% in those ≥ 60 years of age to 9% in people ≥ 80 years of age. (Go, 2001)
Risk minimization measures	Routine risk minimization measures: SmPC • AF listed as an ADR in Section 4.8. PL • AF listed in PL. Additional risk minimization measures: None proposed.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Study CC-4047-MM-015: Noninterventional posauthorisation registry of patients treated with pomalidomide for RRMM to monitor incidence of ADRs in "real world" situation.

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

Study short name: Study CC-4047-MM-015

Purpose of the study: A noninterventional postauthorisation registry of patients treated with pomalidomide for RRMM to monitor the incidence of ADRs in the "real world situation", as well as monitoring the implementation and compliance of the BMS PPP and controlled access system on a country basis in agreement with the relevant NCA. **II.C.2 Other studies or activities in post-authorisation development plan**

Solicited Reporting of SPM in all BMS-Sponsored Clinical Studies

Purpose of activity: To monitor incidence of SPM in all BMS-sponsored clinical studies.

Long-term Follow-up of SPM in all BMS-Sponsored Clinical Studies

Purpose of activity: Long-term follow-up of SPM in all BMS-sponsored clinical studies.

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ANNEX 4: SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

Table of Contents

Bristol Myers Squibb™
P.O BOX 4000, B.3140,
Princeton, NJ-08543-4000

Event-Specific Questionnaire for HCP – Pregnancy Background

(Patient or Partner of Patient)
Telephone: 1-800-721-5072
Fax: 609-818-3804
Email: Worldwide.Safety@BMS.com

Reporter Information			
REPORTER NAME:			
ADDRESS:		CITY, STATE, ZIP, COUNTRY:	
PHONE NO.:		FAX NO.:	
Obstetrician Information (Please provide)			
OBSTETRICIAN NAME:			
ADDRESS:		CITY, STATE, ZIP, COUNTRY:	
PHONE NO.:		FAX NO.:	
Patient Information			
PATIENT ID:	DATE OF BIRTH:	ETHNICITY: ☐ WHITE ☐ BLACK ☐ ASIAN ☐ OTHER, SPECIFY:	
Partner of Patient Information ☐ Not applicable			
DATE OF BIRTH:	ETHNICITY: ☐ WHITE ☐ BLACK ☐ ASIAN ☐ OTHER, SPECIFY:		
Patient Treatment Information: [DRUG NAME]®			
LOT NO.:	EXPIRY DATE:	DOSE:	FREQUENCY:
ROUTE:	START DATE:	STOP DATE:	
INDICATION FOR USE:			
CYTOGENETIC ABNORMALITIES: ☐ NO ☐ YES If Yes, specify:			

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Current Pregnancy			
Date of Last Menstrual Period:		Estimated Delivery Date:	
PREGNANCY TEST	DATE	REFERENCE RANGE	RESULT
Urine qualitative			
Serum quantitative			
Prenatal Tests			
	DATE	RESULT	
Ultrasound			
Ultrasound			
Ultrasound			
Amniocentesis			
Maternal serum AFP			

Pregnancy History		
No. of previous pregnancies: Date of last pregnancy:	No. of full term births:	No. of preterm births:
No. of fetal deaths:	No. of living children:	No. of abortions: Elective _____ Spontaneous _____

Type of delivery: ☐ Vaginal ☐ C-section

Did birth defect occur in any previous pregnancy? ☐ No ☐ Yes ☐ Unknown

If Yes,
specify: _____

Did a stillbirth or spontaneous abortion occur in any previous pregnancy? ☐ No ☐ Yes ☐ Unknown

1) If Yes, in what week of pregnancy did the stillbirth or spontaneous abortion occur?
Week: _____

2) Was there any birth defect noted? ☐ No ☐ Yes, If Yes, specify: _____

Relevant Medical History

☐ NO ☐ YES IF YES, SPECIFY:

Medical History	Date of Diagnosis	Medical History	Date of Diagnosis

Social History

Alcohol Use ☐ No ☐ Yes, if yes, amount/unit consumed per day:

Tobacco Use ☐ No ☐ Yes	IV or recreational drug use ☐ No ☐ Yes, If Yes, specify:

Family History: Congenital Abnormalities ☐ No ☐ Yes, If Yes, specify:

If there is a family history of congenital abnormalities, was there a consultation with a Geneticist?

☐ No ☐ Yes, If Yes, specify:

Environmental Exposure (e.g. Radiation, Chemical EXPOSURE) ☐ No ☐ Yes, If Yes, specify:

Medications/Treatments (including herbal, alternative and over-the-counter medicines and dietary supplements) During Pregnancy

Medication/Treatment	Start Date	Stop Date/ Ongoing	Indication

Adverse Event(s) During Pregnancy

Event(s)	Onset Date	Stop Date / Ongoing	Serious		Causal Relationship to [DRUG NAME] ®	
			Y/N	Serious Criteria[1]	Y/N	If no, what medications, disease states, etc, played a role in the event?

[1] Serious Criteria: **1**) death, **2**) life-threatening, **3**) required inpatient hospitalization or prolongation of existing hospitalization, **4**) a persistent or significant disability/incapacity, **5**) a congenital anomaly/birth defect, **6**) medically significant

Root Cause of Pregnancy

1. What forms of birth control was your patient using while on [Drug Name] before becoming pregnant or impregnating their partner? Please check all that apply.

Tubal ligation	☐ Yes	☐ No
IUD	☐ Yes	☐ No
Hormonal birth control	☐ Yes	☐ No
Partner's vasectomy	☐ Yes	☐ No
Male latex or synthetic condom	☐ Yes	☐ No
Diaphragm	☐ Yes	☐ No
Cervical cap or shield	☐ Yes	☐ No
Spermicide or sponge	☐ Yes	☐ No
Withdrawal	☐ Yes	☐ No
Abstinence	☐ Yes	☐ No

2. Was your patient or their partner without contraception for even one day at any time during use of [DRUG NAME] **®?**

☐ No, please proceed to Question 5

☐ Yes, please answer Question 3, Question 4, Question 5, and Question 6

3. If applicable per Question 2, how often did your patient have unprotected sexual intercourse?

☐ Multiple times

☐ Once a week

☐ Once every 2 weeks

☐ Once a month

☐ Not at all

☐ Other, specify _____

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4. If applicable per Question 2, why did your patient and/or their partner interrupt or stop using contraception?

☐ Wanted a child

¨ Partner disapproved

☐ Side effects

☐ Health concerns

☐ Inconvenient to use

☐ Other, specify _____

5. Please ask your patient if they received the [Drug Name**]® Patient Information (e.g. Medication Guide or patient leaflet).**

☐ No, please proceed to Question 5.3

☐ Yes, please answer Question 5.1

5.1 Please ask your patient if they read the [Drug Name**]® Patient Information (e.g. Medication Guide or patient leaflet).**

☐ No, please proceed to Question 5.3

☐ Yes, please answer Question 5.2

5.2 Please ask your patient if they understood the information in the [Drug Name**]® Patient Information (e.g. Medication Guide or patient leaflet).**

☐ No, please proceed to Question 5.3

☐ Yes, please proceed to Question 5.3

5.3 Please ask your patient where most of their knowledge about contraception during [Drug Name**]® use came from.**

☐ Physician who prescribed [Drug Name]®

☐ Patient Guide to the [Drug Name] REMS® Program

☐ [Drug Name]® Patient Information (e.g. Medication Guide or patient leaflet)

☐ Other, specify: _____

6. Please ask your patient if they felt that they and their partner had a good understanding of the risk of pregnancy during [Drug Name**]® use.**

☐ No

☐ Yes

☐ Don't know

SIGNATURE OF PERSON COMPLETING THIS FORM: _____ **DATE:** _____

MCN:

Bristol Myers Squibb™
P.O BOX 4000, B.3140,
Princeton, NJ-08543-4000

Event-Specific Questionnaire for HCP – Pregnancy Follow-up
(Patient or Partner of Patient)
Telephone: 1-800-721-5072
Fax: 609-818-3804
Email: Worldwide.Safety@BMS.com

Date:	**Period Covered:** _____ (Date) to _____ (Date)

Reporter Information	
REPORTER NAME:	
ADDRESS:	CITY, STATE, ZIP, COUNTRY:
PHONE NO.:	FAX NO.:
Name of Patient or Pregnant Partner of Male Patient:	
Current Pregnancy	

Prenatal Tests (If any additional medical records relating to these prenatal tests are available, please attach along with this form)

TEST	DATE	RESULT
Ultrasound		
Ultrasound		
Ultrasound		
Amniocentesis		
Maternal Serum AFP		
Other Tests, Specify:		

Pregnancy Type

☐ SINGLETON ☐ TWIN ☐ TRIPLET ☐ OTHER, SPECIFY: _____

Bristol Myers Squibb™
P.O BOX 4000, B.3140,
Princeton, NJ-08543-4000

Medications/Treatments (including herbal, alternative and over-the-counter medicines and dietary supplements) During Pregnancy

MEDICATION/TREATMENT	START DATE	STOP DATE/ CONTINUING	INDICATION

Adverse Event(s) During Pregnancy

EVENT(S)	ONSET DATE	STOP DATE / ONGOING	SERIOUS		CAUSAL RELATIONSHIP TO [Drug Name] ®	
			Y/N	SERIOUS CRITERIA[1]	Y/N	IF NO, WHAT MEDICATIONS, DISEASE STATES, etc., PLAYED A ROLE IN THE EVENT?

[1] Serious Criteria: **1**) death, **2**) life-threatening, **3**) required inpatient hospitalization or prolongation of existing hospitalization, **4**) a persistent or significant disability/incapacity, **5**) a congenital anomaly/birth defect, **6**) medically significant

DATE:

SIGNATURE OF PERSON COMPLETING THIS FORM: _____ _____

MCN:

Bristol Myers Squibb™
P.O BOX 4000, B.3140,
Princeton, NJ-08543-4000

Event-Specific Questionnaire for HCP – Pregnancy Follow-up
(Patient or Partner of Patient)
Telephone: 1-800-721-5072
Fax: 609-818-3804
Email: Worldwide.Safety@BMS.com

Date:	**Period Covered:** _____ (Date) to _____ (Date)

Reporter Information	
REPORTER NAME:	
ADDRESS:	CITY, STATE, ZIP, COUNTRY:
PHONE NO.:	FAX NO.:
Name of Patient or Pregnant Partner of Male Patient:	
Current Pregnancy	

Prenatal Tests (If any additional medical records relating to these prenatal tests are available, please attach along with this form)

TEST	DATE	RESULT
Ultrasound		
Ultrasound		
Ultrasound		
Amniocentesis		
Maternal Serum AFP		
Other Tests, Specify:		

Pregnancy Type

☐ SINGLETON ☐ TWIN ☐ TRIPLET ☐ OTHER, SPECIFY: _____

Bristol Myers Squibb™
P.O BOX 4000, B.3140,
Princeton, NJ-08543-4000

Medications/Treatments (including herbal, alternative and over-the-counter medicines and dietary supplements) During Pregnancy

MEDICATION/TREATMENT	START DATE	STOP DATE/ CONTINUING	INDICATION

Adverse Event(s) During Pregnancy

EVENT(S)	ONSET DATE	STOP DATE / ONGOING	SERIOUS		CAUSAL RELATIONSHIP TO [Drug Name] ®	
			Y/N	SERIOUS CRITERIA[1]	Y/N	IF NO, WHAT MEDICATIONS, DISEASE STATES, etc., PLAYED A ROLE IN THE EVENT?

[1] Serious Criteria: **1**) death, **2**) life-threatening, **3**) required inpatient hospitalization or prolongation of existing hospitalization, **4**) a persistent or significant disability/incapacity, **5**) a congenital anomaly/birth defect, **6**) medically significant

DATE:

SIGNATURE OF PERSON COMPLETING THIS FORM: _____ _____

MCN:

Bristol Myers Squibb™
P.O BOX 4000, B.3140,
Princeton, NJ-08543-4000

Event-Specific Questionnaire for HCP – Pregnancy Follow-up
(Patient or Partner of Patient)
Telephone: 1-800-721-5072
Fax: 609-818-3804
Email: Worldwide.Safety@BMS.com

Date:	**Period Covered:**	Date	to Date
Reporter Information			
REPORTER NAME:			
ADDRESS:	CITY, STATE, ZIP, COUNTRY:		
PHONE NO.:	FAX NO.:		
Name of Patient or Pregnant Partner of Male Patient:			
Current Pregnancy			
Prenatal Tests (If any additional medical records relating to these prenatal tests are available, please attach along with this form)			
TEST	DATE	RESULT	
Ultrasound			
Ultrasound			
Ultrasound			
Amniocentesis			
Maternal Serum AFP			
Other Tests, Specify:			
Pregnancy Type ☐ SINGLETON ☐ TWIN ☐ TRIPLET ☐ OTHER, SPECIFY:			

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P.O BOX 4000, B.3140,
Princeton, NJ-08543-4000

Medications/Treatments (including herbal, alternative and over-the-counter medicines and dietary supplements) During Pregnancy

MEDICATION/TREATMENT	START DATE	STOP DATE/ CONTINUING	INDICATION

Adverse Event(s) During Pregnancy

EVENT(S)	ONSET DATE	STOP DATE / ONGOING	SERIOUS		CAUSAL RELATIONSHIP TO [Drug Name] ®	
			Y/N	SERIOUS CRITERIA[1]	Y/N	IF NO, WHAT MEDICATIONS, DISEASE STATES, etc., PLAYED A ROLE IN THE EVENT?

[1] Serious Criteria: **1**) death, **2**) life-threatening, **3**) required inpatient hospitalization or prolongation of existing hospitalization, **4**) a persistent or significant disability/incapacity, **5**) a congenital anomaly/birth defect, **6**) medically significant

SIGNATURE OF PERSON COMPLETING THIS FORM: _____ **DATE:** _____

MCN:

Bristol Myers Squibb™
P.O BOX 4000, B.3140,
Princeton, NJ-08543-4000

Event-Specific Questionnaire for HCP – Pregnancy Outcome
(Patient or Partner of Patient)
Telephone: 1-800-721-5072
Fax: 609-818-3804
Email: Worldwide.Safety@BMS.com

Reporter Information			
REPORTER NAME:			
ADDRESS:			CITY, STATE, ZIP, COUNTRY:
PHONE NO.:			FAX NO.:
Patient Information			
PATIENT ID:	DATE OF BIRTH:		ETHNICITY: ☐ WHITE ☐ BLACK ☐ ASIAN ☐ OTHER, SPECIFY:
Partner of Patient Information ☐ Not applicable			
DATE OF BIRTH:	ETHNICITY: ☐ WHITE ☐ BLACK ☐ ASIAN ☐ OTHER, SPECIFY:		
Pregnancy Type ☐ SINGLETON ☐ TWIN ☐ TRIPLET ☐ OTHER, SPECIFY: _____			
Pregnancy Outcome			
DATE OF DELIVERY:			GESTATION AGE AT DELIVERY:
DELIVERY DETAILS	NO	YES	ADDITIONAL COMMENTS
Normal	☐	☐	
C-section	☐	☐	
Induced	☐	☐	
Assisted (e.g., forceps)	☐	☐	
Elective Termination	☐	☐	Date:
Spontaneous Abortion (≤ 20 weeks)	☐	☐	Weeks from LMP:
Fetal Death/Stillbirth (> 20 weeks)	☐	☐	
Were the Products of Conception Examined?	☐	☐	If yes, was the fetus normal? ☐ Yes ☐ No ☐ Unknown If no, describe: _____

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Princeton, NJ-08543-4000

Obstetrics Information			
	NO	YES	
Complications During Pregnancy	☐	☐	If Yes, specify:
Complications During Labor/Delivery	☐	☐	If Yes, specify:
Post-partum Maternal Complications	☐	☐	If Yes, specify:
Fetal and Neonatal Status			
	NO	YES	
Live Normal Infant	☐	☐	
Fetal Distress	☐	☐	If Yes, specify:
Intra-uterine Growth Retardation	☐	☐	If Yes, specify:
Neonatal Complications*	☐	☐	If Yes, specify:
Birth Defect Noted?	☐	☐	If Yes, specify:

Sex: ☐ Male ☐ Female **Birth Weight:** ____ lbs ____ oz ***or*** ____ kg **Length:** ____ inches ***or*** ____ cm

Apgar Score:	Unknown:	1 min:	5 mins:	10 mins:

***PLEASE PROVIDE A BRIEF SUMMARY OF THE MANAGEMENT OF THE COMPLICATIONS.**

SIGNATURE OF PERSON COMPLETING THIS FORM: _____ **DATE:** _____

MCN:

Bristol Myers Squibb™
P.O BOX 4000, B.3140,
Princeton, NJ-08543-4000

Event-Specific Questionnaire for Primary Care Physician or Pediatrician – Infant Follow-up

Telephone: 1-800-721-5072
Fax: 609-818-3804
Email: Worldwide.Safety@BMS.com

Date of Assessment: _____

Age in Months: _____

Weight (at the time of this assessment): _____ lbs _____ oz ***or*** _____ kg

Length (at the time of this assessment): _____ inches ***or*** _____ cm

Name of Patient on [Drug Name]®: _____

Name of Infant (if known): _____

Please provide information for the period from _____ (Date) to _____ (Date)

Birth Defects/Anomalies:

New birth defects or anomalies noted since previous report? ☐ Yes ☐ No

If **Yes**, please list the birth defects/anomalies below:

BIRTH DEFECT/ANOMALY	**WAS THE DEFECT/ ANOMALY ATTRIBUTED TO [Drug Name]® THERAPY?** (Y/N/UNKNOWN)	**FACTORS THAT MAY HAVE CONTRIBUTED TO THIS OUTCOME:** (e.g. FAMILY HISTORY, MATERNAL AGE, OBESITY, ALCOHOL CONSUMPTION DURING PREGNANCY, etc.)	**DEFECT/ ANOMALY NOTED PRIOR TO BIRTH?** (Y/N)	**INFANT AGE WHEN DEFECT/ ANOMALY WAS NOTED** (SPECIFY WEEKS OR MONTHS)

Developmental Assessment:

Is the child developing normally for his/her age? ☐ Yes ☐ No

If No, please define your concerns regarding any developmental issues or abnormalities:

Diagnosis date of any developmental issues: _____

Infant Illnesses, Hospitalizations, Drug Therapies:

Infant Illnesses	Hospitalized?	Drug Therapies
	☐ Yes ☐ No	
	☐ Yes ☐ No	
	☐ Yes ☐ No	
	☐ Yes ☐ No	
	☐ Yes ☐ No	
	☐ Yes ☐ No	

SIGNATURE OF PERSON COMPLETING THIS FORM: _____ **DATE:** _____

MCN:

Bristol Myers Squibb™
P.O BOX 4000, B.3140,
Princeton, NJ-08543-4000

Event-Specific Questionnaire for Primary Care Physician or Pediatrician – Infant Follow-up

Telephone: 1-800-721-5072
Fax: 609-818-3804
Email: Worldwide.Safety@BMS.com

Date of Assessment: _____

Age in Months: _____

Weight (at the time of this assessment): _____ lbs _____ oz ***or*** _____ kg

Length (at the time of this assessment): _____ inches ***or*** _____ cm

Name of Patient on [Drug Name]®: _____

Name of Infant (if known): _____

Please provide information for the period from _____ (Date) to _____ (Date)

Birth Defects/Anomalies:

New birth defects or anomalies noted since previous report? ☐ Yes ☐ No

If **Yes**, please list the birth defects/anomalies below:

BIRTH DEFECT/ANOMALY	**WAS THE DEFECT/ ANOMALY ATTRIBUTED TO [Drug Name] ® THERAPY?** (Y/N/UNKNOWN)	**FACTORS THAT MAY HAVE CONTRIBUTED TO THIS OUTCOME:** (e.g. FAMILY HISTORY, MATERNAL AGE, OBESITY, ALCOHOL CONSUMPTION DURING PREGNANCY, etc.)	**DEFECT/ ANOMALY NOTED PRIOR TO BIRTH?** (Y/N)	**INFANT AGE WHEN DEFECT/ ANOMALY WAS NOTED** (SPECIFY WEEKS OR MONTHS)

Developmental Assessment:

Is the child developing normally for his/her age? ☐ Yes ☐ No

If No, please define your concerns regarding any developmental issues or abnormalities:

Diagnosis date of any developmental issues: _____

Infant Illnesses, Hospitalizations, Drug Therapies:

Infant Illnesses	Hospitalized?	Drug Therapies
	☐ Yes ☐ No	
	☐ Yes ☐ No	
	☐ Yes ☐ No	
	☐ Yes ☐ No	
	☐ Yes ☐ No	
	☐ Yes ☐ No	

SIGNATURE OF PERSON COMPLETING THIS FORM: _____ **DATE:** _____

MCN:

Bristol Myers Squibb™
P.O BOX 4000, B.3140,
Princeton, NJ-08543-4000

Event-Specific Questionnaire for Primary Care Physician or Pediatrician – Infant Follow-up

Telephone: 1-800-721-5072
Fax: 609-818-3804
Email: Worldwide.Safety@BMS.com

Date of Assessment: _____

Age in Months: _____

Weight (at the time of this assessment): _____ lbs _____ oz ***or*** _____ kg

Length (at the time of this assessment): _____ inches ***or*** _____ cm

Name of Patient on [Drug Name]®: _____

Name of Infant (if known): _____

Please provide information for the period from _____ (Date) to _____ (Date)

Birth Defects/Anomalies:

New birth defects or anomalies noted since previous report? ☐ Yes ☐ No

If **Yes**, please list the birth defects/anomalies below:

BIRTH DEFECT/ANOMALY	**WAS THE DEFECT/ ANOMALY ATTRIBUTED TO [Drug Name]® THERAPY?** (Y/N/UNKNOWN)	**FACTORS THAT MAY HAVE CONTRIBUTED TO THIS OUTCOME:** (e.g., FAMILY HISTORY, MATERNAL AGE, OBESITY, ALCOHOL CONSUMPTION DURING PREGNANCY, etc.)	**DEFECT/ ANOMALY NOTED PRIOR TO BIRTH?** (Y/N)	**INFANT AGE WHEN DEFECT/ ANOMALY WAS NOTED** (SPECIFY WEEKS OR MONTHS)

Developmental Assessment:

Is the child developing normally for his/her age? ☐ Yes ☐ No

If No, please define your concerns regarding any developmental issues or abnormalities:

Diagnosis date of any developmental issues: _____

Infant Illnesses, Hospitalizations, Drug Therapies:

Infant Illnesses	Hospitalized?	Drug Therapies
	☐ Yes ☐ No	
	☐ Yes ☐ No	
	☐ Yes ☐ No	
	☐ Yes ☐ No	
	☐ Yes ☐ No	
	☐ Yes ☐ No	

SIGNATURE OF PERSON COMPLETING THIS FORM: _____ **DATE:** _____

MCN:

Bristol Myers Squibb™
P.O BOX 4000, B.3140,
Princeton, NJ-08543-4000

Event-Specific Questionnaire for Primary Care Physician or Pediatrician – Infant Follow-up

Telephone: 1-800-721-5072
Fax: 609-818-3804
Email: Worldwide.Safety@BMS.com

Date of Assessment: _____

Age in Months: _____

Weight (at the time of this assessment): _____ lbs _____ oz ***or*** _____ kg

Length (at the time of this assessment): _____ inches ***or*** _____ cm

Name of Patient on [Drug Name]®: _____

Name of Infant (if known): _____

Please provide information for the period from _____ (Date) to _____ (Date)

Birth Defects/Anomalies:

New birth defects or anomalies noted since previous report? ☐ Yes ☐ No

If **Yes**, please list the birth defects/anomalies below:

BIRTH DEFECT/ANOMALY	**WAS THE DEFECT/ ANOMALY ATTRIBUTED TO [Drug Name]® THERAPY?** (Y/N/UNKNOWN)	**FACTORS THAT MAY HAVE CONTRIBUTED TO THIS OUTCOME:** (e.g., FAMILY HISTORY, MATERNAL AGE, OBESITY, ALCOHOL CONSUMPTION DURING PREGNANCY, etc.)	**DEFECT/ ANOMALY NOTED PRIOR TO BIRTH?** (Y/N)	**INFANT AGE WHEN DEFECT/ ANOMALY WAS NOTED** (SPECIFY WEEKS OR MONTHS)

Developmental Assessment:

Is the child developing normally for his/her age? ☐ Yes ☐ No

If No, please define your concerns regarding any developmental issues or abnormalities:

Diagnosis date of any developmental issues: _____

Infant Illnesses, Hospitalizations, Drug Therapies:

Infant Illnesses	Hospitalized?	Drug Therapies
	☐ Yes ☐ No	
	☐ Yes ☐ No	
	☐ Yes ☐ No	
	☐ Yes ☐ No	
	☐ Yes ☐ No	
	☐ Yes ☐ No	

SIGNATURE OF PERSON COMPLETING THIS FORM: _____ **DATE:** _____

MCN:

Bristol Myers Squibb™
P.O BOX 4000, B.3140
Princeton, NJ-08543-4000

[Case_ ID]

Adverse Event Report Questionnaire
TL Cardiac Arrhythmia and ECG Changes Pomalyst Revlimid

INFORMATION PREVIOUSLY PROVIDED DOES NOT NEED TO BE REPEATED ON THIS FORM:

Patient Demographics:

Patient's date of birth (DD-MMM-YYYY): _____ Gender: ☐Male ☐ Female

Age: _____

Race/Ethnicity: _____ ☐ Aborginal ☐African American ☐ Asian
☐ American Indian or Alaskan Native ☐ Native Hawaiian or other Pacific Islander
☐ Torres Strait Islander ☐ White ☐ Black ☐ Non Hispanic

Age Group:_____

Note: Please provide Age Group if Patient's Date of Birth or Age is not available.

Age Group Definition: Neonate: 0 - 27 days, Infant: 28 days to 23 months, Child: 2 years to 11years, Adolescent: 12 years to 18 years, Adult: More than 18 years and less than or equal to 65 years and Elderly: equal or greater than 66 years)

Suspect Products: Please provide suspect product(s) information [those product(s) that are suspected to be associated with one or more adverse events]:

	Suspect Product #1	Suspect Product #2	Suspect Product #3
Product name			
Daily dose and regimen			
Route of administration			
Indication			
Start date or treatment duration (DD-MMM-YYYY)			
Stop date (DD-MMM-YYYY)			
Lot/Batch number(s)			
Expiration date(s)			
Action Taken with the suspect product			

(Choose from one of the following for action Taken with Suspect Product: Drug withdrawn, Dose reduced, Dose increased, Dose not changed, Unknown)

Adverse Event (AE) Description: Please provide diagnosis or symptoms/signs if diagnosis is unavailable.

	Adverse Event #1	Adverse Event #2	Adverse Event #3	Adverse Event #4

Add Diagnosis Here →				
Start Date (DD/MMM/YYYY)				
Stop Date (DD/MMM/YYYY)				
Time lag if AE occurred after cessation of treatment with the suspect product(s):				
Required Hospitalization (Yes/No)				
Life-Threatening (Yes/No)				
Persistent or significant disability (Yes/No)				
Congenital abnormality (Yes/No)				
Cause of Death (Yes/No)				
Treatment of Adverse Event				
Outcome (recovery and sequelae, if any)				
Did the event(s) abate after suspect Product was stopped or dose reduced? (Yes/No)				
Did the event recur after reintroducing (Yes/No)				

Please summarize course of reported events including signs and symptoms in chronological order:

_____

_____

_____

Diagnostic tests (use additional pages if needed)**:** Please indicate test unit where applicable.

Date	Test Name	Pre-treatment value	AE onset value	AE resolution value	Normal low	Normal high
	CPK					
	CPK-MB					
	Troponin					
	RBC					
	Hemoglobin					
	Metabolic Panel (specify)					
	Serum potassium					
	Serum magnesium					
	Phosphorus					
	Calcium					
	Uric acid					
	Creatinine					
	BUN					

Please provide causal relationship assessment between the suspect product(s) and adverse event(s):

_____

_____

Concomitant Medications (use additional pages if needed)**:**

Did the Patient take any concomitant medication? ☐ Yes (please complete below) ☐ No ☐ Unknown
Please include any antiemetics.

Medication Name	Daily dose and regimen	Route of administration	Indication	Start date DD-MMM-YYYY	Stop date DD-MMM-YYYY

Other Etiological Factors: ☐ Yes (please complete below) ☐ None ☐ Unknown

☐ Relevant medical and/or drug history (please specify), including start date or duration:

_____

_____

_____

☐ Family history (please specify): _____
☐ Drug/alcohol/tobacco abuse: _____
☐ Other (please specify): _____

Additional questions:

Please provide a brief description of the cardiac arrhythmia, or ECG change, including the type and the clinical signs/symptoms observed, including start and stop dates:

Please specify the type of arrhythmia/ECG change.

Clinical signs and symptoms, if present (if none please state)
Start date Stop date

Does this patient have a relevant cardiac history? If yes, please specify. If no, please state.

Does this patient have a history of cardiac risk factors (e.g. hypertension, hyperlipidemia, hypercholesterolemia, diabetes, sepsis, obesity, smoking, renal disease, cardio respiratory problems)? If yes, please specify below. If no, please state.

Please provide the available results of the diagnostic workup (include dates of baseline, event onset, and resolution results)

Test Name	Pre-treatment results	AE onset results	AE resolution results
EKG findings			
Echocardiogram			
Chest x-ray			
Holter, Stress Test			

Please describe specific treatments and interventions of the arrhythmia

_____

Health Practitioner Name (Print)

_____

Health Practitioner Name (Signature)

Additional information regarding this Adverse Event Report:

Description of event: [narrative]

Bristol Myers Squibb™
P.O BOX 4000, B.3140
Princeton, NJ-08543-4000

[Case_ ID]

Adverse Event Report Questionnaire
TL Cardiac Failure Pomalyst Revlimid

INFORMATION PREVIOUSLY PROVIDED DOES NOT NEED TO BE REPEATED ON THIS FORM:

Patient Demographics:

Patient's date of birth (DD-MMM-YYYY): _____ Gender: ☐ Male ☐ Female

Age: _____

Race/Ethnicity: _____ ☐ Aborginal ☐ African American ☐ Asian
☐ American Indian or Alaskan Native ☐ Native Hawaiian or other Pacific Islander
☐ Torres Strait Islander ☐ White ☐ Black ☐ Non Hispanic

Age Group:_____

Note: Please provide Age Group if Patient's Date of Birth or Age is not available.

Age Group Definition: Neonate: 0 - 27 days, Infant: 28 days to 23 months, Child: 2 years to 11years, Adolescent: 12 years to 18 years, Adult: More than 18 years and less than or equal to 65 years and Elderly: equal or greater than 66 years)

Suspect Products: Please provide suspect product(s) information [those product(s) that are suspected to be associated with one or more adverse events]:

	Suspect Product #1	Suspect Product #2	Suspect Product #3
Product name			
Daily dose and regimen			
Route of administration			
Indication			
Start date or treatment duration (DD-MMM-YYYY)			
Stop date (DD-MMM-YYYY)			
Lot/Batch number(s)			
Expiration date(s)			
Action Taken with the suspect product			

(Choose from one of the following for action Taken with Suspect Product: Drug withdrawn, Dose reduced, Dose increased, Dose not changed, Unknown)

Adverse Event (AE) Description: Please provide diagnosis or symptoms/signs if diagnosis is unavailable.

	Adverse Event #1	Adverse Event #2	Adverse Event #3	Adverse Event #4

Add Diagnosis Here →				
Start Date (DD/MMM/YYYY)				
Stop Date (DD/MMM/YYYY)				
Time lag if AE occurred after cessation of treatment with the suspect product(s):				
Required Hospitalization (Yes/No)				
Life-Threatening (Yes/No)				
Persistent or significant disability (Yes/No)				
Congenital abnormality (Yes/No)				
Cause of Death (Yes/No)				
Treatment of Adverse Event				
Outcome (recovery and sequelae, if any)				
Did the event(s) abate after suspect Product was stopped or dose reduced? (Yes/No)				
Did the event recur after reintroducing (Yes/No)				

Please summarize course of reported events including signs and symptoms in chronological order:

_____

_____

_____

Diagnostic tests (use additional pages if needed)**:** Please indicate test unit where applicable.

Date	Test Name	Pre-treatment value	AE onset value	AE resolution value	Normal low	Normal high
	Calcium					
	Magnesium					
	Total CPK					
	CK-MB					
	Troponins					
	BNP					
	WBC					
	RBC					
	Platelets					
	Hemoglobin					
	Hematocrit					

Please provide causal relationship assessment between the suspect product(s) and adverse event(s):

_____

Concomitant Medications (use additional pages if needed)**:**

Did the Patient take any concomitant medication? ☐ Yes (please complete below) ☐ No ☐ Unknown

Medication Name	Daily dose and regimen	Route of administration	Indication	Start date DD-MMM-YYYY	Stop date DD-MMM-YYYY

Other Etiological Factors: ☐ Yes (please complete below) ☐ None ☐ Unknown

☐ Relevant medical and/or drug history (please specify), including start date or duration:

☐ Family history (please specify): _____
☐ Drug/alcohol/tobacco abuse: _____
☐ Other (please specify): _____

Additional questions:

Did the cardiac failure occur prior to therapy? ☐ Yes ☐ No

If the cardiac failure occurred prior to therapy, would you consider it an exacerbation?
☐ Yes ☐ No

Please provide the date the exacerbation was diagnosed_____

Please circle classification of cardiac failure:

a. Class I (mild) Patients with cardiac disease but without limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea or angina pain

b. Class II (mild) Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or angina pain.

c. Class III (moderate) Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or angina pain.

d. Class IV (severe) Patients with cardiac disease resulting in the inability to carry on any physical activity without discomfort. Symptoms of heart failure or the angina syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased

Please provide results for EKG, echocardiogram, angiogram, CT scan, MRI and ejection fraction.

Did the patient receive any recent blood transfusions or IV infusions? ☐ Yes ☐ No
If yes, please specify what was transfused and provide the amount transfused with dates.

Does the patient have other cardiac history including congenital heart disease, coronary artery disease, cardiac stents, myocardial infarction, valvular heart disease, cardiomyopathy, endocarditis, or myocarditis?

Please provide any associated risk factors including history of hyperlipidemia, obesity, hypertension COPD, renal disease, diabetes, sepsis, substance abuse, and family history of heart disease.

Any exposure to other chemotherapeutic agents (previous and/or ongoing)? Please specify.

Are there any concurrent events that contributed to or led up to the cardiac failure? Please specify.

What treatments/interventions were provided to the patient for the cardiac failure?

_____
Health Practitioner Name (Print)

_____
Health Practitioner Name (Signature)

Additional information regarding this Adverse Event Report:

Description of event: [narrative]

Bristol Myers Squibb™
P.O BOX 4000, B.3140
Princeton, NJ-08543-4000

[Case_ ID]

Adverse Event Report Questionnaire
TL Neutropenia Pomalyst Revlimid

INFORMATION PREVIOUSLY PROVIDED DOES NOT NEED TO BE REPEATED ON THIS FORM:

Patient Demographics:

Patient's date of birth (DD-MMM-YYYY): _____ Gender: ☐Male ☐ Female

Age: _____

Race/Ethnicity: _____ ☐ Aborginal ☐African American ☐ Asian
☐ American Indian or Alaskan Native ☐ Native Hawaiian or other Pacific Islander
☐ Torres Strait Islander ☐ White ☐ Black ☐ Non Hispanic

Age Group:_____

Note: Please provide Age Group if Patient's Date of Birth or Age is not available.

Age Group Definition: Neonate: 0 - 27 days, Infant: 28 days to 23 months, Child: 2 years to 11years, Adolescent: 12 years to 18 years, Adult: More than 18 years and less than or equal to 65 years and Elderly: equal or greater than 66 years)

Suspect Products: Please provide suspect product(s) information [those product(s) that are suspected to be associated with one or more adverse events]:

	Suspect Product #1	Suspect Product #2	Suspect Product #3
Product name			
Daily dose and regimen			
Route of administration			
Indication			
Start date or treatment duration (DD-MMM-YYYY)			
Stop date (DD-MMM-YYYY)			
Lot/Batch number(s)			
Expiration date(s)			
Action Taken with the suspect product			

(Choose from one of the following for action Taken with Suspect Product: Drug withdrawn, Dose reduced, Dose increased, Dose not changed, Unknown)

Adverse Event (AE) Description: Please provide diagnosis or symptoms/signs if diagnosis is unavailable.

	Adverse Event #1	Adverse Event #2	Adverse Event #3	Adverse Event #4

Add Diagnosis Here →				
Start Date (DD/MMM/YYYY)				
Stop Date (DD/MMM/YYYY)				
Time lag if AE occurred after cessation of treatment with the suspect product(s):				
Required Hospitalization (Yes/No)				
Life-Threatening (Yes/No)				
Persistent or significant disability (Yes/No)				
Congenital abnormality (Yes/No)				
Cause of Death (Yes/No)				
Treatment of Adverse Event				
Outcome (recovery and sequelae, if any)				
Did the event(s) abate after suspect Product was stopped or dose reduced? (Yes/No)				
Did the event recur after reintroducing (Yes/No)				

Please summarize course of reported events including signs and symptoms in chronological order:

_____

_____

_____

Diagnostic tests (use additional pages if needed)**:** Please indicate test unit where applicable.

Date	Test Name	Pre-treatment value	AE onset value	AE resolution value	Normal low	Normal high
	WBC					
	ANC					

Please provide causal relationship assessment between the suspect product(s) and adverse event(s):

_____

_____

Concomitant Medications (use additional pages if needed)**:**

Did the Patient take any concomitant medication? ☐ Yes (please complete below) ☐ No ☐ Unknown

Medication Name	Daily dose and regimen	Route of administration	Indication	Start date DD-MMM-YYYY	Stop date DD-MMM-YYYY

Other Etiological Factors: ☐ Yes (please complete below) ☐ None ☐ Unknown

☐ Relevant medical and/or drug history (please specify), including start date or duration:

_____

_____

_____

☐ Family history (please specify): _____
☐ Drug/alcohol/tobacco abuse: _____
☐ Other (please specify): _____

Additional questions:

What treatments were given for the neutropenia? Please include dates. Did the patient receive G-CSF? GM-CSF? Please provide details.

Did your patient experience an infection in association with the neutropenia?
☐ **Yes** ☐ **No**
If yes, please provide location of the infection.

Does the patient have a history of recurrent infection? ☐ **Yes** ☐ **No**
If yes, please explain.

Please provide the stage/classification of the patient's disease at the time of the infection.

Does your patient have a medical history of autoimmune disease, abnormal disease of spleen, bone marrow disease, etc.?

Has your patient received prior radiation therapy? If so, please provide treatment details including dates.

Does your patient have a medical history of cancer effecting bone marrow?

Please include culture / serology / bone marrow studies / x-ray results for the event of infection.

_____

Health Practitioner Name (Print)

_____

Health Practitioner Name (Signature)

Additional information regarding this Adverse Event Report:

Description of event: [narrative]

Bristol Myers Squibb™
P.O BOX 4000, B.3140
Princeton, NJ-08543-4000

[Case_ ID]

Adverse Event Report Questionnaire
TL Second Primary Malignancies (Pomalyst Revlimid Thalidomide)

INFORMATION PREVIOUSLY PROVIDED DOES NOT NEED TO BE REPEATED ON THIS FORM:

Patient Demographics:

Patient's date of birth (DD-MMM-YYYY): _____ Gender: ☐Male ☐ Female
Age: _____

Race/Ethnicity: _____ ☐ Aborginal ☐African American ☐ Asian
☐ American Indian or Alaskan Native ☐ Native Hawaiian or other Pacific Islander
☐ Torres Strait Islander ☐ White ☐ Black ☐ Non Hispanic

Age Group:_____

Note: Please provide Age Group if Patient's Date of Birth or Age is not available.

Age Group Definition: Neonate: 0 - 27 days, Infant: 28 days to 23 months, Child: 2 years to 11years, Adolescent: 12 years to 18 years, Adult: More than 18 years and less than or equal to 65 years and Elderly: equal or greater than 66 years)

Suspect Products: Please provide suspect product(s) information [those product(s) that are suspected to be associated with one or more adverse events]:

	Suspect Product #1	Suspect Product #2	Suspect Product #3
Product name			
Daily dose and regimen			
Route of administration			
Indication			
Start date or treatment duration (DD-MMM-YYYY)			
Stop date (DD-MMM-YYYY)			
Lot/Batch number(s)			
Expiration date(s)			
Action Taken with the suspect product			

(Choose from one of the following for action Taken with Suspect Product: Drug withdrawn, Dose reduced, Dose increased, Dose not changed, Unknown)

Adverse Event (AE) Description: Please provide diagnosis or symptoms/signs if diagnosis is unavailable.

	Adverse Event #1	Adverse Event #2	Adverse Event #3	Adverse Event #4

Add Diagnosis Here →				
Start Date (DD/MMM/YYYY)				
Stop Date (DD/MMM/YYYY)				
Time lag if AE occurred after cessation of treatment with the suspect product(s):				
Required Hospitalization (Yes/No)				
Life-Threatening (Yes/No)				
Persistent or significant disability (Yes/No)				
Congenital abnormality (Yes/No)				
Cause of Death (Yes/No)				
Treatment of Adverse Event				
Outcome (recovery and sequelae, if any)				
Did the event(s) abate after suspect Product was stopped or dose reduced? (Yes/No)				
Did the event recur after reintroducing (Yes/No)				

Please summarize course of reported events including signs and symptoms in chronological order:

_____

_____

_____

Diagnostic tests (use additional pages if needed)**:** Please indicate test unit where applicable.

Date	Test Name	Pre-treatment value	AE onset value	AE resolution value	Normal low	Normal high
	Calcium					
	Phosphate					
	Uric Acid					
	Creatinine					
	Potassium					
	LDH					
	Albumin					
	Protein					

Please provide causal relationship assessment between the suspect product(s) and adverse event(s):

_____

_____

Concomitant Medications (use additional pages if needed)**:**

Did the Patient take any concomitant medication? ☐ Yes (please complete below) ☐ No ☐ Unknown
Please include drugs that are potentially nephrotoxic (NSAIDS, antibiotics) including over the counter drugs.

Medication Name	Daily dose and	Route of	Indication	Start date	Stop date

	regimen	administration		DD-MMM-YYYY	DD-MMM-YYYY

Other Etiological Factors: ☐ Yes (please complete below) ☐ None ☐ Unknown

☐ Relevant medical history (including history of malignancies) and/or drug history (please specify), including start date or duration:

_____

_____

_____

☐ Family history (please specify), including history of malignancies with estimated dates: _____
☐ Drug/alcohol/tobacco abuse: _____
☐ Other (please specify): _____

Additional questions:

When querying about SPMs, specify the malignancy or diagnosis. Do not use the term SPM when diagnosis is known.

Core Questions for Follow-up of SPMs:

1. Dates of the underlying disease's diagnosis.
2. Date of first clinical symptoms of SPM.
3. Stage of the underlying disease treated with [*BMS product*] at baseline, the end of treatment if applicable, and at the time of the event with supportive documentation if available.
4. Medical history of bone marrow transplant including dates, type, donor details, source, and conditioning regimens such as treatment with alkylating agents (i.e. Cyclophosphamide, Melphalan, etc.).
5. Environmental exposure e.g. atmospheric pollutants/toxic chemicals (pesticides, herbicides, benzene, solvents); occupation/hobbies.
6. Full SPM (*specify malignancy or diagnosis if known*) biopsy reports. If not available please provide the detailed results.

In addition to the Core Questions, specific information should be requested based on the risk factors for individual types of cancer, including:

Hematologic Malignancies (including Lymphoma and B-cell malignancy):

- ◊ Previous chemotherapy rounds (dates, type) and /or radiotherapy (zone, duration, cumulative dose) or subsequent ones if SPM (specify malignancy or diagnosis) detected after product discontinuation
- ◊ Medical conditions that compromise the immune system – HIV/AIDS, autoimmune diseases, diseases requiring immune suppressive therapy-organ transplant
- ◊ For lymphoma: Infection with HIV, Epstein-Barr virus+++, Helicobacter pylori, hepatitis B or C, human T-lymphotrophic virus type I, Burkitt's lymphoma

- Concurrent or medical/family history of inherited syndromes with genetic changes that raise the risk of acute lymphocytic leukemia (ALL) including: Down syndrome, Klinefelter syndrome, Fanconi anemia, Bloom syndrome, Ataxia-telangiectasia, Neurofibromatosis.
- Exposure to benzene (solvent used in the rubber industry, oil refineries, chemical plants, shoe manufacturing, and gasoline-related industries, and is also present in cigarette smoke, as well as some glues, cleaning products, detergents, art supplies, and paint strippers).
- Smoking history – Product smoked (i.e. cigars, cigarettes, etc.) and depth of inhalation, length of time, number of cigarettes/days or pack-years, age at starting
- Exposure to high levels of radiation
- Medical history of treated hematologic malignancies or concurrent leukemias or lymphomas including: Chronic Lymphocytic Leukemia (CLL), Richter transformation, and Diffuse Large B-cell lymphoma (DLBCL) such as Hodgkin's disease and plasmablastic lymphoma.
- Relevant diagnostic test results (if available), including: biopsy, immunohistochemistry, flow cytometry, cytogenetics, reverse transcriptase polymerase chain reaction, Fluorescence in situ hybridization (FISH), and next generation sequencing

Lung Cancer:

- Smoking history – Product smoked (i.e. cigars, cigarettes, etc.) and depth of inhalation, length of time, number of cigarettes/days or pack-years, age at starting
- Pre-existing pulmonary disease
- Family history of lung cancer

Thyroid Cancer:

- Personal or family history of thyroid and/or autoimmune diseases – hypo or hyperthyroidism, goiter, benign thyroid nodules, Hashimoto's disease, Graves disease
- Family history of familial medullary thyroid cancer, multiple endocrine neoplasia and familial adenomatous polyposis
- Living in iodine deficient area
- History of radiation exposure

Breast Cancer:

- Receptor status of the tumor – ER, PR, Her2/neu
- Age at onset of menses and age of menopause
- Number of pregnancies and age at first birth
- History of breastfeeding children
- Use of oral contraceptives or hormone replacement therapy
- Obesity
- Economic status, and dietary iodine deficiency

Ovarian Cancer:

- Number of pregnancies and childbearing status
- History of hormone replacement therapy
- History of breast cancer

Uterine Cancer:

- Age at onset of menses and age of menopause
- Number of pregnancies
- Use of oral contraceptives
- Obesity

Colon Cancer:

- Family or personal history of adenomatous polyposis (FAP), Lynch syndrome (Hereditary nonpolyposis colorectal cancer)
- Diet high in red meat and animal fat, refined carbohydrates, low-fiber diet, and low overall intake of fruits and vegetables
- Obesity and sedentary habits
- Any history of inflammatory conditions of digestive tract - Chronic ulcerative colitis, Crohn's disease longer duration, greater extent of colon involvement

Anorectal Cancer:

- History of infection with human papillomavirus, HIV, chronic fistulas, irradiated anal skin, leukoplakia, lymphogranulomatoma venereum, condyloma acuminatum

Gastric Cancer:

- Diet rich in pickled vegetables, salted fish, salt, and smoked meats
- Helicobacter pylori infection
- Obesity
- Previous gastric surgery
- Pernicious anemia, adenomatous polyps, gastric ulcer
- Chronic atrophic gastritis
- Radiation exposure
- History of alcohol use/smoking

Oesophageal Cancer:

- Genetic causes - tylosis (hyperkeratosis palmaris et plantaris)
- History of alcohol use/smoking
- History of chronic or acute inflammation (e.g. GERD, Barrett's esophagus, caustic ingestion), achalasia (esophageal motility disorder)
- Human papilloma virus
- Sclerotherapy
- Plummer-Vinson syndrome (dysphagia, associated with iron deficiency anemia)

Liver cancer:

- History of cirrhosis (including alcoholic, biliary cirrhosis), other chronic liver dysfunction
- History of alcohol use/smoking
- Hepatitis B, C
- Hemochromatosis
- Indigestion of food contaminated with fungal aflatoxins (in subtropical regions)

Pancreatic Cancer:

- History of alcohol use/smoking
- Obesity
- Diet (red meat)
- History of chronic pancreatitis or long-standing diabetes mellitus (primarily in women).
- Inherited predisposition (hereditary pancreatitis, familial adenomatous polyposis, etc.)

Renal Cancer (renal cell carcinoma):

- Smoking history – Product smoked (i.e. cigars, cigarettes, etc.) and depth of inhalation, length of time, number of cigarettes/days or pack-years, age at starting
- Obesity
- Hypertension
- Phenacetin-containing analgesics taken in large amounts

- History of renal transplantation
- Exposure to radiopaque dyes, asbestos, cadmium, and leather tanning and petroleum products
- Inherited von Hippel-Lindau disease (VHL) disease, Adult polycystic kidney disease, Tuberous sclerosis

Bladder Cancer:

- Smoking history – Product smoked (i.e. cigars, cigarettes, etc.) and depth of inhalation, length of time, number of cigarettes/days or pack-years, age at starting
- Industrial exposure to aromatic amines in dyes, paints, solvents, leather dust, inks, combustion products, rubber, and textiles
- Occupation - painting, driving trucks, and working with metal
- Prior spinal cord injuries with long-term indwelling catheters

Prostate Cancer:

- Smoking history – Product smoked (i.e. cigars, cigarettes, etc.) and depth of inhalation, length of time, number of cigarettes/days or pack-years, age at starting
- History of high-grade prostatic intraepithelial neoplasia (PIN)
- Genome changes-deletion of chromosome 3 and fusion of TMPRSS2 and ERG genes
- Testosterone level
- History of sexually transmitted diseases
- History of vasectomy
- History of exposure to cadmium
- History of genitor-urinary infections

Head and Neck Cancer:

- History of alcohol use/smoking
- Exposure to Human papilloma virus (HPV) or Epstein-Barr virus (EBV)
- History of poor oral hygiene and/or poor nutrition
- Exposure to asbestos, wood dust, paint fumes or chemicals
- History of Gastroesophageal reflux disease (GERD) or laryngopharyngeal reflux disease (LPRD)

Brain tumors (gliomas and meningiomas):

- Exposure to radiation
- Exposure to vinyl chloride, Pesticides
- Immune system disorders
- Hormone replacement therapy

Larynx Cancer:

- History of alcohol use/smoking
- Asbestos exposure
- Any activity requiring loud speech, exposure to sudden and frequent temperature changes
- Frequent hoarseness, frequent and persistent cough
- Persistently swollen neck glands
- Tonsillectomy and laryngeal surgery

Nasal and Paranasal Sinus Cancer:

- Woodworking, any dust/flour chronic exposure
- History of Infection with human papillomavirus (HPV)
- Smoking history – Product smoked (i.e. cigars, cigarettes, etc.) and depth of inhalation, length of time, number of cigarettes/days or pack-years, age at starting

Mouth and Oropharyngeal Cancer:

- History of alcohol use/smoking
- History of poor oral hygiene
- Chronic mucosal/gum irritation / ill-fitting dentures
- Betel-Nut Chewing (Indian populations)
- History of syphilis or viral infections
- Impaired immunity – AIDS, transplant with anti-rejection drugs
- Precancerous mouth plaques – Leukoplakia or erythroplasia
- History of cancer of the aero-digestive tract

Melanoma, basal cell carcinoma, squamous cell carcinoma of skin:

- History of prolonged sun exposure (UV radiation) – severe blistering sunburns, frequent tanning, use of sunlamps and tanning booths
- History of living close to equator or at high elevation
- History of skin conditions – Dysplastic nevus, Xeroderma pigmentosum, nevoid basal cell carcinoma syndromes
- Skin type – fair (pale) skin – burns easily, freckles
- Eye color – blue, green or gray, Hair color – blond or red
- Use of medication causing sensitivity to sun – antibiotics, hormones, antidepressants,
- Immune system depression – AIDS, leukemias, etc.
- Exposure to arsenic, coal tar or creosote
- For eye localization- history of oculodermal melanocytosis or Dysplastic nevus syndrome

_____

Health Practitioner Name (Print)

_____

Health Practitioner Name (Signature)

Additional information regarding this Adverse Event Report:

Description of event: [narrative]

Bristol Myers Squibb™
P.O BOX 4000, B.3140
Princeton, NJ-08543-4000

[Case_ ID]

Adverse Event Report Questionnaire
TL Thrombocytopenia-Bleeding Vidaza Inrebic Pomalyst Onureg

INFORMATION PREVIOUSLY PROVIDED DOES NOT NEED TO BE REPEATED ON THIS FORM:

Patient Demographics:

Patient's date of birth (DD-MMM-YYYY): _____ Gender: ☐ Male ☐ Female

Age: _____

Race/Ethnicity: _____ ☐ Aborginal ☐ African American ☐ Asian
☐ American Indian or Alaskan Native ☐ Native Hawaiian or other Pacific Islander
☐ Torres Strait Islander ☐ White ☐ Black ☐ Non Hispanic

Age Group:_____

Note: Please provide Age Group if Patient's Date of Birth or Age is not available.

Age Group Definition: Neonate: 0 - 27 days, Infant: 28 days to 23 months, Child: 2 years to 11years, Adolescent: 12 years to 18 years, Adult: More than 18 years and less than or equal to 65 years and Elderly: equal or greater than 66 years)

Suspect Products: Please provide suspect product(s) information [those product(s) that are suspected to be associated with one or more adverse events]:

	Suspect Product #1	Suspect Product #2	Suspect Product #3
Product name			
Daily dose and regimen			
Route of administration			
Indication			
Start date or treatment duration (DD-MMM-YYYY)			
Stop date (DD-MMM-YYYY)			
Lot/Batch number(s)			
Expiration date(s)			
Action Taken with the suspect product			

(Choose from one of the following for action Taken with Suspect Product: Drug withdrawn, Dose reduced, Dose increased, Dose not changed, Unknown)

Adverse Event (AE) Description: Please provide diagnosis or symptoms/signs if diagnosis is unavailable.

	Adverse Event #1	Adverse Event #2	Adverse Event #3	Adverse Event #4

Add Diagnosis Here →				
Start Date (DD/MMM/YYYY)				
Stop Date (DD/MMM/YYYY)				
Time lag if AE occurred after cessation of treatment with the suspect product(s):				
Required Hospitalization (Yes/No)				
Life-Threatening (Yes/No)				
Persistent or significant disability (Yes/No)				
Congenital abnormality (Yes/No)				
Cause of Death (Yes/No)				
Treatment of Adverse Event				
Outcome (recovery and sequelae, if any)				
Did the event(s) abate after suspect Product was stopped or dose reduced? (Yes/No)				
Did the event recur after reintroducing (Yes/No)				

Please summarize course of reported events including signs and symptoms in chronological order:

Diagnostic tests (use additional pages if needed)**:** Please indicate test unit where applicable.

Date	Test Name	Pre-treatment value	AE onset value	AE resolution value	Normal low	Normal high
	Platelets					
	PT					
	aPTT					
	INR					
	ESR					
	LFTs					
	Factor VIII					
	Factor IX					

Please provide causal relationship assessment between the suspect product(s) and adverse event(s):

Concomitant Medications (use additional pages if needed)**:**

Did the Patient take any concomitant medication? ☐ Yes [please complete below; Please provide relevant concomitant medications, including thromboprophylaxis (type/dose/dates as well as corresponding lab monitoring values if applicable), and possible platelet transfusion need to prevent hemorrhagic event]
☐ No ☐ Unknown

Medication Name	Daily dose and regimen	Route of administration	Indication	Start date DD-MMM-YYYY	Stop date DD-MMM-YYYY

Other Etiological Factors: ☐ Yes (please complete below) ☐ None ☐ Unknown

☐ Relevant medical and/or drug history (please specify), including start date or duration:

_____

_____

_____

☐ Family history (please specify): _____
☐ Drug/alcohol/tobacco abuse: _____
☐ Other (please specify): _____

Additional questions:

Please provide location of the bleeding/hemorrhage.

Relevant medical history:

Does the patient have:

History of anemia?

Was patient transfusion dependent? If yes, since when and how frequent?

Episodes of Hypotension? Hypertension? Gingivorrhagia or epistaxis? Headaches? Pallor? Dyspnea? Weakness?

Please describe. History of bleeding/hemorrhage? Coagulation disorder? Please describe.

Please provide date of diagnosis of underlying disease, stage at the time of diagnosis and stage of the patient's disease at the time of the event.

Please include bone marrow studies / x-ray / CT scan results for the event of thrombocytopenia/ bleeding/hemorrhage.

What treatments were given for the thrombocytopenia/ bleeding/ hemorrhage? Please include dates/dose.

_____

Health Practitioner Name (Print)

_____

Health Practitioner Name (Signature)

Additional information regarding this Adverse Event Report:

Description of event: [narrative]

ANNEX 6: DETAILS OF PROPOSED ADDITIONAL RISK MINIMISATION ACTIVITIES

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

- Prior to launch, all doctors who intend to prescribe Imnovid and all pharmacists who may dispense Imnovid receive a Direct Healthcare Professional Communication as described below.
- Prior to prescribing (where appropriate, and in agreement with the National Competent Authority, dispensing) all healthcare professionals who intend to prescribe (and dispense) Imnovid are provided with an Educational Healthcare Professional's Kit containing the following:
  - Educational Healthcare Professional brochure
  - Educational brochures for patients
  - Patient card
  - Risk awareness forms
  - Information on where to find latest Summary of Product Characteristics (SmPC)

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

The MAH should agree the final text of the Direct Healthcare Professional Communication and the contents of the Educational Healthcare Professional's Kit with the National Competent Authority in each Member State prior to launch of the medicinal product and ensure that the materials contain the key elements as described below.

The MAH should agree on the implementation of the controlled access programme in each Member State.

Key elements to be included

Direct Healthcare Professional Communication (prior to launch)

The Direct Healthcare Professional Communication shall consist of two parts:

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

Educational Healthcare Professional's Kit

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

Educational Healthcare Professional brochure

- Brief background on pomalidomide
- Maximum duration of treatment prescribed
    - 4 weeks for women with childbearing potential
    - 12 weeks for men and women without childbearing potential
- The need to avoid foetal exposure due to teratogenicity of pomalidomide in animals and the expected teratogenic effect of pomalidomide in humans
- Guidance on handling the blister or capsule of Imnovid for healthcare professionals and caregivers
- Obligations of the healthcare professionals who intend to prescribe or dispense Imnovid
    - Need to provide comprehensive advice and counselling to patients
    - That patients should be capable of complying with the requirements for the safe use of Imnovid
    - Need to provide patients with appropriate patient educational brochure, patient card and/or equivalent tool

- Safety advice relevant to all patients
    - Description and management of thrombocytopenia including incidence rates from clinical studies
    - Description and management of cardiac failure
    - Local country specific arrangements for a prescription for pomalidomide to be dispensed
    - That any unused capsules should be returned to the pharmacist at the end of the treatment
    - That the patient should not donate blood during treatment (including during dose interruptions) and for at least 7 days following discontinuation of Imnovid
- Description of the PPP and categorisation of patients based on sex and childbearing potential
    - Algorithm for implementation of PPP
    - Definition of women of childbearing potential (WCBP) and actions the prescriber should take if unsure
- Safety advice for women of childbearing potential
    - The need to avoid foetal exposure
    - Description of the PPP
    - Need for effective contraception (even if the woman has amenorrhoea) and definition of effective contraception
    - That if she needs to change or stop using her method of contraception she should inform:
        - The physician prescribing her contraception that she is on pomalidomide
        - The physician prescribing pomalidomide that she has stopped or changed her method of contraception
    - Pregnancy test regime
        - Advice on suitable tests
        - Before commencing treatment
        - During treatment based on method of contraception
        - After finishing treatment
    - Need to stop Imnovid immediately upon suspicion of pregnancy
    - Need to tell treating doctor immediately upon suspicion of pregnancy
- Safety advice for men
    - The need to avoid foetal exposure

    - The need to use condoms if sexual partner is pregnant or a WCBP not using effective contraception (even if the man has had a vasectomy)
        - During Imnovid treatment
        - For at least 7 days following final dose
    - That he should not donate semen or sperm during treatment (including during dose interruptions) and for at least 7 days following discontinuation of Imnovid treatment
    - That if his partner becomes pregnant whilst he is taking Imnovid or shortly after he has stopped taking Imnovid he should inform his treating doctor immediately
- Requirements in the event of pregnancy
    - Instructions to stop Imnovid immediately upon suspicion of pregnancy, if female patient
    - Need to refer patient to physician specialised or experienced in dealing with teratology and its diagnosis for evaluation and advice
    - Local contact details for reporting of any suspected pregnancy immediately
    - Pregnancy reporting form
- Local contact details for reporting adverse reactions

Educational Brochures for patients

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

All educational brochures for patients should contain the following elements:
- That pomalidomide is teratogenic in animals and is expected to be teratogenic in humans
- That pomalidomide may cause thrombocytopenia and the need for regular blood tests
- Description of the patient card and its necessity
- Guidance on handling Imnovid for patients, caregivers and family members
- National or other applicable specific arrangements for a prescription for Imnovid to be dispensed
- That the patient must not give Imnovid to any other person
- That the patient should not donate blood during treatment (including during dose interruptions) and for at least 7 days after discontinuation of Imnovid treatment
- That the patient should tell their doctor about any adverse events
- That any unused capsules should be returned to the pharmacist at the end of the treatment

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

Brochure for women patients with childbearing potential
- The need to avoid foetal exposure
- Description of the PPP
- The need for effective contraception and definition of effective contraception
- That if she needs to change or stop using her method of contraception she should inform:
    - The physician prescribing her contraception that she is on pomalidomide

    - The physician prescribing pomalidomide that she has stopped or changed her method of contraception
- Pregnancy test regime
    - Before commencing treatment
    - During treatment (including dose interruptions), at least every 4 weeks except in case of confirmed tubal sterilisation
    - After finishing treatment
- The need to stop Imnovid immediately upon suspicion of pregnancy
- The need to contact their doctor immediately upon suspicion of pregnancy

Brochure for male patients

- The need to avoid foetal exposure
- The need to use condoms if sexual partner is pregnant or a WCBP and not using effective contraception (even if the man has had vasectomy)
    - During Imnovid treatment (including dose interruptions)
    - For at least 7 days following final dose
- That if his partner becomes pregnant, he should inform his treating doctor immediately
- That he should not donate semen or sperm during treatment (including during dose interruptions) and for at least 7 days following discontinuation of Imnovid treatment

Patient Card or equivalent tool

The patient card shall contain the following elements:

- Verification that appropriate counselling has taken place
- Documentation of childbearing potential status
- Check box (or similar) which physician ticks to confirm that patient is using effective contraception (if woman of childbearing potential)
- Pregnancy test dates and results

Risk Awareness Forms

There should be 3 types of risk awareness forms:

- Women of childbearing potential
- Women of non-childbearing potential
- Male patient

All risk awareness forms should contain the following elements:
- teratogenicity warning
- patients receive the appropriate counselling prior to treatment initiation
- affirmation of patient understanding regarding the risk of pomalidomide and the PPP measures
- date of counselling
- patient details, signature and date
- prescriber name, signature and date
- aim of this document i.e. as stated in the PPP: “The aim of the risk awareness form is to protect patients and any possible foetuses by ensuring that patients are fully informed of and understand the risk of teratogenicity and other adverse reactions associated with the use of pomalidomide. It is not a contract

and does not absolve anybody from his/her responsibilities with regard to the safe use of the product and prevention of foetal exposure."

Risk awareness forms for women of childbearing potential should also include:

- Confirmation that the physician has discussed the following:
  - the need to avoid foetal exposure
  - that if she is pregnant or plans to be, she must not take pomalidomide
  - that she understands the need to avoid pomalidomide during pregnancy and to apply effective contraceptive measures without interruption, at least 4 weeks before starting treatment, throughout the entire duration of treatment, and at least 4 weeks after the end of treatment
  - that if she needs to change or stop using her method of contraception she should inform:
    - the physician prescribing her contraception that she is taking Imnovid
    - the physician prescribing Imnovid that she has stopped or changed her method of contraception
  - of the need for pregnancy tests i.e. before treatment, at least every 4 weeks during treatment and after treatment
  - of the need to stop Imnovid immediately upon suspicion of pregnancy
  - of the need to contact their doctor immediately upon suspicion of pregnancy
  - that she should not share the medicinal product with any other person
  - that she should not donate blood during treatment (including during dose interruptions) and for at least 7 days following discontinuation of Imnovid
  - that she should return the unused capsules to the pharmacist at the end of treatment

Risk awareness forms for women with no childbearing potential should also include:

- Confirmation that the physician has discussed the following:
  - that she should not share the medicinal product with any other person
  - that she should not donate blood during treatment (including during dose interruptions) and for at least 7 days following discontinuation of Imnovid
  - that she should return the unused capsules to the pharmacist at the end of treatment

Risk awareness forms for male patients should also include:

- Confirmation that the physician has discussed the following:
  - the need to avoid foetal exposure
  - that pomalidomide is found in semen and the need to use condoms if sexual partner is pregnant or is a WCBP not on effective contraception (even if the man has had a vasectomy)
  - that if his partner becomes pregnant, he should inform his treating doctor immediately and always use a condom
  - that he should not share the medicinal product with any other person

- that he should not donate blood or semen during treatment (including during dose interruptions) and for at least 7 days following discontinuation of Imnovid
- that he should return the unused capsules to the pharmacist at the end of treatment