EU-RISK MANAGEMENT PLAN FOR REVLIMID® (LENALIDOMIDE)

VERSION 37.0, 20 DEC 2019

EU RISK MANAGEMENT PLAN FOR LENALIDOMIDE

RMP Version to be Assessed as Part of this Application	Version 37.0
Data Lock Point for this Current European Union–Risk Management Plan (EU-RMP)	26 Dec 2017
Date of Final Sign Off	20 Dec 2019
Rationale for Submitting an Updated RMP	Inclusion of approved additional indication of previously treated follicular lymphoma.

Table 1: Summary of Significant Changes in this RMP

Part	Module/Annex	Significant Changes in Each Module
Part I	--	Inclusion of approved additional indication of previously treated follicular lymphoma.
Part II Safety Specification	Module SI Epidemiology of the Indication and Target Population(s)	Epidemiology information added for approved additional indication of previously treated follicular lymphoma.
	Module SII Nonclinical Part of the Safety Specification	No changes.
	Module SIII Clinical Trial Exposure	Exposure data added for Studies NHL-007 and NHL-008.
	Module SIV Populations Not Studied in Clinical Trials	Exclusion criteria for Studies NHL-007 and NHL-008 added.
	Module SV Postauthorisation Experience	No changes.
	Module SVI Additional EU Requirements for the Safety Specification	No changes.
	Module SVII Identified and Potential Risks	Inclusion of approved additional indication of previously treated follicular lymphoma.
	Module SVIII Summary of the Safety Concerns	No changes.
Part III Pharmacovigilance Plan	--	No changes.
Part IV Plan for Postauthorisation Efficacy Studies	--	No changes.
Part V Risk Minimisation Measures	--	Inclusion of approved additional indication of previously treated follicular lymphoma.

Table 1: Summary of Significant Changes in this RMP (Continued)

Part	Module/Annex	Significant Changes in Each Module
Part VI Summary of RMP	--	Inclusion of approved additional indication of previously treated follicular lymphoma.
Part VII Annexes	ANNEX 1 Eudravigilance Interface	No significant changes.
	ANNEX 2 Tabulated Summary of Planned, Ongoing, and Completed Pharmacovigilance Study Programme	No changes
	ANNEX 3 Protocols for Proposed, Ongoing and Completed Studies in the Pharmacovigilance Plan	No changes
	ANNEX 4 Specific Adverse Drug Reaction Follow-up Forms	No changes.
	ANNEX 5 Protocols for Proposed and Ongoing Studies in RMP Part IV	No changes.
	ANNEX 6 Details of Proposed Additional Risk Minimisation Activities (if Applicable)	Updated.
	ANNEX 7 Other Supporting Data (Including Referenced Material)	Updated.
	ANNEX 8 Summary of Changes to the Risk Management Plan Over Time	Updated to reflect changes in the RMP.

Other RMP Versions under Evaluation:

RMP Version Number	Submitted On	Procedure Number
None		

Details of the Currently Approved RMP:

Version Number	37.0
Approved with Procedure	EMEA/H/C/000717/II/0107
Date of Approval (Opinion Date)	European Commission (EC) Decision: 18 Dec 2019

QPPV NAME AND CONTACT PERSON FOR THIS EU-RISK MANAGEMENT PLAN

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LIST OF ABBREVIATIONS

AdEERS	Adverse Event Expedited Reporting System
ADR	Adverse drug reaction
AE	Adverse event
AFSSAPS	Agence Française de Sécurité Sanitaire des Produits de Santé
ALF	Acute liver failure
AMI	Acute myocardial infarction
AML	Acute myeloid leukaemia
ANC	Absolute neutrophil count
ANSM	Agence nationale de sécurité du médicament et des produits de santé
ASCT	Autologous stem cell transplantation
ASR	Age-standardised incidence rates
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical Classification
ATE	Arterial thromboembolic event
ATLL	Adult T-cell leukaemia-lymphoma
AUC	Area under the curve
BCRP	Breast cancer resistance protein
BID	Twice daily
BSEP	Bile salt export pump
BUMEL	Busulfan with melphalan
CALGB	Cancer and Leukaemia Group B
CCDS	Company Core Data Sheet
CD	Clusters of differentiation
CDC	Centers for Disease Control and Prevention
CHD	Coronary heart disease
CHF	Congestive heart failure
CHMP	Committee for Medicinal Products for Human Use
CHOP	Cyclophosphamide, doxorubicin, vincristine and prednisolone
CI	Confidence interval
CLcr	Creatinine clearance
CL/F	Apparent clearance
CLL	Chronic lymphocytic leukaemia

LIST OF ABBREVIATIONS (CONTINUED)

C_{max}	Maximum concentration
CML	Chronic myeloid leukaemia
CMML	Chronic myelomonocytic leukaemia
CNS	Central nervous system
CPRD	Clinical Practice Research Datalink
CRF	Case report form
CSC	Corrected serum calcium
CSF	Cerebrospinal fluid
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CVA	Cerebrovascular accident
CYP	Cytochrome P450
Del 5q	Deletion 5q
Del 13q	Deletion 13q
Del 17p	Deletion 17p
Dex	Dexamethasone
DHPC	Direct Healthcare Professional Communication
DILI	Drug-induced liver injury
DLBCL	Diffuse large B-cell lymphoma
DLP	Data lock point
DNA	Deoxyribonucleic acid
DSUR	Development Safety Update Report
DVT	Deep vein thrombosis
E	Evaluation
EBMT	European Society for Bone and Marrow Transplantation
EBV	Epstein-Barr virus
EC	European Commission
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EEA	European Economic Area
EMA/EMEA	European Medicines Agency

LIST OF ABBREVIATIONS (CONTINUED)

EPAR	European public assessment report
EPITT	European Pharmacovigilance Issues Tracking Tool
EPO	Erythropoietin
ESA	Erythropoiesis-stimulating agent
ESMO	European Society for Medical Oncology
EU	European Union
FAB	French-American-British
FCBP	Females of childbearing potential
FDA	Food and Drug Administration
FL	Follicular lymphoma
FLIPI	Follicular Lymphoma International Prognostic Index
G-CSF	Granulocyte colony-stimulating factor
GLSG	German Low Grade Lymphoma Study Group
GvHD	Graft versus host disease
GVP	Good pharmacovigilance practices
HBV	Hepatitis B virus
(β-)hCG	(β-)human chorionic gonadotropin
HCP	Healthcare professional
HCV	Hepatitis C virus
HDM	High dose melphalan
HDT	High-dose therapy
HHV-8	Human herpes virus-8
HIV	Human immunodeficiency virus
HLGT	High Level Group Term
HLT	Higher Level Term
HMRN	Haematological Malignancy Research Network
hpf	High-power field
HR	Hazard ratio
HRQoL	Health related quality of life
HSC	Haematopoietic stem cell
(auto-)HSCT	(autologous) Haematopoietic stem cell transplantation
ICUS	Idiopathic cytopenia of undetermined significance

LIST OF ABBREVIATIONS (CONTINUED)

IFI	Invasive fungal infection
IFM	Intergroupe Francophone du Myelome
Ig	Immunoglobulin
IHC	Immunohistochemistry
IHD	Ischaemic heart disease
IIT	Investigator-initiated trial
IL	Interleukin
IMiD	Immunomodulatory drug
INN	International Nonproprietary Name
INR	International normalised ratio
INT	Intermediate
INT-1/INT-2	Intermediate-1/Intermediate-2
IPSS	International Prognostic Scoring System
IQR	Interquartile range
ISS	International Staging System
ITT	Intent-to-treat
IV	Intravenous(ly)
KLSG	Kiel Lymphoma Study Group
LEG	Legally binding measure
Len	Lenalidomide
LFS	Leukaemia-free survival
LMWH	Low-molecular-weight heparin
MAA	Marketing Authorisation Application
MAH	Marketing Authorisation Holder
MALT	Mucosa-associated lymphoid tissue
MATE	Multi antimicrobial extrusion protein
MCL	Mantle cell lymphoma
MDS	Myelodysplastic syndrome(s)
MedDRA	Medical Dictionary for Regulatory Activities
MEL200	Melphalan 200 mg/m^2
MGUS	Monoclonal gammopathy of undetermined significance

LIST OF ABBREVIATIONS (CONTINUED)

MI	Myocardial infarction
MIPI	Mantle cell lymphoma International Prognostic Index
MM	Multiple myeloma
MPp+p	Induction therapy (up to 9 cycles) with melphalan/prednisone plus placebo followed by maintenance therapy with single-agent placebo
MPR+p	Induction therapy (up to 9 cycles) with melphalan/prednisone plus lenalidomide followed by maintenance therapy with single-agent placebo
MPR+R	Induction therapy (up to 9 cycles) with melphalan/prednisone plus lenalidomide followed by maintenance therapy with single-agent lenalidomide
MPT	Melphalan, prednisone and thalidomide
MRP	Multidrug resistance-associated protein
MTD	Maximum tolerated dose
MZL	Marginal zone lymphoma
N/A	Not applicable
N/n	Number of patients
NA	Not available
NC	Not calculated/not collected
NCA(s)	National Competent Authority(ies)
NCI	National Cancer Institute
NCCN	National Comprehensive Cancer Network
NDMM	Newly diagnosed multiple myeloma
NEC	Not elsewhere classified
NHL	Non-Hodgkin's lymphoma
NK	Natural killer
NMSC	Non-melanoma skin cancer
NOAEL	No observed adverse effect level
NOL	No Objection Letter
NOS	Not otherwise specified
OAT	Organic anion transporter
OCT	Organic cation transporter
ONJ	Osteonecrosis of the jaw
OS	Overall survival
PASS/PASSes	Postauthorisation Safety Study/Studies

LIST OF ABBREVIATIONS (CONTINUED)

PBO	Placebo
PD	Progressive disease
PDCO	Paediatric Committee
PFS	Progression-free survival
P-gp	P-glycoprotein
PI	Prescribing information
PK	Pharmacokinetic(s)
PL	Package leaflet
PMC	Postmarketing Commitment
PPP	Pregnancy Prevention Programme
PRAC	Pharmacovigilance Risk Assessment Committee
PSUR	Periodic Safety Update Report
PT	Preferred term
PTLD	Post-Transplant Lymphoproliferative Disorders
QD	Once daily
QOD	Every other day
QPPV	Qualified Person for Pharmacovigilance
QTc	Corrected QT interval
R	Reporting
RA	Refractory anaemia
RAEB	Refractory Anaemia with Excess Blasts
RARS	Refractory Anaemia with Ringed Sideroblasts
RBC	Red blood cell
R-CHOP	Rituximab, cyclophosphamide, doxorubicin, vincristine and predniso(lo)ne
RCMD	Refractory cytopenia with multilineage dysplasia
R-CVP	Rituximab, cyclophosphamide, vincristine and prednisolone
Rd	Lenalidomide and low-dose dexamethasone given in 28-day cycles until documentation of progressive disease
Rd18	Lenalidomide and low-dose dexamethasone given in 28-day cycles for up to 18 cycles (72 weeks)
REMS	Risk Evaluation and Mitigation Strategies
Rit	Rituximab

LIST OF ABBREVIATIONS (CONTINUED)

RMP	Risk Management Plan
RRMCL	Relapsed or refractory MCL
RRMM	Relapsed or refractory MM
RSI	Request for Supplementary Information
RVd	Lenalidomide, bortezomib and dexamethasone
SAE	Serious adverse event
SC	Subcutaneous
SCS	Summary of Clinical Safety
SD	Standard deviation
SEER	Surveillance, Epidemiology and End Results
SIR	Standardised incidence ratio
SmPC	Summary of Product Characteristics
SMQ	Standardised MedDRA Query
SMR	Standardised Mortality Ratio
SOC	System Organ Class
SPM	Second primary malignancies
STR	Safety topic review
SUSAR	Suspected unexpected serious adverse reaction
SWOG	Southwest Oncology Group (until 2010; thereafter referred to as SWOG)
$t_{1/2}$	Half-life
$t_{1/2,z}$	Terminal half-life
tAML	Therapy-associated AML
TBD	To be determined
TCL	T-cell lymphoma
TD	Thalidomide and dexamethasone
TE	Transplant eligible
TEAE	Treatment-emergent adverse event
TFR	Tumour flare reaction
TLS	Tumour lysis syndrome
t_{max}	Time to maximum concentration
tMDS	Therapy-associated MDS

LIST OF ABBREVIATIONS (CONTINUED)

TNE	Transplant non-eligible
TP	Tumour protein
TTP	Time to disease progression
UGT	5'-diphospho-glucuronosyltransferase
UK	United Kingdom
ULN	Upper limit of normal
US/USA	United States/United States of America
VCD	Cyclophosphamide, bortezomib and dexamethasone
VD	Bortezomib and dexamethasone
VMP	Bortezomib, melphalan and prednisone
VTD	Bortezomib, thalidomide and dexamethasone
VTE	Venous thromboembolic event
WHO	World Health Organization
WPSS	WHO Classification-based Prognostic Scoring System

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PART I: PRODUCT(S) OVERVIEW

Table 2: Product Overview Lenalidomide

Active Substance(s) (INN or common name)	Lenalidomide
Pharmacotherapeutic Group(s) (ATC Code)	Other immunosuppressants L04 AX04
Marketing Authorisation Holder or Applicant	Celgene Europe B.V. Winthontlaan 6 N 3526 KV Utrecht The Netherlands
Medicinal Products to which this RMP Refers	1
Invented Name(s) in the European Economic Area (EEA)	Revlimid®
Marketing Authorisation Procedure	Centralised – European Medicines Agency (EMA); Procedure Number: EMEA/H/C/717
Brief Description of Product Including Chemical Class, Summary of Mode of Action, Important Information About its Composition (e.g. origin of active substance of biologicals, relevant adjuvants or residual vaccines)	Lenalidomide [3-(4'-amino-1,3-dihydro-1-oxo-2H-isoindol-2y1)-2-6-piperidinedione] is an immunomodulatory agent and belongs to a class of drugs known as Immunomodulatory Drugs (IMiD). The mechanism of action of lenalidomide includes direct cytotoxic and immunomodulatory effects. Specifically, lenalidomide inhibits proliferation of certain haematopoietic tumour cells (including multiple myeloma [MM] plasma tumour cells, follicular lymphoma [FL] tumour cells and those with deletions of chromosome 5), enhances T-cell- and natural killer (NK) cell-mediated immunity and increases the number of NK, T and NK T cells. In myelodysplastic syndrome (MDS) associated with a deletion 5q (del 5q) cytogenetic abnormality, lenalidomide selectively inhibits the abnormal clone by increasing the apoptosis of del 5q cells. The combination of lenalidomide and rituximab increases antibody-dependent cellular cytotoxicity and direct tumour apoptosis in FL cells. The lenalidomide mechanism of action also includes additional activities such as anti-angiogenic and pro-erythropoietic properties. Lenalidomide inhibits angiogenesis by blocking the migration and adhesion of endothelial cells and the formation of microvessels, augments foetal haemoglobin production by cells expressing clusters of differentiation (CD)34 (CD34+) haematopoietic stem cells, and inhibits production of pro inflammatory cytokines (eg, tumour necrosis factor alpha and interleukin-6 [IL-6]) by monocytes. Direct tumour cytotoxic effects of lenalidomide have also been shown to result from actin polymerisation and relocalisation of membrane proteins leading to cytoskeletal reorganisation, cell cycle arrest, and alterations in gene expression. The cytoskeletal effects play a key role in the restoration of a defective immune synapse in mantle cell lymphoma (MCL). In MCL, lenalidomide treatment induced formation of F-actin and polarisation of F-actin-rich structures to the plasma membrane within minutes and induced the polarisation of antigen-presenting proteins, such as CD1c, and the increase of co-stimulatory molecules, such as CD54.

Table 2: Product Overview Lenalidomide (Continued)

Hyperlink to the Product Information	*Summary of Product Characteristics (SmPC)*
Indication(s) in the EEA **Current**	Newly Diagnosed Multiple Myeloma (NDMM) in Transplant Eligible (TE) Patients Revlimid as monotherapy is indicated for the maintenance treatment of adult patients with NDMM who have undergone autologous stem cell transplantation (ASCT). NDMM in Transplant Non-eligible (TNE) Patients Revlimid as combination therapy with dexamethasone, or bortezomib and dexamethasone, or melphalan and prednisone is indicated for the treatment of adult patients with previously untreated MM who are not eligible for transplant. Relapsed or Refractory Multiple Myeloma (RRMM) Revlimid in combination with dexamethasone is indicated for the treatment of MM in adult patients who have received at least one prior therapy. Myelodysplastic syndrome (MDS) Revlimid as monotherapy is indicated for the treatment of adult patients with transfusion-dependent anaemia due to low- or intermediate-1 (INT-1) risk MDS associated with an isolated del 5q cytogenetic abnormality when other therapeutic options are insufficient or inadequate. Mantle Cell Lymphoma (MCL) Revlimid as monotherapy is indicated for the treatment of adult patients with relapsed or refractory mantle cell lymphoma (RRMCL). Follicilar Lymphoma (FL) Revlimid in combination with rituximab (anti-CD20 antibody) is indicated for the treatment of adult patients with previously treated FL (Grade 1 – 3a).
Proposed	None
Dosage in the EEA **Current**	For all indications described below, dosing is modified based upon clinical and laboratory findings. NDMM in TE Patients Who Have Undergone ASCT The recommended starting dose is lenalidomide 10 mg orally once daily (QD) continuously (on Days 1 to 28 of repeated 28-day cycles) given until disease progression or intolerance. After 3 cycles of lenalidomide maintenance, the dose can be increased to 15 mg orally QD if tolerated. NDMM in TNE Patients <u>Combination with dexamethasone until disease progression or intolerance in patients who are not eligible for transplant</u> The recommended starting dose of lenalidomide is 25 mg QD 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 repeated 28-day cycles. Patients may continue lenalidomide and dexamethasone therapy until disease progression or intolerance.

Table 2: Product Overview Lenalidomide (Continued)

	Initial treatment: Lenalidomide in combination with bortezomib and dexamethasone The recommended starting dose is lenalidomide 25 mg orally QD on Days 1 to 14 of each 21-day cycle, in combination with bortezomib and dexamethasone. Bortezomib should be administered via subcutaneous injection (1.3 mg/m^2 body surface area) twice weekly on Days 1, 4, 8 and 11 of each 21-day cycle. Up to eight 21-day treatment cycles (24 weeks of initial treatment) are recommended. Continued treatment: Lenalidomide in combination with dexamethasone Continue lenalidomide 25 mg orally QD on Days 1 to 21 of repeated 28-day cycles in combination with dexamethasone. Treatment should be continued until disease progression or unacceptable toxicity. Combination with melphalan and prednisone followed by lenalidomide maintenance in patients who are not eligible for transplant The recommended starting dose is lenalidomide 10 mg orally QD on Days 1 to 21 of repeated 28-day cycles for up to 9 cycles, melphalan 0.18 mg/kg orally on Days 1 to 4 of repeated 28-day cycles, and prednisone 2 mg/kg orally on Days 1 to 4 of repeated 28-day cycles. Patients who complete 9 cycles or who are unable to complete the combination therapy due to intolerance are treated with lenalidomide monotherapy as follows: 10 mg orally QD on Days 1 to 21 of repeated 28-day cycles given until disease progression. RRMM In combination with dexamethasone: The recommended starting dose of lenalidomide is 25 mg orally QD on Days 1 to 21 of repeated 28-day cycles. The recommended dose of dexamethasone is 40 mg orally QD on Days 1 to 4, 9 to 12, and 17 to 20 of each 28-day cycle for the first 4 cycles of therapy and then 40 mg QD on Days 1 to 4 every 28 days for all subsequent cycles. MDS Del 5q MDS: The recommended starting dose of lenalidomide is 10 mg orally QD on Days 1 to 21 of repeated 28-day cycles. MCL The recommended starting dose of lenalidomide is 25 mg orally QD on Days 1 to 21 of repeated 28-day cycles. FL The recommended starting dose of lenalidomide is 20 mg, orally QD on Days 1 to 21 of repeated 28-day cycles for up to 12 cycles of treatment. The recommended starting dose of rituximab is 375 mg/m^2 intravenously (IV) every week in Cycle 1 (Days 1, 8, 15, and 22) and Day 1 of every 28-day cycle for Cycles 2 through 5.
Proposed	None
Pharmaceutical Form(s) and Strength(s)	
Current	Hard capsules, available in 2.5, 5, 7.5, 10, 15, 20 and 25 mg.
Proposed	None
Is the Product Subject to Additional Monitoring in the EU?	Yes

PART II: SAFETY SPECIFICATION

PART II – MODULE SI: EPIDEMIOLOGY OF THE INDICATION(S) AND TARGET POPULATION(S)

1. INDICATION

Approved Indications:

NDMM in Transplant Eligible Patients

Revlimid as monotherapy is indicated for the maintenance treatment of adult patients with NDMM who have undergone ASCT.

NDMM in Transplant Non-eligible Patients

Revlimid as combination therapy with dexamethasone, or bortezomib and dexamethasone, or melphalan and prednisone is indicated for the treatment of adult patients with previously untreated MM who are not eligible for transplant.

RRMM

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

Myelodysplastic Syndrome

Revlimid as monotherapy is indicated for the treatment of adult patients with transfusion-dependent anaemia due to low- or INT-1 risk MDS associated with an isolated deletion 5q (del 5q) cytogenetic abnormality when other therapeutic options are insufficient or inadequate.

Mantle Cell Lymphoma

Revlimid as monotherapy is indicated for the treatment of adult patients with RRMCL.

FL

Revlimid in combination with rituximab (anti-CD20 antibody) is indicated for the treatment of adult patients with previously treated FL (Grade 1 – 3a).

2. EPIDEMIOLOGY OF THE DISEASE

2.1. Incidence, Prevalence, Mortality and Demographic Profile of the Follicular Lymphoma, Multiple Myeloma, Myelodysplastic Syndromes and Mantle Cell Lymphoma Populations

The incidence, prevalence, mortality, and demographics of the population of patients with FL are summarised in Table 3.

Table 3: Epidemiology of Patients with Follicular Lymphoma

Indication/Target Population	Follicular Lymphoma
Incidence and Prevalence of Target Indication	- FL is the second most common form of indolent lymphoma in the United States (US) and Europe, and accounts for about 10% to 20% of non-Hodgkin lymphoma (NHL) (Fischer, 2018). - Age-adjusted incidence rate of FL in the US was 3.4 per 100,000 person-years from 2011 to 2012, and estimated new cases of FL was 13,960 in 2016 (Teras, 2016). In the UK, the crude incidence rate from the Haematological Malignancy Research Network (HMRN) from 2004 to 2012 was 3.23 (95% confidence interval [CI]: 3.03-3.45) per 100,000; age-standardised (European 2013) incidence rate was 2.81 (95% CI: 2.74-2.88) per 100,000 (Smith, 2015). - The 3-, 5-, and 10-year prevalence rates per 100,000 estimated from the UK HMRN database were 9.7 (95% CI: 8.7-10.7), 14.8 (95% CI: 13.6-16.1), and 25.2 (95% CI: 23.5-26.9) respectively (Smith, 2015).
Natural History, Including Mortality and Morbidity	- The natural history of FL is indolent in nature, with most patients developing several relapses over their lifetime. As the disease progresses, subsequent relapses can become progressively aggressive and refractory, and some cases may transform into aggressive lymphoma (Becnel, 2018). According to the World Health Organization (WHO) criteria, FL tumours are histologically divided into three grades: Grade 1 (< 5 centroblasts per high-power field [hpf]), Grade 2 (6 to 15 centroblasts/hpf) and Grade 3 (> 15 centroblasts/hpf). Grade 3 is further subdivided into Grade 3A (centrocytes still present) and Grade 3B (the follicles consist almost entirely of centroblasts). Grades 1 through 3A are considered to be indolent and incurable, whereas Grade 3B is considered an aggressive but curable disease similar to diffuse large B-cell lymphoma (DLBCL) (Ma, 2012). The Ann Arbor staging system includes: Stage I (IE) – single lymph node region or extralymphatic site; Stage 2 (IIE) – multiple lymph node regions or at least one lymph node region plus a localised extralymphatic site on the same side of the diaphragm; Stage 3 (IIIE, IIIS) – multiple lymph node regions or lymphoid structures (eg, thymus, Waldeyer's ring) on both sides of the diaphragm with optional localised extranodal site (IIIE) or spleen (IIIS); Stage 4 – diffuse or disseminated extralymphatic organ involvement. The Follicular Lymphoma International Prognostic Index (FLIPI) risk factors include: number of nodal sites or long diameter of largest lymph node; age > 60 years; elevated lactate dehydrogenase or elevated β2-microglobulin; Ann Arbor Stage III to IV or bone marrow involvement; and haemoglobin < 12 g/dL (Dreyling, 2016).

Table 3: Epidemiology of Patients with Follicular Lymphoma (Continued)

Indication/Target Population	Follicular Lymphoma
Natural History, Including Mortality and Morbidity (Continued)	- The overwhelming majority of FL patients have advanced stage disease at diagnosis, whereas less than 10% of patients have Stage 1/2 disease at diagnosis. Studies have reported that 10% to 70% of patients transform to DLBCL over time, with an estimated risk of 3% per year. Common symptoms include rapid progression of lymphadenopathy, extranodal disease, B symptoms (fever, night sweats, and weight loss) and elevated serum lactate dehydrogenase (Freedman, 2011). - 5-year relative survival rates (the ratio of observed survival in the patient group to expected survival in a comparable group of the general population assumed to be free of the cancer of interest) for patients with FL ranged from 81% in black males to 87% in white females in the US (Teras, 2016). - 5-year overall and relative survival rates in the UK HMRN patients diagnosed between 2004 and 2012, and followed through to 2014 were 75.6% (95% CI: 72.4-78.5) and 86.5% (95% CI: 83.0-89.4), respectively (Smith, 2015).
Risk Factors for the Disease	- Risk factors for FL are poorly understood. Other than age, gender and ethnicity, environmental and occupational exposure to benzenes and pesticides have been implicated, but a clear association has not been established. Lifestyle factors such as smoking, alcohol use, and obesity have also been implicated in various studies, but conflicting results have not established a clear association with increased risk of FL (Ma, 2012). - Genetic risk factors include variants at the 6p21.32 region of the Major Histocompatibility Complex II locus, polymorphisms of the DNA repair gene XRCC3, and ultraviolet exposure in individuals with certain polymorphisms of the vitamin D receptor (Ambinder, 2012). - Risk factors for transformation to DLBCL have been controversial. Clinical risk factors include elevated β2-microglobulin levels, high international prognostic index, high FLIPI score, and advanced stage (III and IV). Some studies suggest that time and treatment approach (watch and wait as first-line therapy versus treatment with rituximab) are possible risk factors for transformation. However, due to the variable follow-up time, inclusion criteria and treatments, findings in various studies have been inconsistent (Fischer, 2018).
Demographic Profile of Target Population	- The median age at diagnosis is 60 to 65 years, and there is a slight female predominance. In the US, African-Americans have a higher incidence than Caucasians (Ma, 2012). - In the UK HMRN population, median age at diagnosis was 64.9 (interquartile range [IQR] 55.8-73.3) (Smith, 2015). Similarly, in the EUROCARE study, the median age at diagnosis was 62 years (IQR 51 to 72) and females accounted for 53% of all 13,988 cases (Mournier, 2015).
Main Treatment Options	- Treatment options are currently recommended for patients with FL by the European Society for Medical Oncology (ESMO) (Dreyling, 2016) and National Comprehensive Cancer Network (NCCN) (NCCN Version 4.2018). - In the EU, approved first-line treatment options include rituximab, interferon alpha, Y90 ibritumomab tiuxetan, bendamustine, and obinutuzumab.

Table 3: Epidemiology of Patients with Follicular Lymphoma (Continued)

Indication/Target Population	Follicular Lymphoma
Main Treatment Options (Continued)	- At relapse, the selection of salvage treatment depends on the patient's prior regimens. In symptomatic cases with low tumour burden, rituximab monotherapy may be utilized. In early relapses, (< 12 to 24 months), consideration should be given to a non-cross resistant therapy, such as cyclophosphamide, doxorubicin, vincristine and prednisolone (CHOP) followed by bendamustine. Fludararabine, platinum or alkylator based regimens are other treatment options. Rituximab may be added if the previous antibody containing regimen achieved a duration of remission > 6 to 12 months. In rituximab refractory cases, obinutuzumab may be used. In patients with short lived remissions (< 2 to 3 years), high dose chemotherapy followed by ASCT, should be considered. In late relapses, monotherapy is considered palliative treatment, eg idelalisib. Other subsequent treatment options recommended by the NCCN include idelalisib and copanilisib, as well as the following regimens: cyclophosphamide, vincristine and prednisone with obinutuzumab or rituximab, and lenalidomide with or without rituximab. For elderly patients whose treatment options may be limited by comorbidities, radioimmunotherapy (Y^{90} ibritumomab tiuxetan) may be an effective treatment option. Additional treatment options recommended by the NCCN for the elderly patient population include rituximab and CHOP (R-CHOP); rituximab, cyclophosphamide, vincristine and prednisolone (R-CVP); and bendamustine and rituximab.
Important Comorbidities	- Comorbidities associated with FL are usually due to the advanced age of the patient. Such patients are more likely to develop cardiovascular, neurological, kidney injuries and complications as well as mucositis (Castellino, 2017).

The incidence, prevalence, mortality, and demographics of the population of patients with MM are summarised in Table 4.

Table 4: Epidemiology of Patients with Multiple Myeloma

Indication/Target Population	Multiple Myeloma
Incidence and Prevalence of Target Indication	- MM accounts for about 10% to 18% of haematologic malignancies (Mateos, 2015; Siegel, 2016). - The prevalence of MM varies from country to country in the European Union (EU). Overall, the estimated prevalence of MM in the EU in 2018 ranges from 1.79 to 3.61 in 10,000 persons (data on file). In Europe, 38,900 new cases of MM and 24,300 deaths due to MM were estimated in 2012 (Ferlay, 2013). - Crude and age-standardised incidence rates (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 data (Ferlay, 2013). - 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 (Ferlay, 2013). - Gains in survivorship associated with new therapies will increase the prevalence of MM.

Table 4: Epidemiology of Patients with Multiple Myeloma (Continued)

Indication/Target Population	Multiple Myeloma
Natural History, Including Mortality and Morbidity	- 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 (Ferlay, 2013). Within the EU-28 population, 20,462 men and women died with MM in 2012 (Ferlay, 2013). The cumulative mortality risk of MM (ages 0 to 74 years) is 0.17%. - According to GLOBOCAN 2012 data, MM accounts for 1.2% of all deaths among persons with invasive malignancy in the European population (Ferlay, 2013). - Between 1989 and 2009, 1206 patients with MM were identified through the Modena Cancer Registry (Pozzi, 2013), corresponding to periods of conventional therapy (1988 to 1996), high dose melphalan (HDM) and ASCT (1997 to 2005) and novel agents (2006 to 2009). Relative survival and overall survival (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 (EBMT) 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) (Auner, 2015). - In a retrospective analysis of MM patients who received haematopoietic stem cell transplantation (HSCT), median OS was 79.5 months in those < 60 years of age and 63.4 months in those ≥ 60 years of age (Lamm, 2015).
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 (Alexander, 2007; Kazandjian, 2016).
Demographic Profile of Target Population	- 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) (Ferlay, 2013). - 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 (Ferlay, 2013). - 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 (Ferlay, 2013). - Analysing 18,824 MM registrations with ethnicity obtained by linkage to the English Hospital Episodes Statistics Database, (Shirley, 2013) 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 US, where

Table 4: Epidemiology of Patients with Multiple Myeloma (Continued)

Indication/Target Population	Multiple Myeloma
Demographic Profile of Target Population (Continued)	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) (Howlader, 2017). Racial differences in rates were also observed in the US population (Kazandjian, 2016).
Main Treatment Options	- Treatment options are currently recommended for patients with NDMM by ESMO (Moreau, 2017), the European Myeloma Network (EMN) (Engelhardt, 2014 [TNE]; Gay, 2018 [TE]; Larocca, 2018 [elderly]); and NCCN (Kumar, 2018). In the EU, treatment options available for NDMM approved for TE NDMM include bortezomib and dexamethasone (VD) and bortezomib, thalidomide and dexamethasone (VTD). Regimens approved for TNE NDMM include lenalidomide; lenalidomide and low-dose dexamethasone (Rd); induction therapy with lenalidomide, melphalan prednisone followed by single-agent lenalidomide (MPR+R); bortezomib; bortezomib, melphalan and prednisone(VMP); melphalan, prednisone and thalidomide (MPT); bendamustine. In addition, although not regulatory authorised, currently recommended per European clinical treatment guidelines and widely accepted as a standard of care and pending market authorisation is the combination of lenalidomide, bortezomib and dexamethasone (RVd), in the TE and TNE populations (Moreau, 2017; Gay, 2018; Larocca, 2018). - Treatment should be initiated in all patients with MM according to the updated definition proposed by the International Myeloma Working Group in 2014 (Rajkumar, 2014). ***Newly diagnosed MM*** - For patients with NDMM, the choice of initial therapy is determined by the patient's age, fitness/frailty status, and the presence of comorbidities, and thus the ability to undergo autologous hematopoietic stem cell transplantation (auto-HSCT) (Kumar, 2018; Ludwig, 2014; Moreau, 2017; Harousseau, 2007; Kyle, 2009). - The current ESMO MM guidelines recommend auto-HSCT for patients < 65 years or fit patients < 70 years in good clinical condition (Moreau, 2017). Similarly, the EMN guideline for TE MM patients recommends auto-HSCT for non-frail patients < 65 years; auto-HSCT should still be considered for patients < 65 years who have reduced performance status or comorbidities when the benefit of transplant outweighs the risk (Gay, 2018). The recently published EMN guidelines for elderly MM patients note that non-frail, elderly MM patients up to the age of 70 years (or even 75 years) without prohibitive comorbidities and adequate organ function may benefit from HDM followed by auto-ASCT (Larocca, 2018). - In Europe, TE NDMM patients are most often treated with bortezomib-containing triplet regimens such as VTD (27%) and cyclophosphamide, bortezomib, and dexamethasone (VCD; 23%) (Kantar-Health, 2017). In addition, a proportion of patients still receive the bortezomib-containing doublet regimen, VD (10%).

Table 4: Epidemiology of Patients with Multiple Myeloma (Continued)

Indication/Target Population	Multiple Myeloma
Main Treatment Options (Continued)	- For non-transplant candidates with NDMM, the choice of treatment is more heterogeneous, with bortezomib, melphalan, and prednisone (VMP; 24%), VD (15%), and Rd (10%) the most commonly used regimens (Kantar-Health, 2017). ***Relapsed/Refractory MM*** - The choice of therapy in the relapse setting depends on several parameters such as age, performance status, comorbidities, the type, efficacy and tolerance of the previous treatment, the number of prior treatment lines, the available remaining treatment options, the interval since the last therapy and the type of relapse (ie, clinical versus biochemical relapse; in the case of biochemical relapse, treatment can be delayed) (Laubach, 2016). Major treatment regimens in MM for R/R disease include: carfilzomib, lenalidomide and dexamethasone; bortezomib, dexamethasone and panobinostat; carfilzomib and dexamethasone; lenalidomide, dexamethasone and elotuzumab; lenalidomide, dexamethasone and ixazomib; bortezomib, dexamethasone and daratumumab; lenalidomide, dexamethasone and daratumumab (Moreau, 2017). - In young patients (< 65 years of age), a second ASCT may be considered, provided the patient responded well to the previous ASCT and had a progression-free survival (PFS) of more than 24 months (Lemieux, 2013). In the relapse setting, allogenic stem cell transplant should only be carried out in the context of a clinical trial. In RRMM, the EMA has approved lenalidomide in combination with dexamethasone (Weber, 2007; Dimopoulos, 2007) and bortezomib either alone as a single agent (Richardson, 2005) or in combination with pegylated doxorubicin (Orlowski, 2007). Nevertheless, bortezomib is mostly used in combination with dexamethasone in the relapse setting. Thalidomide and bendamustine are effective drugs, often used, but not approved (Moreau, 2012). Triplet combinations have proved effective in Phase 2 trials, but only one single randomised trial has shown the superiority of VTD over thalidomide and dexamethasone (TD) for PFS in patients relapsing following ASCT (Garderet, 2012). - Thalidomide is also used in multiple combinations with clinical benefit in patients with relapsed and/or refractory myeloma (Palumbo, 2008). - When possible, patients should be offered participation in clinical trials. Pomalidomide (Moreau, 2012), the third-in-class IMiD, and carfilzomib (Moreau, 2012), the second-in-class proteasome inhibitor, both are approved in the US and the EU. - Other drugs or classes of drugs such as histone-deacetylase inhibitors, monoclonal antibodies and other CAR-T therapy are currently under development.
Important Comorbidities	- Renal impairment (Clark, 1999; Barosi, 2004; Augustson, 2005). - Peripheral neuropathy (Dispenzieri, 2003; Richardson, 2006a; Mileshkin, 2006). - Thromboembolic events (Hussein, 2006; Kristinsson, 2008; Srkalovic, 2004; Zonder, 2006). - Anaemia, leucopenia and infection (Birgegård, 2006; Augustson, 2005; Fernandez-Mosteirin, 2005).

Table 4: Epidemiology of Patients with Multiple Myeloma (Continued)

Indication/Target Population	Multiple Myeloma
	- Secondary primary malignancies (Dong, 2001; Dores, 2006; Hasskarl, 2011; Mailankody, 2011; Razavi, 2013; Travis, 2006). - Graft versus Host Disease (GvHD) (Kumar, 2011; Bashir, 2012). - Bone diseases (Raue, 1994; Mercadante, 1997; Melton, 2005). - Gastrointestinal haemorrhage (Talamo, 2006; Lin, 2013).

The incidence, prevalence, mortality, and demographics of the population of patients with MDS are summarised in Table 5.

Table 5: Epidemiology of Patients with Myelodysplastic Syndromes

Indication/Target Population	Myelodysplastic Syndromes
Incidence and Prevalence of Target Indication	- Among 216 patients newly diagnosed with MDS (WHO subtypes) during the interval 1996 to 2005 and identified on the Düsseldorf Registry, the overall crude incidence rate (per 100,000 person-years) was 3.78 (95% CI: 3.31-4.32). The overall age-standardised incidence was 2.51 per 100,000 person-years (Neukirchen, 2011). - In an analysis of data from the North American Association of Central Cancer Registries (encompassing 82% of the US population), the average annual age-adjusted incidence rate for MDS in 2001 to 2003 was 3.3 per 100,000 (Rollison, 2008). MDS incidence rates were highest among whites and non-Hispanics. - There are no prevalence data for MDS from the US and EU cancer registry databases. Using data from the Düsseldorf MDS Registry, in which the point prevalence of MDS was assessed, an age-standardised prevalence of approximately 7 per 100,000 persons was reported. Given the similar incidence and no known differences in disease duration or treatment options between Western European countries, the prevalence of MDS is expected to be similar throughout the EU (Neukirchen, 2011).
Natural History, Including Mortality and Morbidity	In the Multicentre Registry study, the median time of survival from diagnosis was 75 months (range, 1.7 to 350). The 2- and 5-year survival probabilities were 86% and 61%, respectively. Transfusion-dependent patients had a median survival of 44 months compared to 97 months for transfusion-independent patients (Germing, 2012). - Among MDS patients reported to the SEER 17 regions database during 2001to 2003, the 3-year observed survival was 35%. Age and sex were significantly associated with survival, whereas race was not. Younger patients demonstrated better survival, and men with MDS were 25% more likely to die than women (Ma, 2007). - Progression to acute myeloid leukaemia (AML) occurs at a variable rate depending on the presence of adverse prognostic risk factors. In the Multicentre Registry study, the cumulative AML progression risk was 4.7% after 2 years of diagnosis and 14.7% (competing risk method). In the first 2 years following diagnosis, the probability of developing AML was 11% for patients presenting with transfusion dependency compared with 2% among patients without transfusion dependency (Germing, 2012).

Table 5: Epidemiology of Patients with Myelodysplastic Syndromes (Continued)

Indication/Target Population	Myelodysplastic Syndromes
Risk Factors for the Disease	- Although the aetiology of MDS remains unclear, risk factors for the disease include gender, age and exposure to ionising radiation, chemicals, drugs or other environmental agents (Silverman, 2000).
Demographic Profile of Target Population	- The overall ASR was 4.30 and 3.32 per 100,000 person-years for men and women, respectively, in the Düsseldorf MDS Registry. The incidence rate ratio comparing men to women was 1.78 (Neukirchen, 2011). However, the incidence of MDS with the del 5q cytogenetic abnormality is greater in women than men. On the Düsseldorf MDS Registry in 2003, 2 (7%) female patients had the del 5q cytogenetic abnormality compared with no male patients (Neukirchen, 2011). - Using data from the Düsseldorf MDS Registry, in 2003 the median age of prevalent male and female patients was 69 and 78 years, respectively (Neukirchen, 2011). - In an analysis of data from the North American Association of Central Cancer Registries, age adjusted incidence of MDS was significantly higher among males and a sharp increase was observed with age; rates were 5 times greater among those aged 80 years and older (35.5 per 100,000) compared with those aged 60 to 69 years (7.1 per 100,000) (Rollison, 2008).
Main Treatment Options	- The only potentially curative approach that currently exists for treating MDS patients is allogeneic HSCT (Greenberg, 2010). This approach is typically only employed in younger patients with higher-risk disease because of morbidity/mortality and the lack of a suitable donor in older patients; hence, allogeneic HSCT is only a potential solution in a small subset (approximately 5%) of MDS patients (Silverman, 2002; Greenberg, 2010). - Other than transfusion support and iron chelation, the treatment options for low- or INT-1-risk MDS, include erythropoiesis-stimulating agents (ESAs) (erythropoietin [EPO] or darbepoetin-α) alone or in combination with granulocyte colony-stimulating factor (G-CSF); immunosuppressive therapies such as antithymocyte globulin or cyclosporin A; and lenalidomide (Alessandrino, 2002; Jädersten, 2009; Greenberg, 2010). ESAs are unlikely to be effective for patients with transfusion-dependent anaemia due to low- or INT-1 risk del 5q MDS as (1) these patients commonly have increased EPO levels, and ESAs have less effect in patients who already have adequate or high levels of EPO, (2) ESAs have been found to be less effective in patients who have a significant transfusion requirement, and (3) ESAs may be less effective in patients with del 5q MDS. Sanna and colleagues have reported that patients with del 5q MDS may have higher endogenous EPO levels and reduced sensitivity to treatment with EPO (Sanna, 2011). Patients with higher endogenous EPO levels and more substantial transfusion requirements have a relatively low likelihood of responding to treatment with EPO (Hellström-Lindberg, 2003; Park, 2008; Park, 2012).
Important Comorbidities	- Anaemia (List, 2002; Steensma, 2006). - Neutropenia and Infections (Steensma, 2006; Greenberg, 1999). - Thrombocytopenia and Bleeding (Steensma, 2006; Greenberg, 1999). - Other Neoplasms, Including Progression to AML (Greenberg, 1997).

The incidence, prevalence, mortality, and demographics of the population of patients with MCL are summarised in Table 6.

Table 6: Epidemiology of Patients with Mantle Cell Lymphoma

Indication/Target Population	Mantle Cell Lymphoma
Incidence and Prevalence of Target Indication	- The HAEMACARE project has identified 1012 cases of MCL, which were diagnosed in 2000 to 2002 and archived in 44 European cancer registries. (Sant, 2010). Based on these cases, the crude incidence of MCL is 0.45 per 100,000 (95% CI: 0.42-0.48). The estimated prevalence of MCL is 1 per 25,000 (Orphanet, 2014).
Natural History, Including Mortality and Morbidity	- Despite intensive induction therapies in the front-line setting of young and fit patients, the clinical course is typically that of repeated relapses, and median survival of patients with MCL is only 3 to 5 years (Abrahamsson, 2014; Salek, 2014). Following the initial relapse, the median OS decreases to 1 to 2 years (Goy, 2011). - Based on a 2004 to 2012 analysis of the United Kingdom (UK)'s population-based HMRN, a registry with 5796 lymphoma patients and 247 MCL patients, the 5-year OS was 25% and relative survival was 31.4% (Smith, 2015). - Among 150 patients with advanced-stage nonblastoid MCL identified either in the Kiel Lymphoma Study Group (KLSG; 1975 to 1986) or in the German Low Grade Lymphoma Study Group (GLSG; 1996 to 2004), median OS has almost doubled over the past 30 years. Five-year survival rates were 22% in the KLSG and 47% in the GLSG. Poor performance status, elevated serum lactate dehydrogenase and higher age negatively influenced mortality.
Risk Factors for the Disease	- Given the rarity of MCL, large-scale epidemiologic studies of risk factors for NHL frequently do not include sufficient numbers of MCL patients to adequately assess risk factors for this disease. Little evidence exists to link MCL with environmental or occupational exposures, and lifestyle factors (eg, cigarette smoking, alcohol intake, body mass index) have not been implicated in the aetiology of MCL. - Unlike other lymphomas where immune suppression and exposure to specific infectious agents increase lymphoma risk, evidence for association between specific infectious agents and MCL is scarce. However, some studies have shown that the immunoglobulin (Ig) gene repertoire in MCL is restricted and features precisely targeted, and probably functionally driven, somatic hypermutation. - Family history of haematopoietic malignancies has been linked with a two-fold increased risk of MCL. In the context of genetic susceptibility to NHL, there is little evidence of highly penetrant genetic traits in association with the disease. Instead, candidate gene studies focusing on low-penetrance polymorphic variants in the risk of NHL and its subtypes have consistently revealed associations with variants in genes encoding the proinflammatory cytokines tumour necrosis factor, lymphotoxin-alpha and interleukin-10 (Smedby, 2011).
Demographic Profile of Target Population	- According to the HAEMACARE project, the incidence of MCL in Europe is 0.64 (95% CI: 0.60-0.69) in males and 0.27 (95% CI: 0.24–0.30) in females. Typically, patients with MCL are predominantly male, with a median age of > 60 years and present with advanced stage disease at diagnosis, as well as extranodal involvement (Armitage, 1998; Bosch, 1998; Tiemann, 2005).

Table 6: Epidemiology of Patients with Mantle Cell Lymphoma (Continued)

Indication/Target Population	Mantle Cell Lymphoma
Main Treatment Options	- In the front-line setting, MCL is a chemosensitive disease, and (immuno-) chemotherapy regimens (particularly rituximab, cyclophosphamide, doxorubicin, vincristine, predniso(lo)ne [R-CHOP]) can achieve high response rates. However, almost all patients will eventually relapse. - Treatment strategies generally depend on the individual risk profile and the patient's comorbidities, as indicated in the recommendations of the European MCL Network and ESMO (Dreyling, 2009; Dreyling, 2013). - Subsequent to the completion of enrollment and analysis of data in Study MCL-002, updated Clinical Practice Guidelines for diagnosis, treatment, and follow-up of newly diagnosed and relapsed MCL were approved by the ESMO Guidelines Working Group in Aug 2014 (Dreyling, 2014). - According to the European MCL Network Guidelines (Dreyling, 2009) and the ESMO recommendations (Dreyling, 2013), there is no single standard treatment for patients with relapsed disease (McKay, 2012). In first relapse in younger fit patients (< 65 years of age, without severe comorbidities), the treatment goal is to achieve the best possible remission as a bridge to stem cell transplantation, whereas in transplant-ineligible patients, the objective is to induce long-lasting remissions. - The treatment guidelines of the European MCL Network (Dreyling, 2009), ESMO (Dreyling, 2013), Spain (Caballero, 2013), and the UK (McKay, 2012), recommend that patients with multiple relapses and elderly frail patients should be treated with single-agent therapy. The European MCL Network Guidelines and the current ESMO therapeutic recommendations (Dreyling, 2013) recommend treatment with temsirolimus, lenalidomide, bortezomib, and ibrutinib preferably in combination (excluding elderly, frail patients). Other single agents such as fludarabine (Zinzani, 2000; Tobinai, 2006), gemcitabine (Dumontet, 2001), rituximab (Ghielmini, 2000), cytarabine (Kantarjian, 1983), or chlorambucil (Rai, 2000; Ardeshna, 2003) can also be considered. These agents are typically used sequentially. If a patient relapses or is refractory to one agent, then that patient is treated with another agent from this list of available agents. - Temsirolimus is approved for the treatment of RRMCL in the EU (Hess, 2009). In Feb 2012, pixantrone received a conditional Marketing Authorisation in the EU for the treatment of adults with multiple relapsed and/or refractory aggressive NHL, but is not included in any of the MCL treatment guidelines. Ibrutinib was authorised in the EU for MCL in Oct 2014, indicated for the treatment of adult patients with RRMCL. - In the US, ibrutinib is approved for MCL patients who have received at least one prior therapy. This was an accelerated approval.

Table 6: Epidemiology of Patients with Mantle Cell Lymphoma (Continued)

Indication/Target Population	Mantle Cell Lymphoma
Main Treatment Options (Continued)	- The treatment guidelines also recommend bortezomib in patients with multiple relapses (Dreyling, 2013; McKay, 2012). This agent is approved in the US and several other countries for the treatment of MCL. In Jan 2015, bortezomib was authorised in combination with rituximab, cyclophosphamide, doxorubicin and prednisone, for the treatment of adult patients with previously untreated MCL who are unsuitable for HSCT. - In the EU, lenalidomide is currently available for MCL via clinical trials. Lenalidomide single agent treatment is included in the treatment guidelines for MCL (Dreyling, 2009; Dreyling, 2013; Caballero, 2013), which is in line with the indication.
Important Comorbidities	- Second Primary Malignancies (Dong, 2001; Barista, 2002; Pirani, 2011; Brewer, 2012). - Thromboembolic Events (Mohren, 2005; Caruso, 2010; Zhou, 2010).

PART II – MODULE SII: NONCLINICAL PART OF THE SAFETY SPECIFICATION

1. NONCLINICAL PART OF THE SAFETY SPECIFICATION

Full details of the nonclinical safety data for lenalidomide are presented in the Nonclinical Overview (Marketing Authorisation Application [MAA], Module 2, Section 2.4 Nonclinical Overview).

1.1. Outline of Nonclinical Safety Concerns

A summary of the nonclinical findings and their relevance to human usage is outlined in Table 7.

Table 7: Nonclinical Risks and Relevance to Human Use

Key Safety Findings (from Nonclinical Studies)	Relevance to Human Usage
Toxicity Including: • Single and Repeat-dose Toxicity Lenalidomide has a low potential for acute toxicity; minimum lethal doses after single-dose oral administration were > 2000 mg/kg in rodents. Chronic administration of lenalidomide to rats resulted in kidney pelvis mineralisation, most notably in females. The changes were minor and did not affect renal function, and were not considered to be adverse. In the rat, reports of crystals in the urine and kidneys are likely to be due to drug or drug metabolites that have crystallised during renal elimination due to the high doses used. The histological changes in the kidney were reversible, and therefore appear to be of limited clinical relevance. The no observed adverse effect level (NOAEL) in rats was determined to be 300 mg/kg/day. In monkeys, repeated oral administration of lenalidomide resulted in a dose-dependent decrease in neutrophil count, an effect that is related to the pharmacodynamic effect of the drug. Repeated oral administration of 4 and 6 mg/kg/day to monkeys produced mortality and significant toxicity (marked weight loss, reduced red and white blood cell and platelet counts, multiple organ haemorrhage, gastrointestinal tract inflammation, lymphoid, and bone marrow atrophy). Monkeys dosed with 1 and 2 mg/kg/day for up to 52 weeks exhibited changes in bone marrow cellularity, a slight decrease in myeloid: erythroid cell ratio, and thymic atrophy. Mild suppression of the white blood cell count was observed at 1 mg/kg/day. The NOAEL in monkeys was 1 mg/kg, based on the minimal severity, lack of associated toxicologically significant haematologic effect, and expected recovery of thymic atrophy at this dose as demonstrated by a recovery at higher doses.[a]	The primary toxicities observed in the nonclinical studies following repeated oral administrations of lenalidomide were associated with the haematopoietic/lymphoreticular systems and the kidneys. Dose adjustments to be made in case of haematological toxicity are described in Section 4.2 of the SmPC. Monitoring of complete blood counts is included in Section 4.4 and haematological events are described in Section 4.8 of the SmPC. Dose adjustments to be made in patients with impaired renal function are described in Section 4.2 of the SmPC. Careful dose selection and monitoring of renal function in patients with renal impairment is included in Section 4.4 of the SmPC. Renal and urinary disorders are described in Section 4.8 of the SmPC.
• Reproductive and Developmental Toxicity Reproductive and developmental toxicity studies with lenalidomide have been conducted in rats, rabbits and monkeys. Embryofoetal developmental toxicity studies were conducted in rats, rabbits, and monkeys. In monkeys, malformations occurred in the foetuses at 0.5 mg/kg, the lowest lenalidomide dose tested. Exposure in monkeys at this dose (area under the curve [AUC] of 378 ng•hr/mL) was 0.17 to 0.41 times the exposure from a human clinical dose of 25 mg/day (AUC of 2262 ng•hr/mL) and 10 mg/day (933 ng•hr/mL), respectively.	Lenalidomide is structurally related to thalidomide, a known human teratogenic active substance that causes severe life-threatening birth defects (Sections 4.4, 4.6 and 4.8). In monkeys, lenalidomide induced malformations similar to those described with thalidomide (SmPC, Sections 4.4, 4.6, 4.8 and 5.3).

Table 7: Nonclinical Risks and Relevance to Human Use (Continued)

Key Safety Findings (from Nonclinical Studies)	Relevance to Human Usage
Malformations ranged from stiff and slightly malrotated hindlimbs at 0.5 mg/kg/day to severe external malformations, such as bent, shortened, malformed, malrotated and/or partially absent parts of extremities, oligo- and/or polydactyly and/or non patent anus at 4 mg/kg/day. Limb and digital defects correlated with skeletal findings at ≥ 1 mg/kg/day. These malformations were similar to those seen with the positive control thalidomide, a known human teratogen. In rats, oral doses up to 500 mg/kg lenalidomide did not affect embryofoetal development. In the definitive embryofoetal development study in rabbits conducted at doses up to 20 mg/kg/day, maternal toxicity was seen at ≥ 10 mg/kg/day, and a dose of 20 mg/kg/day resulted in a single abortion. At ≥ 10 mg/kg/day, developmental toxicity consisted of increased postimplantation loss (early and late resorptions and intrauterine deaths), reduced foetal body weights, increased incidence of gross external findings in foetuses associated with morbidity, and soft tissue and skeletal variations. The NOAEL for maternal and developmental toxicity was 3 mg/kg/day. Exposure of rabbits at this dose (AUC of 2836 ng•hr/mL) was 1.3 to 3 times the exposure from a human clinical doses of 25 mg/day (AUC of 2262 ng•hr/mL) or 10 mg/day (933 ng•hr/mL), respectively. Studies in rats administered lenalidomide at doses of up to 500 mg/kg/day indicated that it has no effects on male or female reproductive performance or fertility, or pre- and postnatal reproductive toxicity.	If lenalidomide is taken during pregnancy, a teratogenic effect of lenalidomide in humans is expected (SmPC, Sections 4.4, 4.6 and 4.8). For details, see Part II Module SVII and Part III.
• Nephrotoxicity Included as part of single and repeat-dose toxicity findings above.	As above.
• Genotoxicity/Carcinogenicity Carcinogenicity studies have not been conducted with lenalidomide as its intended use is in the treatment of advanced cancer. In rats administered lenalidomide orally for 26 weeks (up to 300 mg/kg/day), no hyperplastic or proliferative lesions were identified at the dosing phase or the recovery phase necropsies (4 weeks after last dose). In monkeys administered lenalidomide orally for 52 weeks (up to 2 mg/kg/day), no neoplastic or pre-neoplastic changes were identified at the dosing phase necropsy. In vitro and in vivo genotoxicity studies indicated no mutagenic or clastogenic potential for lenalidomide. In addition, lenalidomide spiked with up to 5% of the predominant impurity RC4 and was not genotoxic in a reverse mutation (Ames) test.	Many antineoplastic agents are mutagenic and/or test positive in rodent carcinogenicity assays. The negative results achieved in genotoxicity studies of lenalidomide alone or spiked with the impurity RC4 suggest that a risk of mutagenic or clastogenic potential is absent and provides some assurance that lenalidomide is not carcinogenic. In addition, there were no observations of pre-neoplastic lesions in the chronic rat and monkey studies.
General Safety Pharmacology Evaluation of the safety pharmacology of lenalidomide showed no behavioural or physiological changes in rats treated with up to 2000 mg/kg lenalidomide compared to control animals.	None

Table 7: Nonclinical Risks and Relevance to Human Use (Continued)

Key Safety Findings (from Nonclinical Studies)	Relevance to Human Usage
• Cardiovascular The potential for cardiovascular effects was evaluated in vitro and in vivo. Lenalidomide has a low potential to block the human Ether-à-go-go-Related Gene channel. The in vivo effects were evaluated in anaesthetised dogs following IV administration of lenalidomide at doses of 2, 10, and 20 mg/kg. No biologically important changes were observed in any of the haemodynamic parameters measured.	Cardiac disorders are described in Section 4.8 of the SmPC.
• Nervous System Lenalidomide did not induce behavioural, autonomic, or motor activity changes when administered orally to rats at doses up to 2000 mg/kg.	Effects on the nervous system are described in Section 4.8 of the SmPC.
Mechanisms for Drug Interactions Lenalidomide is not a substrate of human cytochrome P450 (CYP) enzymes, and hence is not likely to be subject to drug-drug interactions when co-administered with CYP inhibitors or inducers. Lenalidomide did not significantly inhibit CYP1A2, 2C9, 2C19, 2D6, 2E1, or 3A4 isoforms and was not a CYP inducer in vitro. Hence, lenalidomide is not likely to precipitate clinically relevant drug-drug interactions when co-administered with CYP substrates. Furthermore, at concentrations up to 150 µM, lenalidomide is not an inhibitor of the bile salt export pump (BSEP), human multidrug resistance-associated protein (MRP)2, human organic anion transporter (OAT)1 and OAT3, organic anion-transporting polypeptide (OATP1B1 and OATP1B3), and organic cation transporter (OCT)2. Lenalidomide is not a substrate of MRP1, MRP2, or MRP3 efflux transporters, or OAT1, OAT3, OATP1B1 (OATP2), OCT1, OCT2, OCTN1, OCTN2, or multi antimicrobial extrusion protein (MATE)1. Lenalidomide is a weak substrate but not an inhibitor of P-glycoprotein (P-gp). Lenalidomide is not a substrate or inhibitor (at concentrations up to 150 µM) of breast cancer resistance protein (BCRP). Therefore, clinically relevant drug-drug interactions are unlikely between lenalidomide and substrates or inhibitors of these transporters. Lenalidomide is not an inhibitor of bilirubin glucuronide formation mediated by uridine 5'-diphospho-glucuronosyltransferase (UGT)1A1 genotypes UGT1A1*1/*1, UGT1A1*1/*28, and UGT1A1*28/*28. Therefore, lenalidomide is not anticipated to cause any drug-drug interactions due to UGT1A1 inhibition.	As lenalidomide is not metabolised by CYP enzymes, administration with medicinal products that inhibit CYP enzymes is not likely to result in metabolic medicinal product interactions in man (SmPC, Section 5.2). Furthermore, clinically relevant drug-drug interactions are unlikely between lenalidomide and substrates/inhibitors of the following transporters: BSEP; MRP1, MRP2 and MRP3 efflux transporters; human OAT1, OAT3, OATP1B1 (OATP2), OATP1B3, OCT1, OCT2, OCTN1, OCTN2 and MATE1; P-gp, and BCRP. Lenalidomide is not anticipated to cause any drug-drug interactions due to UGT1A1 inhibition.
Other Toxicity-related Information or Data • Pre-clinical Pharmacokinetics In rats and monkeys, lenalidomide pharmacokinetics and disposition are characterised by moderate clearance, rapid absorption, and good oral bioavailability, with excretion of unchanged parent as the major clearance pathway. Protein-protein binding was low (19% to 29% bound) in all species. In rhesus monkeys, lenalidomide distributed into cerebrospinal fluid (CSF) with a CSF-to-plasma exposure ratio of 0.11. ^{14}C-Lenalidomide derived radioactivity distributes widely into rat tissues,	Lenalidomide is eliminated predominantly through urinary excretion and patients with renal impairment may require dose adjustment. Low lenalidomide protein binding suggests limited potential for pharmacokinetic

Table 7: Nonclinical Risks and Relevance to Human Use (Continued)

Key Safety Findings (from Nonclinical Studies)	Relevance to Human Usage
except brain. Distribution of radioactivity to the foetus is limited after oral administration to pregnant rats. Lenalidomide was excreted largely as unchanged drug and hydrolysis of the glutarimide ring in both rats and monkeys. In these species, the major route of elimination of radioactivity following IV administration was renal. Following oral administration to rats and monkeys, radioactivity was eliminated in almost equal proportions in urine and faeces.	variability in patients with abnormal plasma protein concentrations. Lenalidomide distribution into rhesus monkey CSF suggests the potential for lenalidomide to cross the human blood brain barrier. Despite limited distribution of ^{14}C-lenalidomide into the foetus of pregnant rats, lenalidomide is structurally related to thalidomide, a known human teratogenic active substance that causes severe life-threatening birth defects (Sections 4.4, 4.6 and 4.8). In monkeys, lenalidomide induced malformations similar to those described with thalidomide (SmPC, Sections 4.4, 4.6, 4.8 and 5.3). If lenalidomide is taken during pregnancy, a teratogenic effect of lenalidomide in humans is expected (SmPC, Section 4.4, 4.6 and 4.8).

[a] The NOAEL previously provided was incorrect due to typographical error and has been corrected.

PART II – MODULE SIII: CLINICAL TRIAL EXPOSURE

1. CLINICAL TRIAL EXPOSURE

1.1. Clinical Study Information

The data presented in this section represent the main studies supporting the FL, TE NDMM, TNE NDMM, RRMM, del 5q MDS and MCL indications. Data from Studies MDS-001, MDS-002 and MDS-007 are not included in this Risk Management Plan (RMP). MDS-001 and MDS-002 represent a broader indication which does not reflect the target population in detail and would therefore dilute safety signals. These clinical trials are not related to the approved indication (which would be in accordance with the GVP as only proposed and approved indications should be pooled and not studies in different indications under development ie, paediatrics). MDS-007 represents the approved indication, but represents solely the Japanese population. This study was considered for the overall safety of lenalidomide and no differences in risk due to ethnic origin have been identified.

In addition, data from Study CC-5013-MCL-003 have not been presented in this RMP. Study MCL-003 was a Phase 3, multi-centre, randomised, double-blind, placebo-controlled, first-line maintenance study of lenalidomide in patients with newly diagnosed mantle cell lymphoma (the "RENEW" trial), that was stopped prematurely for reasons other than safety concerns after only nine patients had been enrolled (four in the lenalidomide arm, five in the placebo arm).

Data published subsequent to the time of the study planning suggested that the duration of remission and OS time after a response to R-CHOP were significantly shorter among patients who were not assigned to any maintenance therapy, as compared with those who received maintenance therapy (rituximab or interferon alpha) (Kluin-Nelemans, 2012). In light of these findings, the MCL-003 study design, which included a placebo control arm, was no longer considered clinically appropriate.

The study population in Study MCL-003 was different to those in Studies MCL-002 and MCL-001 as it consisted of newly diagnosed MCL patients achieving a complete response or partial response after first-line induction chemoimmunotherapy (anthracycline based, fludarabine based, or rituximab-bendamustine combination). In addition, the starting dose of lenalidomide maintenance treatment in Study MCL-003 was 15 mg compared to a lenalidomide starting dose of 25 mg in the other studies. Finally, all four patients in the lenalidomide arm had short treatment durations.

Details of the main FL, TE NDMM, TNE NDMM, RRMM, del 5q MDS and MCL clinical studies included in this RMP are listed below.

FL:

- **CC-5013-NHL-007:** Phase 3, double-blind, randomised study to compare the efficacy and safety of rituximab plus lenalidomide versus rituximab plus placebo for relapsed/refractory indolent lymphoma (follicular lymphoma and marginal zone lymphoma) (AUGMENT).
- **CC-5013-NHL-008:** Phase 3, randomised study of lenalidomide plus rituximab followed by lenalidomide single agent maintenance versus rituximab maintenance for relapsed/refractory follicular, marginal zone or mantle cell lymphoma (MAGNIFY).

TE NDMM (post-autologous stem cell transplant):

- **Cancer and Leukaemia Group B (CALGB) 100104:** Phase 3, multi-centre, randomised, double-blind, placebo-controlled, 2-arm study to evaluate the efficacy and safety of continuous lenalidomide maintenance following single ASCT in patients ≥ 18 to 70 years of age with NDMM.
- **Intergroupe Francophone du Myélome (IFM) 2005-02:** Phase 3, multi-centre, randomised, double-blind, placebo-controlled, 2-arm study to evaluate the efficacy and safety of continuous lenalidomide maintenance therapy in patients < 65 years of age with MM after induction therapy followed by a single ASCT or tandem ASCT.

In addition, data from GIMEMA are included for the risks relating to second primary malignancies (SPM) only (Part II Module SVII) and are only included in the total exposure data in this module.

TNE NDMM:

- **SWOG S0777**: A randomised Phase 3 trial of lenalidomide, dexamethasone versus bortezomib, lenalidomide and dexamethasone for induction, in patients with previously untreated multiple myeloma without an intent for immediate autologous stem cell transplant.
- **CC-5013-MM-020:** Phase 3, multi-centre, randomised, open label, 3-arm efficacy and safety study of lenalidomide and low-dose dexamethasone compared to melphalan, prednisone, and thalidomide (MPT) in patients with NDMM, who were either 65 years of age or older or not candidates for stem cell transplantation.
- **CC-5013-MM-015:** Phase 3, multi-centre, randomised, double-blind, placebo-controlled, 3-arm parallel group, safety and efficacy study of lenalidomide in combination with melphalan and prednisone in NDMM patients who are not stem cell transplant candidates.

RRMM:

- **CC-5013-MM-009:** Phase 3, multi-centre, randomised, parallel-group, double-blind, placebo-controlled, safety and efficacy study of lenalidomide plus dexamethasone.
- **CC-5013-MM-010:** Phase 3, multi-centre, randomised parallel group, double-blind, placebo-controlled, safety and efficacy study of lenalidomide plus dexamethasone.

Del 5q MDS:

- **CC-5013-MDS-003:** Phase 2, multi-centre, single arm, open label, safety and efficacy study (including extension Study CC-5013-MDS-003E/009, which was intended to provide further long-term outcomes for overall survival (OS)/vital status and the possible occurrence of progression to AML).
- **CC-5013-MDS-004:** Phase 3, multi-centre, randomised, double-blind, placebo-controlled, 3-arm safety and efficacy study.

MCL:

- **CC-5013-MCL-002:** A Phase 2, multi-centre, randomised, open-label study to determine the efficacy of lenalidomide versus Investigator's choice in patients with relapsed or refractory mantle cell lymphoma (the "SPRINT" trial).
- **CC-5013-MCL-001:** A Phase 2, multi-centre, single-arm, open-label study to determine the efficacy and safety of single-agent lenalidomide in patients with mantle cell NHL who have relapsed or progressed after treatment with bortezomib or are refractory to bortezomib (the "EMERGE" trial).
- **CC-5013-NHL-002**: A Phase 2, multi-centre, single-arm, open-label study to evaluate the safety and efficacy of single-agent lenalidomide in patients with relapsed or refractory aggressive NHL.
- **CC-5013-NHL-003**: A Phase 2, multi-centre, single-arm, open-label study to evaluate the safety and efficacy of single-agent lenalidomide in patients with relapsed or refractory aggressive NHL.

1.2. Exposure in Pivotal Clinical Trials

1.2.1. Clinical Studies in Follicular Lymphoma

The safety data presented are primarily based on data from 2 Celgene-sponsored studies, CC-5013-NHL-007 (NHL-007) and CC-5013-NHL-008 (NHL-008).

In Study NHL-007, patients were aged ≥ 18 with histologically confirmed marginal zone lymphoma (MZL) or FL previously treated with at least one prior systemic chemotherapy, immunotherapy or chemoimmunotherapy and had received at least 2 previous doses of rituximab. Only data from patients with FL are included in this RMP. Patients had documented relapsed, refractory or progressive disease after treatment with systemic therapy and were not rituximab-refractory. Patients were randomised (1:1 ratio) to treatment with either:

- lenalidomide 20 mg QD orally (Days 1 to 21 in each 28 day cycle) for up to 12 cycles plus rituximab 375 mg/m^2 IV (Days 1, 8, 15 and 22 in Cycle 1 and Day 1 in Cycles 2 to 5 of each 28-day cycle) or,
- matching placebo (QD) plus rituximab 375 mg/m^2 IV (Days 1, 8, 15 and 22 in Cycle 1 and Day 1 in Cycles 2 to 5 of each 28-day cycle).

Study NHL-008 recruited patients aged ≥ 18 with histologically confirmed FL Grades 1 to 3b or transformed FL, MZL, or MCL who had received ≥ 1 prior therapy and had Stage I to IV, measurable disease. Only data from patients with FL are included in this RMP. Patients had documented relapsed, refractory or progressive disease after last treatment with systemic therapy. Patients received induction therapy (ie, initial treatment period) of lenalidomide 20 mg QD orally (Days 1 to 21 in each 28-day cycle) for 12 cycles plus IV rituximab 375 mg/m^2, Days 1, 8, 15, and 22 of Cycle 1 and Day 1 of Cycles 3, 5, 7, 9, and 11 (28-day cycles). Patients were then randomised (1:1 ratio) to maintenance (ie, extended treatment) lenalidomide 10 mg/day on Days 1 to 21 of each 28-day cycle, for Cycles 13 to 30, plus rituximab 375 mg/m^2 IV on Day 1 of Cycles 13, 15, 17, 19, 21, 23, 25, 27, and 29, or rituximab 375 mg/m^2 alone

(same schedule). Safety data included for NHL-008 were based on the initial treatment period (induction phase) in patients with FL Grade 1 to 3a, only.

The demographics and baseline characteristics of FL patients in Studies NHL-007 and NHL-008 are presented in Table 8, while duration of exposure to study medication is presented in Table 9.

In both studies, approximately half of the safety population were younger than 65 years of age, the majority of patients were white and non-Hispanic and the proportion of males to females was balanced in both studies. The majority of FL patients in both studies had a histological diagnosis of Grade 1 to 2. In Study NHL-007, a higher proportion of patients had an Ann Arbor Stage I or II at diagnosis compared with Study NHL-008, whereas a higher proportion of patients in Study NHL-008 had an Ann Arbor Stage IV. In both studies, the majority of patients did not have elevated lactate dehydrogenase and had no B symptoms at baseline.

The median treatment duration was longer in Study NHL-007 (11.0 and 11.2 months in the rituximab plus placebo and lenalidomide plus rituximab arms, respectively) compared to Study NHL-008 (7.4 months). Consistent with this trend, the median number of treatment cycles was higher in Study NHL-007 (12.0 in both arms) compared with Study NHL-008 (7.0), and the majority of patients in both the lenalidomide and placebo arms of Study NHL-007 received 12 cycles (72.6% and 60.1%, respectively) compared with around a third of patients in Study NHL-008 (29.4%). Per the data lock point for this FL RMP, data from Study NHL-008 are based on an ongoing actively enrolling study. Hence, the proportion of the patients who completed all 12 cycles of lenalidomide plus rituximab is less than in Study NHL-007.

Overall, no clinically meaningful differences in demographic and disease-related characteristics were observed, and the treatment arms in NHL-007 were generally balanced with regard to the demographic and disease-related characteristics.

Table 8: Demographic and Baseline Characteristics of FL Patients in Studies NHL-007 and NHL-008 (Safety Population)

Demographic/Baseline Characteristic	**NHL-007**		**NHL-008**	**Pooled NHL-007 and NHL-008**
	PBO+Rit (N = 148)	**Len+Rit (N = 146)**	**Len+Rit (N = 177)**	**Len+Rit (N = 323)**
Age (Years)				
Mean (SD)	60.7 (11.08)	61.6 (11.34)	64.5 (10.70)	63.2 (11.07)
Median (Range)	61.0 (35.0 to 88.0)	62.0 (26.0 to 86.0)	65.0 (35.0 to 91.0)	64.0 (26.0 to 91.0)
< 65 (n [%])	94 (63.5)	86 (58.9)	84 (47.5)	170 (52.6)
≥ 65 (n [%])	54 (36.5)	60 (41.1)	93 (52.5)	153 (47.4)
Sex (n [%])				
Male	80 (54.1)	61 (41.8)	97 (54.8)	158 (48.9)
Female	68 (45.9)	85 (58.2)	80 (45.2)	165 (51.1)

Table 8: Demographic and Baseline Characteristics of FL Patients in Studies NHL-007 and NHL-008 (Safety Population) (Continued)

Demographic/Baseline Characteristic	NHL-007		NHL-008	Pooled NHL-007 and NHL-008
	PBO+Rit (N = 148)	Len+Rit (N = 146)	Len+Rit (N = 177)	Len+Rit (N = 323)
Ethnicity (n [%])				
White	92 (62.2)	90 (61.6)	164 (92.7)	254 (78.6)
Non-white	55 (37.2)	52 (35.6)	11 (6.2)	63 (19.5)
Missing	1 (0.7)	4 (2.7)	2 (1.1)	6 (1.9)
Hispanic	13 (8.8)	19 (13.0)	10 (5.6)	29 (9.0)
Non-Hispanic	133 (89.9)	122 (83.6)	164 (92.7)	286 (88.5)
Missing	2 (1.4)	5 (3.4)	3 (1.7)	8 (2.5)
Histological Diagnosis (n [%])				
FL				
Grade 1 to 2	123 (83.1)	124 (84.9)	149 (84.2)	273 (84.5)
Grade 3a	25 (16.9)	22 (15.1)	28 (15.8)	50 (15.5)
Ann Arbor Stage at Enrollment (n [%])				
I	13 (8.8)	13 (8.9)	3 (1.7)	16 (5.0)
II	29 (19.6)	21 (14.4)	17 (9.6)	38 (11.8)
III	60 (40.5)	69 (47.3)	50 (28.2)	119 (36.8)
IV	46 (31.1)	43 (29.5)	107 (60.5)	150 (46.4)
FL International Prognostic Index (n [%])				
0 to 1	53 (35.8)	45 (30.8)	-	-
2	48 (32.4)	46 (31.5)	-	-
3 to 5	46 (31.1)	54 (37.0)	-	-
Missing	1 (0.7)	1 (0.7)	-	-
LDH Elevated at Baseline (n [%])				
Yes	33 (22.3)	33 (22.6)	50 (28.2)	83 (25.7)
No	114 (77.0)	112 (76.7)	126 (71.2)	238 (73.7)
Missing	1 (0.7)	1 (0.7)	1 (0.6)	2 (0.6)
B Symptoms				
Yes	11 (7.4)	12 (8.2)	23 (13.0)	35 (10.8)
No	137 (92.6)	134 (91.8)	154 (87.0)	288 (89.2)

FL = follicular lymphoma; ISS = International Staging System; LDH = lactate dehydrogenase; Len = lenalidomide; PBO = placebo; Rit = rituximab; SD = standard deviation.

Table 9: Duration of Exposure in FL Studies NHL-007 and NHL-008 (Safety Population)

Parameter	NHL-007		NHL-008	Pooled NHL-007 and NHL-008
	PBO+Rit (N = 148)	Len+Rit (N = 146)	Len+Rit (N = 177)	Len+Rit (N = 323)
Treatment Duration (Months)				
Mean (SD)	9.3 (2.93)	10.0 (2.82)	7.3 (3.75)	8.5 (3.62)
Median	11.0	11.2	7.4	11.0
Range	0.9 to 13.1	0.9 to 15.0	1.2 to 13.1	0.9 to 15.0
Number of Cycles				
Mean (SD)	9.9 (3.10)	10.4 (2.94)	7.1 (4.29)	8.6 (4.09)
Median	12.0	12.0	7.0	11.0
Range	1.0 to 12.0	1.0 to 12.0	0.0 to 12.0	0.0 to 12.0
Number of Cycles Received (n [%])				
1	1 (0.7)	3 (2.1)	14 (7.9)	17 (5.3)
2	4 (2.7)	2 (1.4)	6 (3.4)	8 (2.5)
3	5 (3.4)	3 (2.1)	26 (14.7)	29 (9.0)
4	4 (2.7)	2 (1.4)	3 (1.7)	5 (1.5)
5	3 (2.0)	3 (2.1)	12 (6.8)	15 (4.6)
6	10 (6.8)	7 (4.8)	8 (4.5)	15 (4.6)
7	7 (4.7)	7 (4.8)	16 (9.0)	23 (7.1)
8	4 (2.7)	3 (2.1)	4 (2.3)	7 (2.2)
9	13 (8.8)	5 (3.4)	9 (5.1)	14 (4.3)
10	4 (2.7)	4 (2.7)	2 (1.1)	6 (1.9)
11	4 (2.7)	1 (0.7)	15 (8.5)	16 (5.0)
12	89 (60.1)	106 (72.6)	52 (29.4)	158 (48.9)
Relative Dose Intensity (%)				
Mean (SD)	95.5 (15.21)	85.0 (18.57)	77.9 (23.96)	81.1 (21.94)
Median	98.5	92.1	82.9	88.1
Range	4.8 to 195.0	39.0 to 139.9	4.8 to 175.0	4.8 to 175.0

1.2.2. Clinical Studies in Transplant Eligible Newly Diagnosed Multiple Myeloma Post-autologous Stem Cell Transplantation Maintenance

The safety data presented are primarily based on data from 2 independently-conducted cooperative group studies, CALGB 100104 and IFM 2005-02.

In Study CALGB 100104, patients were aged ≥ 18 to 70 years with active MM requiring treatment and stable disease or responsiveness to at least 2 months of any induction therapy who were candidates and willing to undergo HDM with ASCT rescue. Ninety to 100 days post-ASCT, patients underwent disease and response evaluation and received treatment after stratification and randomisation (1:1 ratio) to maintenance treatment with either lenalidomide or placebo on Days 1 to 28 of a 28-day cycle (28/28 days) until disease progression or treatment intolerance. Randomisation was stratified by baseline β2 microglobulin (elevated, ≥ 2.5 mg/L versus normal), prior therapy with thalidomide (yes/no), and prior therapy with lenalidomide (yes/no). The starting dose of lenalidomide or placebo was 10 mg/day (28/28 days) for the first 3 months, increased to 15 mg/day if the patient's absolute neutrophil count (ANC) ≥ 1000/μL, platelet count ≥ 75,000/μL, and any nonhaematologic toxicity was no greater than Grade 1.

In Study IFM 2005-02, patients were < 65 years of age with MM who had received an initial treatment with induction therapy and ASCT. Within ≤ 6 months after ASCT and randomisation, all patients (ie, after enrolment of the first 32 patients) received 2 cycles of consolidation treatment with lenalidomide 25 mg QD orally (21/28 days) before their assigned maintenance treatment with either lenalidomide or placebo until disease progression. The starting dose of lenalidomide or placebo was 10 mg once a day for the first 3 months, increased to 15 mg/day if tolerated.

The AE data collection methodologies differed in several ways between the 2 studies and appeared to result in noticeable differences in the reported frequencies and severities of several TEAEs both in the lenalidomide and the placebo treatment arms. Many of these disparities can be attributed to the lack of collection of AE start and stop dates on the AE CRF in Study CALGB 100104, for which instead AE reporting periods were used for estimation of AE onset (EU Summary of Clinical Safety [SCS] Section 1.2.1.1), and differences between the 2 studies in how AEs were reported via the design of the AE and other safety-related CRF pages. In Study CALGB 100104 only, the AE CRF reporting form had 8 preprinted Common Terminology Criteria for Adverse Events (CTCAE) terms: "ANC," "platelets," "febrile neutropenia," "weight gain," "rash," "bilirubin," "diarrhea," and "pneumonitis/pulmonary infiltrates". Investigators were instructed to report AEs of all grades for these 8 preprinted AEs, and to report AEs other than these 8 if they were of Grade ≥ 3 severity (other events of Grade 1 or 2 severity could be reported, but this was not a protocol requirement). Also, this CRF page contained prompts and reminders for reporting infections with Grade 3 or 4 neutrophils, mucositis/stomatitis, and new malignancies (SPM) (EU SCS Section 1.2.1.2.1). In Study CALGB 100104, start dates were reported for serious adverse events (SAEs); SAEs represented expedited events in the Adverse Event Expedited Reporting System (AdEERS).

Recognising these differences, the primary data presentation is the evaluation of side-by-side comparisons of individual study arms from both studies to provide a clinically meaningful review of the overall safety data of lenalidomide 10 mg QD maintenance in the post-ASCT setting. Grade 3 or 4 TEAEs occurred more frequently in both treatment arms of

Study CALGB 100104 compared to Study IFM 2005-02. Those differences in Grade 3 or 4 TEAE frequencies observed in the placebo arms (55.2% in Study CALGB 100104 versus 32.1% in Study IFM 2005-02; EU SCS, Table 24) suggest a potential carryover effect from HDM/ASCT in Study CALGB 100104 (ie, close proximity of transplant to start of maintenance). Based on this observation and to further investigate this impact, analyses were conducted comparing the frequencies of all AEs collected post-transplant during maintenance therapy versus the frequencies when AEs possibly occurring before start of maintenance (ie, during the "post-ASCT period") are excluded. The latter analysis was done for TEAEs of all grades and Grade 3 or 4 TEAEs although these 2 categories were possibly impacted by carryover effect of HDM/ASCT due to collection of AE using reporting periods, and not specific stop/start dates.

The median time from ASCT to the start of treatment was 3.3 months for Study CALGB 100104 and 3.4 months for Study IFM 2005-02 (EU Summary of Clinical Efficacy, Table 33). In Study IFM 2005-02, patients in both the lenalidomide and placebo arms underwent 2 cycles of lenalidomide (25 mg/day for 21 of 28 day cycles) consolidation therapy immediately prior to the start of maintenance therapy.

The demographics and baseline characteristics of patients in Studies CALGB 100104 and IFM 2005-02 are presented in Table 10, while duration of exposure to study medication is presented in Table 11.

In Studies CALGB 100104 and IFM 2005-02, the majority of the safety population were younger than 60 years of age, and the proportion of males to females was balanced in both studies. The majority of patients in Study CALGB 100104 were white or Caucasian; race and ethnicity data were not collected in Study IFM 2005-02. In both studies, the majority of patients had an International Staging System (ISS) Stage I or II at diagnosis. In Study CALGB 100104, 3 patients (1.3%) in the lenalidomide arm (no patients in the placebo arm) and in Study IFM 2005-02, no patients in the lenalidomide arm and only one patient in the placebo arm (0.4%) had severe renal insufficiency (creatinine clearance [CLcr] < 30 mL/min) post-ASCT. The proportions of patients with moderate renal impairment (CLcr ≥ 30 mL/min to < 50 mL/min) were 8.5% and 6.3% in the lenalidomide and placebo arms of Study CALGB 100104, respectively, and 3.1% and 2.5% in the lenalidomide and placebo arms of Study IFM 2005-02, respectively, post-ASCT.

Overall, no clinically meaningful differences in demographic and disease-related characteristics were observed, and the treatment arms were balanced with regard to the demographic and disease-related characteristics. In Study IFM 2005-02, at diagnosis there was an imbalance between treatment arms in the distribution of the ISS stage categories, and patients with a reduced CLcr (< 50 mL/min).

Table 10: Demographic and Baseline Characteristics of TE NDMM Patients in Studies CALGB 100104 and IFM 2005-02 (Safety Population; Data Cutoff: 01 Mar 2015)

Demographic/Baseline Characteristic	CALGB 100104 Maintenance		IFM 2005-02 Maintenance	
	Lenalidomide (N = 224)	Placebo (N = 221)	Lenalidomide (N = 293)	Placebo (N = 280)
Age (Years)				
Mean (SD)	57.4 (8.06)	57.1 (7.58)	55.4 (7.06)	55.3 (7.19)
Median (Range)	58.0 (29.0 to 71.0)	58.0 (39.0 to 71.0)	56.7 (21.9 to 67.0)	57.2 (31.7 to 66.3)
< 60 (n [%])	126 (56.3)	128 (57.9)	209 (71.3)	192 (68.6)
≥ 60 (n [%])	98 (43.8)	93 (42.1)	84 (28.7)	88 (31.4)
< 65 (n [%])	176 (78.6)	180 (81.4)	284 (96.9)	272 (97.1)
≥ 65 (n [%])	48 (21.4)	41 (18.6)	9 (3.1)	8 (2.9)
Sex (n [%])				
Male	117 (52.2)	125 (56.6)	164 (56.0)	163 (58.2)
Female	107 (47.8)	96 (43.4)	129 (44.0)	117 (41.8)
Race (n [%])				
White or Caucasian	169 (75.4)	167 (75.6)	NR	NR
Black or African American	39 (17.4)	41 (18.6)	NR	NR
Asian	2 (0.9)	1 (0.5)	NR	NR
Other	0 (0.0)	2 (0.9)	NR	NR
Missing	14 (6.3)	10 (4.5)	NR	NR
ISS Stage at Diagnosis (n [%])				
I or II	117 (52.2)	126 (57.0)	221 (75.4)	228 (81.4)
III	37 (16.5)	34 (15.4)	64 (21.8)	42 (15.0)
Missing	70 (31.3)	61 (27.6)	8 (2.7)	10 (3.6)
Creatinine Clearance at Diagnosis (n [%])[a]				
< 30 mL/min	NR	NR	15 (6.0)	5 (1.9)
≥ 30 to < 50 mL/min	NR	NR	30 (12.0)	20 (7.8)
≥ 50 to < 80 mL/min	NR	NR	86 (34.5)	86 (33.5)
≥ 80 mL/min	NR	NR	118 (47.4)	146 (56.8)
< 50 mL/min	11 (4.9)	9 (4.1)	NR	NR
≥ 50 mL/min	57 (25.4)	61 (27.6)	NR	NR
Missing	156 (69.6)	151 (68.3)	58	50

Table 10: Demographic and Baseline Characteristics of TE NDMM Patients in Studies CALGB 100104 and IFM 2005-02 (Safety Population; Data Cutoff: 01 Mar 2015) (Continued)

Demographic/Baseline Characteristic	CALGB 100104 Maintenance		IFM 2005-02 Maintenance	
	Lenalidomide (N = 224)	Placebo (N = 221)	Lenalidomide (N = 293)	Placebo (N = 280)
Creatinine Clearance at Post-ASCT (n [%])				
< 50 mL/min	22 (9.8)	14 (6.3)	9 (3.1)	8 (2.9)
< 30 mL/min	3 (1.3)	0 (0.0)	0 (0.0)	1 (0.4)
≥ 30 to < 50 mL/min	19 (8.5)	14 (6.3)	9 (3.1)	7 (2.5)
≥ 50 mL/min	195 (87.1)	198 (89.6)	173 (59.0)	185 (66.1)
Missing	7 (3.1)	9 (4.1)	111 (37.9)	87 (31.1)
Time from Transplant to Maintenance (Months)				
Mean (SD)	3.6 (0.24)	3.6 (0.28)	5.9 (1.44)	6.0 (1.42)
Median (Range)	3.5 (3.0 to 5.0)	3.5 (2.7 to 5.4)	5.8 (1.8 to 10.7)	5.8 (2.2 to 10.7)

ASCT = autologous stem cell transplantation; CALGB = Cancer and Leukaemia Group B; CSR = clinical study report; IFM = Intergroupe Francophone du Myelome; ISS = International Staging System; ITT = intent-to-treat; NDMM = newly diagnosed multiple myeloma; NR = not reported (per study design); SD = standard deviation; TE = transplant eligible.

[a] Data are from the ITT Population for Study IFM 2005-02 (lenalidomide N = 307; placebo N = 307).

Source: ISS Table 2.1; Study CALGB 100104 CSR, Table 14.1.3.2; Study IFM 2005-02 CSR, Table 14.2-7.

In Study CALGB 100104, exposure for patients in the lenalidomide arm during maintenance was more than double than in the placebo arm prior to cross over to lenalidomide as reflected in the mean treatment duration. The duration of placebo maintenance treatment was limited by the interim unblinding (EU SCS Section 1.1.4.1.1.1). In Study IFM 2005-02, the mean treatment duration of maintenance therapy of lenalidomide was 24.0 months compared to 19.7 months in the placebo arm. The duration of maintenance treatment in both arms was limited due to changes in the study conduct (EU SCS Section 1.1.4.1.1.2).

Of the 221 patients in Study CALGB 100104 and 280 patients in Study IFM 2005-02 who received placebo maintenance, mean treatment duration for placebo patients was more than 6 months longer in Study IFM 2005-02 compared to Study CALGB 100104 (19.7 months versus 13.2 months, respectively). The shorter exposure in placebo patients can be explained by the timing of the interim analysis and study unblinding (17 Dec 2009) relative to the prolonged enrolment period. These patients either discontinued the study or crossed over to lenalidomide. For Study IFM 2005-02, treatment was also unblinded (07 Jul 2010) and treatment discontinued (with no option for crossover to lenalidomide) for placebo patients.

Of the 224 patients in Study CALGB 100104 and 293 patients in Study IFM 2005-02 who received lenalidomide maintenance, mean treatment duration for lenalidomide exposed patients was about 6 months longer in Study CALGB 100104 compared to Study IFM 2005-02 (30.3 months versus 24.0 months, respectively). The shorter exposure in Study IFM 2005-02 lenalidomide patients was due to termination of the study in Jan 2011.

Table 11: Duration of Exposure in TE NDMM Studies CALGB 100104 and IFM 2005-02 (Safety Population; Data Cutoff: 01 Mar 2015)

Parameter	CALGB 100104 Maintenance		IFM 2005-02[a] Maintenance	
	Lenalidomide (N = 224)	Placebo[b] (N = 221)	Lenalidomide (N = 293)	Placebo (N = 280)
Treatment Duration (Weeks)				
Mean (SD)	131.6 (110.59)	57.3 (41.93)	104.6 (63.14)	85.6 (48.03)
Median	110.3	47.6	113.6	88.6
Range	1.4 to 467.6	1.7 to 220.6	0.6 to 240.0	1.0 to 212.3
Treatment Duration (Months)				
Mean (SD)	30.3 (25.43)	13.2 (9.64)	24.0 (14.52)	19.7 (11.05)
Median	25.4	10.9	26.1	20.4
Range	0.3 to 107.5	0.4 to 50.7	0.1 to 55.2	0.2 to 48.8
Years on Treatment (n [%])				
≥ 1 year Tx	150 (67.0)	95 (43.0)	212 (72.4)	200 (71.4)
≥ 2 years Tx	116 (51.8)	32 (14.5)	159 (54.3)	99 (35.4)
≥ 3 years Tx	82 (36.6)	6 (2.7)	71 (24.2)	23 (8.2)
≥ 4 years Tx	54 (24.1)	1 (0.5)	4 (1.4)	2 (0.7)
Cumulative Dose (mg)				
Mean (SD)	NR	NR	7919.5 (5670.80)	7721.6 (4782.89)
Median	NR	NR	7200.0	7965.0
Range	NR	NR	40.0 to 24360	70.0 to 21,510
Dose Intensity (mg/day)				
Mean (SD)	NR	NR	10.5 (3.20)	12.4 (2.35)
Median	NR	NR	10.1	13.5
Range	NR	NR	2.3 to 15.0	4.8 to 15.0
Person-years of Exposure				
	565.06	242.70	587.17	459.47

CALGB = Cancer and Leukaemia Group B; IFM = Intergroupe Francophone du Myelome; NDMM = newly diagnosed multiple myeloma; NR = not reported (per study design); SD = standard deviation; TE = transplant eligible; Tx = treatment.

[a] The data for 2 cycles of lenalidomide consolidation therapy are excluded.

[b] For placebo patients, only dosing data up to crossing over to lenalidomide are included.

Source: ISS Table 3.1.

1.2.3. Clinical Studies in Transplant Non-eligible Newly Diagnosed Multiple Myeloma

Study SWOG S0777 (RVd initial treatment)

Study SWOG S0777 was a cooperative group study. A total of 523 patients with NDMM who had received no prior chemotherapy were randomised in a 1:1 ratio to 1 of 2 treatment arms:

- **Arm A:** Six 28-day cycles (24 weeks) of Rd (initial treatment); patients who completed ≥ 4 cycles of Rd initial treatment continued Rd therapy until progressive disease (PD).
  - Lenalidomide 25 mg/day administered orally on Days 1 to 21
  - Dexamethasone 40 mg/day administered orally on Days 1, 8, 15, and 22
- **Arm B:** Eight 21-day cycles (24 weeks) of RVd (initial treatment); patients who completed ≥ 6 cycles but were not able to tolerate a total of 8 cycles of initial treatment continued Rd (same regimen as for treatment therapy for Arm A) until PD.
  - Lenalidomide 25 mg/day administered orally on Days 1 to 14
  - Bortezomib 1.3 mg/m^2 IV on Days 1, 4, 8, and 11
  - Dexamethasone 20 mg/day administered orally on Days 1, 2, 4, 5, 8, 9, 11, and 12.

Patients were stratified at progression by ISS stage (I, II, III), and by intent to transplant at progression (yes versus no). As of the 01 Dec 2016 data cutoff date, five patients (one in the RVd arm and four in the Rd arm) were randomised but not treated. Of the 518 treated patients, 201 patients (110 in the RVd arm and 91 in the Rd arm) received initial treatment but did not continue on to the continued Rd treatment phase of the study treatment (ie, discontinued from the study treatment during initial treatment).

1.2.3.1. Safety Data Collection

Adverse events were recorded on paper AE summary forms (teleforms), which contained 80 preprinted CTCAE terms. In addition, investigators were instructed to report all other AEs in the free-text field at the end of AE summary form. The teleform data submission was replaced by an online form that allowed the investigator to select the CTCAE term from a dropdown list of all CTCAE 3.0 terms; the option for a free-text entry was no longer needed.

Per the study protocol, safety assessments were recorded every 3 months while the patient was on protocol treatment and within 14 days after completion of initial treatment and completion of continued Rd therapy. For AEs reported via the original AE paper forms (teleform data submission), specific AE start and stop dates were not collected; only the start date of the 3-month AE reporting period was collected. Celgene used the start date of the corresponding 3-month AE reporting period as the start date for each individual AE; stop dates were not imputed. For AEs reported electronically via the online form, specific AE start and stop dates were not collected; however, the start and end dates of the AE reporting period for routine AEs were collected. The Off Treatment Notice form provided the information for AEs leading to discontinuation.

The demographics and baseline characteristics of patients are presented in Table 12, while duration of exposure to study medication is presented in Table 13.

Patients ranged in age from 28.0 to 87.0 years, with a median age of 63.0 years in each treatment arm. Overall, there were slightly more male patients (57.5%) than female patients (42.5%), and

the majority of patients were Caucasian (79.7%). No clinically meaningful differences in demographics were observed, and the treatment arms were generally balanced.

Table 12: Demographic and Baseline Characteristics of TNE NDMM Patients in Study SWOG S0777 (Safety Population; Data Cutoff: 01 Dec 2016)

Demographic/Baseline Characteristic	Arm B (RVd) (N = 262)	Arm A (Rd) (N = 256)
Age (Years)		
Mean (SD)	62.2 (10.48)	62.6 (10.39)
Median (Range)	63.0 (35.0 to 85.0)	63.0 (28.0 to 87.0)
≤ 65 (n [%])	167 (3.7)	149 (8.2)
> 65 (n [%])	95 (36.3)	107 (41.8)
> 65 and ≤ 75 (n [%])	67 (25.6)	83 (32.4)
> 75 (n [%])	28 (10.7)	24 (9.4)
Sex (n [%])		
Male	163 (62.2)	121 (47.3)
Female	99 (37.8)	135 (52.7)
Race (n [%])		
American Indian or Alaska Native	2 (0.8)	1 (0.4)
Asian	7 (2.7)	5 (2.0)
Black or African American	34 (13.0)	37 (14.5)
Native Hawaiian or other Pacific Islanders	3 (1.1)	3 (1.2)
White or Caucasian	209 (79.8)	204 (79.7)
Unknown	7 (2.7)	6 (2.3)
ISS Stage at Diagnosis (n [%])		
I	78 (29.8)	75 (29.3)
II	98 (37.4)	96 (37.5)
III	86 (32.8)	85 (33.2)
Creatinine Clearance at Diagnosis (n [%])		
< 60 mL/min	78 (29.8)	76 (29.7)
≥ 60 mL/min	184 (70.2)	179 (69.9)
< 50 mL/min	46 (17.6)	43 (16.8)
≥ 50 mL/min	216 (82.4)	212 (82.8)
Missing	0	1 (0.4)

ISS = International Staging System; NDMM = newly diagnosed multiple myeloma; Rd = lenalidomide and dexamethasone given in 28-day cycles until documentation of progressive disease; RVd = lenalidomide plus Velcade (bortezomib) plus dexamethasone; SD = standard deviation; TNE = transplant non-eligible.
Source: SCS Table 1.2

Table 13: Duration of Exposure in TNE NDMM Study SW0G S0777 – Initial Treatment (Safety Population; Data Cutoff: 01 Dec 2016)

Duration (Weeks)	Arm B (RVd) (N = 262)	Arm A (Rd) (N = 256)
Duration of Exposure of Initial Therapy (Weeks)		
Mean (SD)	21.3 (8.09)	22.4 (7.51)
Median	24.0	24.1
Range	0.4 to 36.6	1.3 to 35.1
Treatment Duration Time Period Distribution from 0 to	**n (%)**	
≤ 3 weeks	14 (5.3)	9 (3.5)
≤ 6 weeks	20 (7.6)	17 (6.6)
≤ 9 weeks	28 (10.7)	27 (10.5)
≤ 12 weeks	47 (17.9)	34 (13.3)
≤ 15 weeks	61 (23.3)	40 (15.6)
≤ 18 weeks	81 (30.9)	53 (20.7)
≤ 21 weeks	99 (37.8)	60 (23.4)
≤ 24 weeks	137 (52.3)	128 (50.0)
≤ 27 weeks	201 (76.7)	199 (77.7)
≤ 30 weeks	244 (93.1)	240 (93.8)
≤ 33 weeks	258 (98.5)	251 (98.0)
≤ 36 weeks	261 (99.6)	256 (100)
≤ 40 weeks	262 (100)	256 (100)

NDMM = newly diagnosed multiple myeloma; Rd = lenalidomide and dexamethasone given in 28-day cycles until documentation of progressive disease; RVd = lenalidomide plus Velcade (bortezomib) plus dexamethasone; SD = standard deviation; TNE = transplant non-eligible.
Source: SCS Table 2.1

As of the data cutoff date of 01 Dec 2016, the medium treatment duration was 24.0 weeks (range 0.4 to 36.6) with RVd and 24.1 weeks (range 1.3 to 35.1) with Rd during initial treatment. For 48% of patients treated with RVd and 50% of patients treated with Rd, the duration of initial treatment was > 24 weeks.

Study CC-5013-MM-020

In Study CC-5013-MM-020 (hereafter referred to as Study MM-020), a total of 1613 patients from Europe (Austria, Belgium, France, Germany, Greece, Italy, Portugal, Spain, Sweden, Switzerland, and UK), Asia (China, Taiwan, and Republic of Korea), and North America/Pacific (US, Canada, Australia, and New Zealand) regions were randomised in a 1:1:1 ratio to 1 of 3 treatment arms:

- Treatment Arm A (Rd), lenalidomide (25 mg/day) and low-dose dexamethasone (given on Days 1, 8, 15 and 22) in repeated 28-day cycles until documentation of PD;

- Treatment Arm B (Rd18), lenalidomide (25 mg/day) and low-dose dexamethasone (given on Days 1, 8, 15 and 22) in repeated 28-day cycles for up to 18 cycles (72 weeks);
- Treatment Arm C (MPT), melphalan, prednisone (given on Days 1 to 4) and thalidomide in a 42-day cycle for up to 12 cycles (72 weeks).

Patients were stratified at randomisation by age (≤ 75 years versus > 75 years), stage (ISS Stages I or II versus Stage III), and country.

Of the 1613 enrolled patients, 535 were randomised to Arm Rd, 541 to Arm Rd18, and 547 to Arm MPT; of those, 3 in Arm Rd, 1 in Arm Rd18, and 6 in Arm MPT were never treated. The demographics and baseline characteristics of patients are presented in Table 14, while duration of exposure to study medication is presented in Table 15.

The majority of the study population are elderly patients. The median age is 73.0 years across all 3 treatment arms; 65.2% are ≤ 75 years and 34.9% are > 75 years. The study population also included 92 patients (5.7%) who were < 65 years; these patients were deemed ineligible for stem cell transplant but the reasons for the ineligibility were not systematically captured.

Overall, the intent-to-treat (ITT) population included a balanced proportion of males (52.6%) to females (47.4%) and the majority were white or Caucasian (89.0%), non-Hispanic or Latino (92.8%), and from Europe (68.6%). In general, study patients had advanced stage disease. Of the total study population, 40.6% had ISS Stage III, approximately half had some degree of renal insufficiency (CLcr < 60 mL/min), 71.2% had a history of bone disease, and 13.5% had radiation for MM prior to treatment in the study (see Table 14.1.1.1.1, MM-020 clinical study report [CSR]).

Overall, no clinically meaningful differences in demographic and disease-related characteristics were observed, and the treatment arms were balanced with regard to the demographic and disease-related characteristics. The medical history includes a number of comorbidities and manifestations of the disease for this elderly population: hypertension (59.8%), anaemia (57.5%), back pain (32.3%), bone pain (22.6%), hypercholesterolemia (17.6%), diabetes ("Type 2 diabetes mellitus," 7.6%; "diabetes mellitus," 6.5%), gastroesophageal reflux disease (7.5%), and obesity (2.3%). Of the total patients, 29.3% had a history of cardiac disorders including atrial fibrillation (7.7%), coronary artery disease (4.1%), and myocardial infarction (MI; 4.0%) (see Table 14.1.3.2.1, MM-020 CSR). Other important comorbidities were DVT (1.5%), pulmonary embolism (1.8%), and cerebrovascular accident (CVA; 2.6%). History of invasive malignancies was also documented in 10.4% of the total patients (Table 14.1.4.2.1.4, MM-020 CSR).

Table 14: Demographic and Baseline Characteristics of TNE NDMM Patients in Study MM-020 (ITT Population; Data Cutoff: 24 May 2013)

Demographic/Baseline Characteristic	Rd (N = 535)	Rd18 (N = 541)	Rd and Rd18 (N = 1076)	MPT (N = 547)
Age (Years)				
Mean (SD)	73.2 (6.57)	72.9 (6.50)	73.0 (6.53)	73.1 (6.32)
Median (Range)	73.0 (44.0 to 91.0)	73.0 (40.0 to 89.0)	73.0 (40.0 to 91.0)	73.0 (51.0 to 92.0)

Table 14: Demographic and Baseline Characteristics of TNE NDMM Patients in Study MM-020 (ITT Population; Data Cutoff: 24 May 2013) (Continued)

Demographic/Baseline Characteristic	Rd (N = 535)	Rd18 (N = 541)	Rd and Rd18 (N = 1076)	MPT (N = 547)
≤ 75 (n [%])	349 (65.2)	348 (64.3)	697 (64.8)	359 (65.6)
> 75 (n [%])	186 (34.8)	193 (35.7)	379 (35.2)	188 (34.4)
Sex (n [%])				
Male	294 (55.0)	273 (50.5)	567 (52.7)	287 (52.5)
Female	241 (45.0)	268 (49.5)	509 (47.3)	260 (47.5)
Race (n [%])				
Asian	40 (7.5)	43 (7.9)	83 (7.7)	44 (8.0)
Black or African American	9 (1.7)	6 (1.1)	15 (1.4)	5 (0.9)
Native Hawaiian or other Pacific Islanders	1 (0.2)	0	1 (0.1)	1 (0.2)
Other	6 (1.1)	11 (2.0)	17 (1.6)	3 (0.5)
White or Caucasian	474 (88.6)	480 (88.7)	954 (88.7)	491 (89.8)
Undisclosed	5 (0.9)	1 (0.2)	6 (0.6)	3 (0.5)
Ethnicity (n [%])				
Hispanic or Latino	37 (6.9)	33 (6.1)	70 (6.5)	36 (6.6)
Not Hispanic or Latino	493 (92.1)	505 (93.3)	998 (92.8)	508 (92.9)
Undisclosed	5 (0.9)	3 (0.6)	8 (0.7)	3 (0.5)
ISS Stage (n [%])				
I	115 (21.5)	112 (20.7)	227 (21.1)	108 (19.7)
II	195 (36.4)	204 (37.7)	399 (37.1)	205 (37.5)
III	225 (42.1)	224 (41.4)	449 (41.7)	234 (42.8)
Missing	0	1 (0.2)	1 (0.1)	0
ECOG Performance Status (n [%])				
0	155 (29.0)	163 (30.1)	318 (29.6)	156 (28.5)
1	257 (48.0)	263 (48.6)	520 (48.3)	275 (50.3)
2	119 (22.2)	113 (20.9)	232 (21.6)	111 (20.3)
≥ 3	2 (0.4)	2 (0.4)	4 (0.4)	2 (0.4)
Missing	2 (0.4)	0	2 (0.2)	3 (0.5)

ECOG = Eastern Cooperative Oncology Group; ISS = International Staging System; MPT = melphalan, prednisone and thalidomide given in 42-day cycles for up to 12 cycles (72 weeks); Rd = lenalidomide and low-dose dexamethasone given in 28-day cycles until documentation of PD; Rd18 = lenalidomide and low-dose dexamethasone given in 28-day cycles for up to 18 cycles (72 weeks); SD = standard deviation.

Table 15: Duration of Exposure in TNE NDMM Study MM-020 (Safety Population; Data Cutoff: 24 May 2013)

Duration (Weeks)	Rd (N = 532)	Rd18 (N = 540)	MPT (N = 541)
Treatment Duration Time Period Distribution from 0 to	**(n %)**		
≤ 4 weeks	24 (4.5)	27 (5.0)	19 (3.5)
≤ 12 weeks	50 (9.4)	54 (10.0)	81 (15.0)
≤ 24 weeks	98 (18.4)	102 (18.9)	131 (24.2)
≤ 36 weeks	141 (26.5)	146 (27.0)	175 (32.3)
≤ 48 weeks	179 (33.6)	186 (34.4)	212 (39.2)
≤ 52 weeks (1 year)	194 (36.5)	195 (36.1)	225 (41.6)
≤ 60 weeks	219 (41.2)	217 (40.2)	248 (45.8)
≤ 72 weeks	241 (45.3)	315 (58.3)	332 (61.4)
≤ 84 weeks	281 (52.8)	533 (98.7)	529 (97.8)
≤ 96 weeks	309 (58.1)	539 (99.8)	538 (99.4)
≤ 104 weeks (2 years)	324 (60.9)	540 (100.0)	539 (99.6)
≤ 108 weeks	330 (62.0)	540 (100.0)	540 (99.8)
≤ 120 weeks	347 (65.2)	540 (100.0)	541 (100.0)
≤ 132 weeks	372 (69.9)	540 (100.0)	541 (100.0)
≤ 144 weeks	401 (75.4)	540 (100.0)	541 (100.0)
≤ 156 weeks (3 years)	434 (81.6)	540 (100.0)	541 (100.0)
≤ 168 weeks	455 (85.5)	540 (100.0)	541 (100.0)
≤ 180 weeks	476 (89.5)	540 (100.0)	541 (100.0)
≤ 192 weeks	493 (92.7)	540 (100.0)	541 (100.0)
≤ 200 weeks	505 (94.9)	540 (100.0)	541 (100.0)
> 200 weeks	532 (100.0)	540 (100.0)	541 (100.0)
Duration of Exposure			
Mean (SD)	89.8 (63.45)	54.8 (25.53)	51.9 (27.64)
Median	80.2	72.0	67.1
Range	0.7 to 246.7	0.9 to 102.6	0.2 to 110.0

MPT = melphalan, prednisone and thalidomide given in 42-day cycles for up to 12 cycles (72 weeks); Rd = lenalidomide and low-dose dexamethasone given in 28-day cycles until documentation of PD; Rd18 = lenalidomide and low-dose dexamethasone given in 28-day cycles for up to 18 cycles (72 weeks); SD = standard deviation.

The median treatment duration in Arm Rd, 80.2 weeks (range: 0.7, 246.7), was longer than in either Arm Rd18 (72.0 weeks [range: 0.9, 102.6]) or Arm MPT (67.1 weeks [range: 0.1, 110.0]) owing to the study design, which proposed treatment in Arm Rd to continue until disease

progression. Treatments in Arm Rd18 and Arm MPT were both capped at 72 weeks (eighteen 28-day cycles and six 42-day cycles, respectively). Overall, 58.3% (Arm Rd18) and 61.4% (Arm MPT) of patients were treated for 72 weeks or less, including patients who discontinued treatment.

As of the 24 May 2013 cutoff, 208 patients in Arm Rd (39%) were treated for > 2 years and 98 patients (18%) were treated for > 3 years.

The total number of person-years on study treatment in each treatment arm was 921 in Arm Rd, 587 in Arm Rd18, and 549 in Arm MPT.

Study CC-5013-MM-015

In Study CC-5013-MM-015 (hereafter referred to as Study MM-015), a total of 459 stem cell TNE patients were randomised to treatment in the double-blind treatment phase of the study in a 1:1:1 ratio of:

- Induction therapy (up to 9 cycles) with melphalan/prednisone plus lenalidomide followed by maintenance therapy with single-agent lenalidomide (hereafter referred to as MPR+R); 10 mg/day on Days 1 to 21 of repeated 28-day cycles, given until disease progression.
- Induction therapy (up to 9 cycles) with melphalan/prednisone plus lenalidomide followed by maintenance therapy with single-agent placebo (hereafter referred to as MPR+p).
- Induction therapy (up to 9 cycles) with melphalan/prednisone plus placebo (p) followed by maintenance therapy with single-agent placebo (hereafter referred to as MPp+p).

Patients were stratified at randomisation by age (≤ 75 years versus > 75 years) and disease stage (ISS; Stages I and II versus Stage III) (Greipp, 2005).

Of the 459 patients randomised to treatment, 152, 153 and 154 patients were randomised to receive MPR+R, MPR+p and MPp+p, respectively. Overall, 455 patients were included in the safety population (150, 152 and 153 in the MPR+R, MPR+p and MPp+p arms, respectively). The demographics and baseline characteristics of patients are presented in Table 16, while duration of exposure to study medication is presented in Table 17.

The ITT population included approximately equal numbers of females (50.3%) and males (49.7%), and almost all patients were white (98.7%). Patients ranged in age from 65.0 to 91.0 years (median, 71.0 years), and approximately half of patients in each treatment arm were ISS Stage III. Overall, the three treatment arms were well balanced. The only notable exception was baseline Karnofsky performance status, which was significantly different between the MPR+R and MPp+p arms (median, 80% and 90%, respectively).

In general, no clinically notable differences in medical histories were observed between the three treatment arms. The majority of the patients had a history of musculoskeletal and connective tissue disorders (73.0% of patients; eg, osteoporosis, back pain, bone pain, and osteoarthritis); and vascular disorders (65.7% of patients; eg, hypertension); and blood and lymphatic system disorders (65.3% of patients; eg, anaemia) (see Table 14.1.5, MM-015 CSR). Thirty-one percent

(31.4%) of patients had a history of cardiac disorders, the most common of which included myocardial ischemia (8.4%) and atrial fibrillation (5.7%). Few patients had a history of venous thromboembolism: DVT (1.5%), pulmonary embolism (1.3%), thrombophlebitis (0.9%), and venous thrombosis (< 0.2%). A total of 31/455 patients (6.8%) had a history of prior invasive malignancy that had been inactive for ≥ 3 years prior to screening, with the exception of 1 patient who had prostate cancer diagnosed 1 year and 9 months prior to entering the study. Approximately half of the patients in each treatment arm had CLcr < 60 mL/min.

Table 16: Demographic and Baseline Characteristics of TNE NDMM Patients in Study MM-015 (ITT Population; Data Cutoff: 30 Apr 2013)

Demographic/Baseline Characteristic	MPR+R (N = 152)	MPR+p (N = 153)	MPp+p (N = 154)
Age (Years)			
Mean (SD)	72.0 (5.33)	72.1 (5.20)	72.0 (5.26)
Median (Range)	71.0 (65.0 to 87.0)	71.0 (65.0 to 86.0)	72.0 (65.0 to 91.0)
≤ 75 (n [%])	116 (76.3)	116 (75.8)	116 (75.3)
> 75 (n [%])	36 (23.7)	37 (24.2)	38 (24.7)
Sex (n [%])			
Male	71 (46.7)	82 (53.6)	75 (48.7)
Female	81 (53.3)	71 (46.4)	79 (51.3)
Race (n [%])			
White	151 (99.3)	151 (98.7)	151 (98.1)
Black	1 (0.7)	0	0
Hispanic	0	0	1 (0.6)
Other	0	2 (1.3)	2 (1.3)
ISS Stage (n [%])			
I	28 (18.4)	32 (20.9)	28 (18.2)
II	50 (32.9)	47 (30.7)	48 (31.2)
III	74 (48.7)	74 (48.4)	78 (50.6)
Karnofsky Performance Scale (n [%])			
60	13 (8.6)	16 (10.5)	11 (7.1)
70	40 (26.3)	20 (13.1)	22 (14.3)
80	37 (24.3)	54 (35.3)	43 (27.9)
90	40 (26.3)	40 (26.1)	51 (33.1)
100	21 (13.8)	23 (15.0)	27 (17.5)

Table 16: Demographic and Baseline Characteristics of TNE NDMM Patients in Study MM-015 (ITT Population; Data Cutoff: 30 Apr 2013) (Continued)

Demographic/Baseline Characteristic	MPR+R (N = 152)	MPR+p (N = 153)	MPp+p (N = 154)
Missing	1 (0.7)	0	0
Median	80.0	80.0	90.0

ISS = International Staging System; MM = multiple myeloma; MPp+p = Induction therapy (up to 9 cycles) with melphalan/prednisone plus placebo followed by maintenance therapy with single-agent placebo; MPR+p = Induction therapy (up to 9 cycles) with melphalan/prednisone plus lenalidomide followed by maintenance therapy with single-agent placebo; MPR+R = Induction therapy (up to 9 cycles) with melphalan/prednisone plus lenalidomide followed by maintenance therapy with single-agent lenalidomide; SD = standard deviation.

Table 17: Duration of Exposure in TNE NDMM Study MM-015 (Induction+Maintenance Phase; Safety Population; Data Cutoff: 30 Apr 2013)

Duration (Weeks)	MPR+R (N = 150)	MPR+p (N = 152)	MPp+p (N = 153)
Treatment Duration (n [%])[a]			
0 to ≤ 4	5 (3.3)	7 (4.6)	8 (5.2)
> 4 to ≤ 8	8 (5.3)	2 (1.3)	3 (2.0)
> 8 to ≤ 12	4 (2.7)	2 (1.3)	9 (5.9)
> 12 to ≤ 16	5 (3.3)	7 (4.6)	4 (2.6)
> 16 to ≤ 20	10 (6.7)	5 (3.3)	6 (3.9)
> 20 to ≤ 24	5 (3.3)	10 (6.6)	6 (3.9)
> 24 to ≤ 28	10 (6.7)	2 (1.3)	1 (0.7)
> 28 to ≤ 32	6 (4.0)	5 (3.3)	7 (4.6)
> 32 to ≤ 36	4 (2.7)	8 (5.3)	4 (2.6)
> 36 to ≤ 40	3 (2.0)	11 (7.2)	2 (1.3)
> 40 to ≤ 44	1 (0.7)	3 (2.0)	6 (3.9)
> 44 to ≤ 48	3 (2.0)	5 (3.3)	8 (5.2)
> 48 to ≤ 52	3 (2.0)	7 (4.6)	11 (7.2)
> 52 to ≤ 56	1 (0.7)	8 (5.3)	5 (3.3)
> 56 to ≤ 60	4 (2.7)	7 (4.6)	6 (3.9)
> 60 to ≤ 64	5 (3.3)	9 (5.9)	8 (5.2)
> 64 to ≤ 68	3 (2.0)	3 (2.0)	6 (3.9)
> 68 to ≤ 72	1 (0.7)	10 (6.6)	9 (5.9)
> 72 to ≤ 76	3 (2.0)	2 (1.3)	4 (2.6)
> 76 to ≤ 80	4 (2.7)	1 (0.7)	3 (2.0)

Table 17: Duration of Exposure in TNE NDMM Study MM-015 (Induction+Maintenance Phase; Safety Population; Data Cutoff: 30 Apr 2013) (Continued)

Duration (Weeks)	MPR+R (N = 150)	MPR+p (N = 152)	MPp+p (N = 153)
> 80 to ≤ 84	0	2 (1.3)	1 (0.7)
> 84 to ≤ 88	3 (2.0)	2 (1.3)	4 (2.6)
> 88 to ≤ 92	2 (1.3)	6 (3.9)	3 (2.0)
> 92 to ≤ 96	3 (2.0)	2 (1.3)	2 (1.3)
> 96 to ≤ 100	4 (2.7)	3 (2.0)	3 (2.0)
> 100 to ≤ 104	2 (1.3)	2 (1.3)	4 (2.6)
≥ 104	48 (32.0)	21 (13.8)	20 (13.1)
Duration of Exposure			
Mean (SD)	90.0 (81.83)	58.5 (37.67)	57.7 (36.62)
Median	62.6	53.0	53.0
Range	3.4 to 297.0	2.0 to 162.7	1.0 to 160.3

MPp+p = Induction therapy (up to 9 cycles) with melphalan/prednisone plus placebo followed by maintenance therapy with single-agent placebo; MPR+p = Induction therapy (up to 9 cycles) with melphalan/prednisone plus lenalidomide followed by maintenance therapy with single-agent placebo; MPR+R = Induction therapy (up to 9 cycles) with melphalan/prednisone plus lenalidomide followed by maintenance therapy with single-agent lenalidomide.

[a] Treatment duration is calculated from the first of the dosing start dates to the last of the last cycle end dates of the 3 study drugs.

It should be noted that dosing information in the maintenance period is difficult to compare between arms due to patients in Arms MPR+p and MPp+p stopping treatment (placebo) following unblinding of the study. As a result, the median cumulative dose in the maintenance phase was 3146.3 mg of lenalidomide in Arm MPR+R, 1325.0 mg of placebo in Arm MPR+p, and 1670.0 mg of placebo in Arm MPp+p.

1.2.4. Clinical Studies in Relapsed or Refractory Multiple Myeloma

A total of 353 patients were randomised to treatment with lenalidomide/dexamethasone and 350 patients received placebo/dexamethasone in Studies CC-5013-MM-009 and CC-5013-MM-010 (hereafter referred to as Studies MM-009 and MM-010). Patient populations in the controlled RRMM studies are shown in Table 18, while duration of exposure to study medication is presented in Table 19.

The safety population was approximately 60% male and 40% female, with patients ranging in age from 33 to 86 years (median, 63 years). There was significant comorbidity and cardiac risk factors within this safety population (see Table 14.1.4.1A, MM-009 and MM-010 CSRs), including a history of cardiac disorders (28.6% lenalidomide/dexamethasone and 29.0% placebo/dexamethasone), hypertension (43.4% lenalidomide/dexamethasone and 43.2% placebo/dexamethasone) and hypercholesterolaemia (10.7% lenalidomide/dexamethasone and 10.4% placebo/dexamethasone).

Table 18: Demographic and Baseline Characteristics in the Controlled RRMM Studies (Pooled Studies MM-009 and MM-010; Data Cutoff: 31 Dec 2005)

Demographic/Baseline Characteristic	Len/Dex (N = 353)	PBO/Dex[a] (N = 351)
Age (Years)		
N	353	351
Mean (SD)	62.7 (9.98)	62.7 (9.30)
Median	63.0	63.0
Range	33.0 to 86.0	37.0 to 85.0
18 to 24 (n [%])	0	0
25 to 34 (n [%])	1 (0.3)	0
35 to 44 (n [%])	14 (4.0)	7 (2.0)
45 to 54 (n [%])	56 (15.9)	70 (19.9)
55 to 64 (n [%])	121 (34.3)	121 (34.5)
65 to 74 (n [%])	118 (33.4)	114 (32.5)
> 74 (n [%])	43 (12.2)	39 (11.1)
Sex (n [%])		
Male	210 (59.5)	207 (59.0)
Female	143 (40.5)	144 (41.0)
Race/Ethnicity (n [%])		
White	313 (88.7)	323 (92.0)
Black	27 (7.6)	17 (4.8)
Hispanic	3 (0.8)	5 (1.4)
Asian/Pacific islander	6 (1.7)	2 (0.6)
American Indian/Alaska native	0	0
Other	4 (1.1)	4 (1.1)
Prior Antimyeloma Regimens/Stem Cell Transplantation (n [%])[b]		
0	0	0
1	65 (18.4)	73 (20.8)
2	138 (39.1)	134 (38.2)
3	114 (32.3)	106 (30.2)
> 3	36 (10.2)	38 (10.8)

Dex = dexamethasone; Len = lenalidomide; n = number of patients; PBO = placebo; SD = standard deviation.

[a] One patient randomised to placebo/dexamethasone did not receive treatment; thus 350 patients were treated with placebo/dexamethasone.

[b] Any number of stem cell transplant procedures is considered as one regimen.

Source: Variation II/34

Table 19: Duration of Exposure in the Controlled RRMM Studies (Pooled Studies MM-009 and MM-010; Data Cutoff: 31 Dec 2005)

Duration (Weeks)[a]	Len/Dex (N = 353)	PBO/Dex (N = 350)
Treatment Duration (n [%])		
< 1	1 (0.3)	2 (0.6)
1 to < 4	14 (4.0)	14 (4.0)
4 to < 8	14 (4.0)	38 (10.9)
8 to < 12	27 (7.6)	42 (12.0)
12 to < 16	15 (4.2)	28 (8.0)
16 to < 20	18 (5.1)	31 (8.9)
20 to < 24	16 (4.5)	23 (6.6)
24 to < 28	19 (5.4)	38 (10.9)
28 to < 32	19 (5.4)	27 (7.7)
32 to < 36	10 (2.8)	12 (3.4)
36 to < 40	11 (3.1)	15 (4.3)
40 to < 44	12 (3.4)	14 (4.0)
44 to < 48	8 (2.3)	8 (2.3)
48 to < 52	6 (1.7)	4 (1.1)
52 to < 56	6 (1.7)	6 (1.7)
56 to < 60	12 (3.4)	6 (1.7)
60 to < 64	7 (2.0)	2 (0.6)
64 to < 68	4 (1.1)	2 (0.6)
68 to < 72	5 (1.4)	3 (0.9)
72 to < 76	7 (2.0)	2 (0.6)
76 to < 80	6 (1.7)	3 (0.9)
80 to < 84	4 (1.1)	2 (0.6)
84 to < 88	3 (0.8)	0
88 to < 92	5 (1.4)	1 (0.3)
92 to < 96	2 (0.6)	0
96 to < 100	6 (1.7)	1 (0.3)
100 to < 104	4 (1.1)	2 (0.6)
≥ 104	92 (26.1)	24 (6.9)

Table 19: Duration of Exposure in the Controlled RRMM Studies (Pooled Studies MM-009 and MM-010; Data Cutoff: 31 Dec 2005) (Continued)

Duration (Weeks)[a]	Len/Dex (N = 353)	PBO/Dex (N = 350)
Duration of Exposure		
Mean (SD)	72.3 (69.13)	35.0 (44.29)
Median	44.0	23.1
Range	0.1 to 254.9	0.3 to 238.1

Dex = dexamethasone; Len = lenalidomide; n = number of patients; PBO = placebo; SD = standard deviation.
[a] Treatment duration is number of weeks from day of the first dose to day of the last dose of study drug.
Source: Variation II/34

1.2.5. Clinical Studies in Del 5q MDS with or without Additional Cytogenetic Abnormalities

In Study CC-5013-MDS-003 (hereafter referred to as Study MDS-003), which includes extension Study CC-5013-MDS-003E/009 (hereafter referred to as Study MDS-003E/009), where no additional treatment was given, rather as explained below, additional information was captured, patients with a diagnosis of low- or INT-1-risk del 5q MDS and RBC-transfusion-dependent anaemia were treated with lenalidomide 10 mg orally QD. Initially, this was as a syncopated dosage regimen in which patients received lenalidomide 10 mg orally QD on Days 1 to 21 of a 28-day cycle. Following a protocol amendment, a continuous dosage regimen (ie, 10 mg orally on Day 1 to 28 of a 28-day cycle) was used in which there was no planned rest period. The decision to change the dosing regimen from a syncopated regimen to a continuous regimen was taken when additional data from a Phase 1/2 study (Study MDS-501-001) became available to suggest that a continuous regimen of lenalidomide (10 mg of lenalidomide QD without a planned rest period) produced an earlier response, with no additional safety concerns.

After the MDS-003 study was closed, the need for longer-term follow-up was identified. The MDS-003E (Germany)/MDS-009 (US) (MDS-003E/MDS-009) study was a non-interventional (no study drug was provided under the protocol), multi-centre, follow-up extension study of patients previously enrolled in MDS-003. It was conducted specifically to provide further long-term outcomes for OS/vital status (including date of death or last known date alive, primary underlying cause of death, and other significant conditions contributing to death) and the possible occurrence of progression to AML for patients previously enrolled in the MDS-003 study and to further analyse these outcomes based on the long-term follow-up data obtained.

Overall, 148 patients were enrolled into Study MDS-003, all of whom received lenalidomide and completed the study. Forty-six patients started with the syncopated dosage regimen of which 6 patients switched to a continuous dosage regimen; 102 patients started with the continuous dosage regimen. Study MDS-003 was completed on 27 Aug 2008 and the extension Study MDS-003E/009 was completed on 01 Oct 2010. Study MDS-003E/009 was only intended to collect follow-up data as described above from Study MDS-003. The demographics and

baseline characteristics of patients are summarised in Table 20, while duration of exposure to study medication is presented in Table 21.

The study population reflected that observed in clinical practice, and included more females (65.5%) than males (34.5%), as would be expected for this patient population. Patients ranged in age from 37 to 95 years, with a median age of 71.0 years. Overall 9 (6.1%) patients had INT-2 or high-risk del 5q MDS according to the central review. One hundred and ten (74.3%) patients had an MDS clone with an isolated del 5q cytogenetic abnormality, 25 (16.9%) patients had intermediate cytogenetic complexity, and 12 (8.1%) patients had complex cytogenetic abnormalities.

Overall, the median duration of treatment was 52.5 weeks (range, 0.4 to 253.0 weeks) and 62.8% (93/148) of patients received treatment for at least 32 weeks, indicating a long duration of lenalidomide treatment in the study patients.

Table 20: Demographic and Baseline Characteristics of Del 5q MDS Patients in Study MDS-003 (ITT Population; Data Cutoff: 27 Aug 2008)

Demographic/Baseline Characteristic	Lenalidomide 10 mg (Continuous[a]; N = 102)	Lenalidomide 10 mg (Syncopated[b]; N = 46)	Overall (N = 148)
Age (Years)			
Mean (SD)	69.3 (11.0)	71.4 (9.4)	70.0 (10.5)
Median (Range)	71.0 (37.0 to 95.0)	72.0 (51.0 to 91.0)	71.0 (37.0 to 95.0)
≤ 65 (n [%])	35 (34.3)	13 (28.3)	48 (32.4)
> 65 (n [%])	67 (65.7)	33 (71.7)	100 (67.6)
Sex (n [%])			
Male	33 (32.4)	18 (39.1)	51 (34.5)
Female	69 (67.6)	28 (60.9)	97 (65.5)
Race (n [%])			
White	99 (97.1)	44 (95.7)	143 (96.6)
Hispanic	2 (2.0)	1 (2.2)	3 (2.0)
Asian/Pacific Islander	1 (1.0)	1 (2.2)	2 (1.4)
5q(-) (31-33) Chromosomal Abnormality (n [%])[c]			
Yes	102 (100)	46 (100)	148 (100)
No	0	0	0
IPSS Score (Central Review)[d] (n [%])			
Low (0)	36 (35.3)	13 (28.3)	49 (33.1)
INT-1 (0.5 to 1.0)	44 (43.1)	25 (54.3)	69 (46.6)
INT-2 (1.5 to 2.0)	4 (3.9)	3 (6.5)	7 (4.7)
High risk (≥ 2.5)	1 (1.0)	1 (2.2)	2 (1.4)
Missing	17 (16.7)	4 (8.7)	21 (14.2)

Table 20: Demographic and Baseline Characteristics of Del 5q MDS Patients in Study MDS-003 (ITT Population; Data Cutoff: 27 Aug 2008) (Continued)

Demographic/Baseline Characteristic	Lenalidomide 10 mg (Continuous[a]; N = 102)	Lenalidomide 10 mg (Syncopated[b]; N = 46)	Overall (N = 148)
FAB Classification (Central Haematologic Review) (n [%])			
RA	52 (51.0)	26 (56.5)	78 (52.7)
RARS	13 (12.7)	3 (6.5)	16 (10.8)
RAEB	18 (17.6)	12 (26.1)	30 (20.3)
CMML	2 (2.0)	1 (2.2)	3 (2.0)
Acute Leukaemia	0	1 (2.2)	1 (0.7)
Unable to classify	17 (16.7)	3 (6.5)	20 (13.5)
Cytogenetic Complexity (n [%])[d]			
Isolated 5q	80 (78.4)	30 (65.2)	110 (74.3)
INT (5q + 1 Abnormality)	14 (13.7)	11 (23.9)	25 (16.9)
Complex	7 (6.9)	5 (10.9)	12 (8.1)
Unknown	1 (1.0)	0	1 (0.7)
ECOG Performance Status (n [%])			
0	43 (42.2)	16 (34.8)	59 (39.9)
1	49 (48.0)	26 (56.5)	75 (50.7)
2	10 (9.8)	4 (8.7)	14 (9.5)

CMML = chronic myelomonocytic leukaemia; ECOG = Eastern Cooperative Oncology Group; FAB = French-American-British; IPSS = International Prognostic Scoring System; n = number of patients; RA = refractory anaemia; RAEB = Refractory Anaemia with Excess Blasts; RARS = Refractory Anaemia with Ringed Sideroblasts; SD = standard deviation.

[a] 10 mg on Days 1 to 28 of a 28-day cycle.

[b] 10 mg on Days 1 to 21 of a 28-day cycle.

[c] Standard cytogenetic studies were performed and centrally reviewed by an independent cytogenetic reviewer to confirm the patient's cytogenetic eligibility at baseline.

[d] IPSS Score = Sum of marrow blast + karyotype + cytopenia score. Intermediate: +1 abnormality. Complex: ≥ 2 abnormalities.

Source: Study MDS-003 CSR, Table 11.

Table 21: Duration of Exposure of Del 5q MDS Patients in Study MDS-003 (Data Cutoff: 27 Aug 2008)

	Lenalidomide 10 mg (Continuous[a]; N = 102)	Lenalidomide 10 mg (Syncopated[b]; N = 46)	Overall (N = 148)
Treatment Duration (Weeks)			
Mean (SD)	94.6 (85.1)	74.8 (75.5)	88.5 (82.5)
Median	52.0	55.0	52.5
Range	0.4 to 250.6	2.0 to 253.0	0.4 to 253.0

Table 21: Duration of Exposure of Del 5q MDS Patients in Study MDS-003 (Data Cutoff: 27 Aug 2008) (Continued)

	Lenalidomide 10 mg (Continuous[a]; N = 102)	Lenalidomide 10 mg (Syncopated[b]; N = 46)	Overall (N = 148)
Distribution of Treatment Duration (n [%])			
At least 4 weeks	98 (96.1)	40 (87.0)	138 (93.2)
At least 8 weeks	95 (93.1)	36 (78.3)	131 (88.5)
At least 16 weeks	86 (84.3)	34 (73.9)	120 (81.1)
At least 24 weeks	76 (74.5)	30 (65.2)	106 (71.6)
At least 32 weeks	67 (65.7)	26 (56.5)	93 (62.8)

n = number of patients; SD = standard deviation.
[a] 10 mg on Days 1 to 28 of a 28-day cycle.
[b] 10 mg on Days 1 to 21 of a 28-day cycle.
Source: Study MDS-003 CSR, Table 35.

Of the 148 patients who were enrolled in Study MDS-003, 76 had died at the time of writing the final MDS-003 CSR and 18 did not participate in the extension study. Thus, 54 patients were included in the extension study follow-up cohort. The median duration of follow-up for all patients in Study MDS-003 at the time of the final MDS-003 CSR was 2.8 years (33.9 months; range, 0.3 to 58.2 months). Following completion of the extension study (intended to collect follow-up data only), the median duration of follow-up for all MDS-003 patients was 3.2 years (38.4 months; range, 0.3 to 81.9 months).

In Study CC-5013-MDS-004 (hereafter referred to as Study MDS-004), patients were randomised in a 1:1:1 ratio to one of three treatment arms:

- **Lenalidomide 10 mg**: oral lenalidomide 10 mg (two 5 mg capsules) QD on Days 1 to 21 and 2 placebo capsules QD on Days 22 to 28, every 28 days.
- **Lenalidomide 5 mg**: oral lenalidomide 5 mg (one 5 mg capsule) plus 1 placebo capsule QD, every 28 days.
- **Placebo**: 2 placebo capsules QD, every 28 days.

In Study MDS-004, all 205 enrolled patients received at least 1 dose of double-blind study medication and were included in the safety population (69, 69 and 67 patients received lenalidomide 10 mg, lenalidomide 5 mg and placebo, respectively). Of the 67 placebo patients, 56 crossed-over to lenalidomide 5 mg; however, 11 received only placebo (ie, the patients received no lenalidomide). The demographics and baseline characteristics of patients are summarised in Table 22, while duration of exposure to study medication is presented in Table 23.

In the safety population, there were more females than males (71.0% to 80.6% of patients were female across the three treatment groups), consistent with the expected demographics for a del 5q MDS population. The mean age was 66.2 to 68.2 years across the treatment groups, with the majority of patients (60.0% overall) over the age of 65 years. Of the 205 patients in the safety population, 191 had a del 5q (31 to 33) chromosomal abnormality and 4 patients did not; these demographic data were missing for 10 patients. The majority of patients were in the IPSS MDS low and INT-1 risk groups (70 and 74 patients overall, respectively). In addition, the majority of

patients had or presented with refractory anaemia (RA) based on central review for French-American-British (FAB) classification, with comparable percentages across treatment groups. The median transfusion burden was 6 units/8 weeks in all 3 treatment groups.

Table 22: Demographic and Baseline Characteristics of Del 5q MDS Patients in Study MDS-004 (Double-blind Safety Population; Data Cutoff: 11 Oct 2010)

Demographic/Baseline Characteristic	Lenalidomide 10 mg (N = 69)	Lenalidomide 5 mg (N = 69)	Placebo[a] (N = 67)
Age (Years)			
Mean (SD)	67.6 (11.68)	66.2 (10.54)	68.2 (9.70)
Median (Range)	68 (36 to 86)	66 (40 to 86)	69 (39 to 85)
≤ 65 (n [%])	29 (42.0)	32 (46.4)	21 (31.3)
> 65 (n [%])	40 (58.0)	37 (53.6)	46 (68.7)
Sex (n [%])			
Male	20 (29.0)	16 (23.2)	13 (19.4)
Female	49 (71.0)	53 (76.8)	54 (80.6)
Race/Ethnicity (n [%])			
White	69 (100.0)	67 (97.1)	66 (98.5)
Other	0	2 (2.9)	1 (1.5)
5q(-) (31-33) Chromosomal Abnormality (n [%])[b]			
Yes	64 (92.8)	64 (92.8)	63 (94.0)
No	1 (1.4)	2 (2.9)	1 (1.5)
Missing	4 (5.8)	3 (4.3)	3 (4.5)
IPSS Score (Central Review) (n [%])			
Low (0)	20 (29.0)	20 (29.0)	30 (44.8)
INT-1 (0.5 to 1.0)	23 (33.3)	29 (42.0)	22 (32.8)
INT-2 (1.5 to 2.0)	3 (4.3)	5 (7.2)	2 (3.0)
High risk (≥ 2.5)	1 (1.4)	0	0
Missing	22 (31.9)	15 (21.7)	13 (19.4)
FAB Classification (Central Review) (n [%])			
RA	32 (46.4)	38 (55.1)	37 (55.2)
RARS	9 (13.0)	7 (10.1)	8 (11.9)
RAEB	9 (13.0)	9 (13.0)	4 (6.0)
CMML	0	2 (2.9)	1 (1.5)
RAEB-T	0	0	1 (1.5)
CML	1 (1.4)	0	0
Specimen not adequate/Other/Missing	17 (24.6)	11 (15.9)	12 (17.9)

Table 22: Demographic and Baseline Characteristics of Del 5q MDS Patients in Study MDS-004 (Double-blind Safety Population; Data Cutoff: 11 Oct 2010) (Continued)

Demographic/Baseline Characteristic	Lenalidomide 10 mg (N = 69)	Lenalidomide 5 mg (N = 69)	Placebo (N = 67)[a]
Transfusion Burden (Units/8 Weeks)			
Median (Range)	6 (2 to 12)	6 (1 to 25)	6 (2 to 12)

CML = chronic myeloid leukaemia; CMML = chronic myelomonocytic leukaemia; FAB = French-American-British; IPSS = International Prognostic Scoring System; n = number of patients; RA = refractory anaemia; RAEB = Refractory Anaemia with Excess Blasts; RARS = Refractory Anaemia with Ringed Sideroblasts; SD = standard deviation.

[a] Including placebo patients who cross over to lenalidomide 5 mg after 16 weeks of double-blind phase.

[b] Standard cytogenetic studies were performed and centrally reviewed by an independent cytogenetic reviewer to confirm the patient's cytogenetic eligibility at baseline.

Source: Study MDS-004 CSR, Table 14.1.3.2.

Across the three treatment groups, there was significant comorbidity (see Table 14.1.4, MDS-004 CSR), which included a history of hypertension (20.3% to 27.5%), osteoarthritis (8.7% to 13.4%), hypercholesterolaemia (7.2% to 11.6%), constipation (5.8% to 10.4%) and atrial fibrillation (8.7% to 10.1%).

The mean duration of exposure was comparable across the lenalidomide groups and slightly lower in the placebo group (including the patients who crossed over to lenalidomide; Table 23), which is consistent with the smaller proportion of patients in the placebo group continuing with treatment beyond 24 weeks. Of note, the study design stipulated that patients with no evidence of at least a minor erythroid response after 16 weeks double-blind treatment were to be discontinued from the double-blind phase and if they had received placebo treatment could enter the open-label phase.

The median daily dose of lenalidomide received per cycle for the first 6 cycles ranged from 5.0 mg to 2.5 mg in the 5 mg group and from 10.0 mg to 5.0 mg in the 10 mg group, and was consistently higher in the 10 mg group. The respective median daily doses remained stable through Month/Cycle 12 (Study MDS-004 CSR, Section 12.1.1).

Table 23: Duration of Exposure of Del 5q MDS Patients in Study MDS-004 (Double-blind Safety Population; Data Cutoff: 11 Oct 2010)

Duration (Weeks)[a]	Lenalidomide 10 mg (N = 69)	Lenalidomide 5 mg (N = 69)	Placebo (N = 67)
Treatment Duration (n [%])			
≥ 4 weeks	63 (91.3)	67 (97.1)	63 (94.0)
≥ 8 weeks	59 (85.5)	62 (89.9)	62 (92.5)
≥ 16 weeks	54 (78.3)	50 (72.5)	42 (62.7)
≥ 24 weeks	41 (59.4)	30 (43.5)	6 (9.0)
≥ 32 weeks	39 (56.5)	29 (42.0)	4 (6.0)
≥ 52 weeks	29 (42.0)	15 (21.7)	3 (4.5)

Table 23: Duration of Exposure of Del 5q MDS Patients in Study MDS-004 (Double-blind Safety Population; Data Cutoff: 11 Oct 2010) (Continued)

Duration (Weeks)[a]	Lenalidomide 10 mg (N = 69)	Lenalidomide 5 mg (N = 69)	Placebo (N = 67)
Duration of Exposure			
Mean (SD)	34.7 (20.22)	28.6 (17.71)	17.4 (9.65)
Median	50.3	18.0	16.0
Range	1.4 to 56.3	2.4 to 53.1	1.3 to 54.4

n = number of patients; SD = standard deviation.
[a] Treatment duration = (date of last dose – date of first dose + 1)/7
Source: Study MDS-004 CSR, Table 14.3.1.1.

1.2.6. Clinical Studies in Mantle Cell Lymphoma

Study CC-5013-MCL-002

A total of 254 patients were enrolled and randomised in a 2:1 ratio to the lenalidomide arm (n = 170) or the control arm (n = 84). Of all patients randomised, 250 (98.4%) received at least 1 dose of study medication, either lenalidomide (n = 167; 98.2%) or Investigator's choice (n = 83; 98.8%). The mean and median treatment duration in the lenalidomide arm were 46.6 and 24.3 weeks, respectively, and ranged from 0.4 to 241.9 weeks as of the data cutoff date 07 Mar 2014 (1 year after the last patient was randomised). The proportion of patients on study in the 2 treatment arms was comparable over time, with > 40% of patients remaining on study for ≥ 80 weeks (≥ 18.5 months) in each arm. Demographics and baseline characteristics of patients are summarised in Table 24, while duration of exposure to study medication is presented in Table 25.

The majority of the safety population (67.6%) were elderly patients (≥ 65 years old), and the median age was 68.5 years. Overall, the study included more men (73.6%) than women (26.4%), in line with distribution of the disease by sex (2.3:1) in Europe (Sant, 2010). Most patients were white or Caucasian (95.2%); race was not reported in the remaining patients (4.8%). Overall, no clinically meaningful differences in demographic characteristics were observed between treatment arms. Review of baseline disease characteristics showed that, in general, patients had advanced relapses, as evidenced by a median of 2 prior systemic anti-lymphoma therapies and a significant number of patients with 2 or more prior relapses.

Table 24: Demographic and Baseline Characteristics of MCL Patients in Studies MCL-002, MCL-001, NHL-002 and NHL-003 (Safety Population)

Demographic/ Baseline Characteristic	MCL-002		All MCL Lenalidomide Patients (MCL-002, MCL-001, NHL-002, NHL-003) (N = 373)
	Lenalidomide (N = 167)	Control (N = 83)	
Age (Years)			
Mean (SD)	68.1 (9.37)	67.4 (8.22)	67.4 (9.27)
Median (Range)	69.0 (44.0 to 88.0)	68.0 (49.0 to 87.0)	68.0 (33.0 to 88.0)
< 65 (n [%])	54 (32.3)	27 (32.5)	130 (34.9)
≥ 65 (n [%])	113 (67.7)	56 (67.5)	243 (65.1)
Sex (n [%])			
Male	122 (73.1)	62 (74.7)	282 (75.6)
Female	45 (26.9)	21 (25.3)	91 (24.4)
Race (n [%])			
White or Caucasian	159 (95.2)	79 (95.2)	353 (94.6)
Black or African American	0	0	1 (0.3)
Asian/Pacific Islander	0	0	3 (0.8)
Hispanic	0	0	4 (1.1)
Other	0	0	4 (1.1)
Missing	8 (4.8)	4 (4.8)	8 (2.1)
MCL Stage at Diagnosis (n [%])			
I	3 (1.8)	2 (2.4)	8 (2.1)
II	10 (6.0)	1 (1.2)	20 (5.4)
III	29 (17.4)	20 (24.1)	57 (15.3)
IV	121 (72.5)	58 (69.9)	279 (74.8)
Missing	4 (2.4)	2 (2.4)	9 (2.4)
ECOG Performance Status (n [%])			
0	65 (38.9)	35 (42.2)	144 (38.6)
1	76 (45.5)	37 (44.6)	178 (47.7)
2	25 (15.0)	11 (13.3)	49 (13.1)
3	0	0	1 (0.3)
Missing	1 (0.6)	0	1 (0.3)

ECOG = Eastern Cooperative Oncology Group; MCL = Mantle cell lymphoma; SD = standard deviation.
Data cutoff dates: Studies MCL-002 (07 Mar 2014); MCL-001 (20 Mar 2013); NHL-002 (23 Jun 2008); NHL-003 (27 Apr 2011).

Table 25: Duration of Exposure in MCL Studies MCL-002, MCL-001, NHL-002 and NHL-003 (Safety Population)

	MCL-002		All MCL Lenalidomide Patients (MCL-002, MCL-001, NHL-002, NHL-003) (N = 373)
	Lenalidomide (N = 167)	Control (N = 83)	
Number of Cycles			
≥ 1	167 (100.0)	83 (100.0)	373 (100.0)
≥ 2	141 (84.4)	68 (81.9)	310 (83.1)
≥ 3	119 (71.3)	51 (61.4)	246 (66.0)
≥ 4	102 (61.1)	41 (49.4)	209 (56.0)
≥ 6	83 (49.7)	28 (33.7)	171 (45.8)
≥ 12	62 (37.1)	7 (8.4)	116 (31.1)
≥ 18	37 (22.2)	3 (3.6)	70 (18.8)
≥ 24	28 (16.8)	0	46 (12.3)
≥ 30	18 (10.8)	0	31 (8.3)
Duration (Weeks)			
Mean (SD)	46.6 (53.53)	21.8 (31.30)	40.5 (49.05)
Median	24.3	13.1	17.0
Range	0.4 to 241.9	0.1 to 157.9	0.1 to 241.9

SD = standard deviation.
Data cutoff dates: Studies MCL-002 (07 Mar 2014); MCL-001 (20 Mar 2013); NHL-002 (23 Jun 2008); NHL-003 (27 Apr 2011).

The study populations in the TE and TNE NDMM, RRMM, del 5q MDS and MCL studies are representative of the patient populations for each condition in terms of age and likely comorbidity.

PART II – MODULE SIV: POPULATIONS NOT STUDIED IN CLINICAL TRIALS

1. EXCLUSION CRITERIA IN PIVOTAL CLINICAL STUDIES WITHIN THE DEVELOPMENT PROGRAMME

The important exclusion criteria in the pivotal clinical studies across the development programme are described in Table 26.

Table 26: Important Exclusion Criteria in Pivotal Clinical Studies

Exclusion Criteria	Reason for Exclusion	Is it Considered to be Included as Missing Information? Yes/No, If No, Rationale.
Studies SWOG S0777, CALGB 100104, IFM 2005-02, MM-020, MM-015, MM-009, MM-010, MDS-003, MDS-004, MCL-002, MCL-001, NHL-003, NHL-002, NHL-007 and NHL-008		
Pregnant and lactating women	Lenalidomide is contraindicated in pregnant women based on malformations seen in an embryofoetal developmental toxicity study in monkeys. Malformations similar to those resulting from thalidomide administration occurred in the offspring of female monkeys who received lenalidomide at doses as low as 0.5 mg/kg/day on gestational days 20 to 50 of pregnancy. It is unknown if lenalidomide is secreted in human milk. There is a potential for adverse reactions in nursing infants from lenalidomide. Pregnant and lactating females are excluded to avoid potential harm to the unborn fetus or breastfeeding newborn.	No Section 4.3 of the SmPC clearly states that lenalidomide is contraindicated in pregnant women and Section 4.4 includes a pregnancy warning. Section 4.6 of the SmPC recommends that female patients must not breastfeed when taking lenalidomide, as it is not known if lenalidomide passes into human milk.
Known human immunodeficiency virus (HIV) positivity or seropositive/ active viral infections (hepatitis B antigen, hepatitis B virus [HBV], hepatitis C virus [HCV] or active infectious hepatitis)	IMiD drugs exert various effects on the immune system, altering cytokine production, regulating T cell costimulation and enhancing NK cell cytotoxicity. Particularly, IMiDs inhibit tumour necrosis factor-alpha, playing an important role in immune response against bacterial and viral infections. Moreover, lenalidomide causes myelosuppression, mainly neutropenia, which is an important risk factor for infections. In addition, patients are at an increased risk of lethal infections when treated with a combination of drugs that have a bone marrow suppressive effect.	No Warnings on infection with or without neutropenia and viral reactivation have been included in Section 4.4 of the SmPC. Hepatic disorder in the context of pre-existing viral disease is also included in Section 4.4 of the SmPC. Guidelines for dose adjustment for patients with neutropenia and MM, MDS, MCL or FL are outlined in Section 4.2 of the SmPC.

Table 26: Important Exclusion Criteria in Pivotal Clinical Studies (Continued)

Exclusion Criteria	Reason for Exclusion	Is it Considered to be Included as Missing Information? Yes/No, If No, Rationale.
Prior history of malignancies	Due to the risk of SPM observed with the use of lenalidomide (monotherapy, combination therapy and with or without the use of alkylating agent and prior ASCT), patients with a history of SPM (except for basal cell or squamous cell carcinoma of the skin or carcinoma in situ of the cervix or breast or incidental finding of prostate cancer stage T1a or T1b) were excluded unless the patient had been free of the disease for ≥ 5 years, due to the risk of SPM.	No, the safety outcome variable was incidence of SPM with the use of lenalidomide. Based on the diseases treated, the age of the target population, and the treatment regimens used (prior alkylating agents/auto ASCT), and SPM follow-up in clinical trials, SPM is an important identified risk. Section 4.4 of the SmPC includes warnings about SPM.
Patients who are unable or unwilling to undergo thromboprophylaxis	Data have shown that patients who do not undergo thromboprophylaxis, especially high risk patients, are at a higher risk for thromboembolism when lenalidomide is given in combination with dexamethasone.	No Section 4.4 of the SmPC includes a warning to minimise all modifiable risk factors, to closely monitor patients with known risk factors, and a recommendation for prophylactic antithrombotics in patients with additional risk factors.
Chronic steroid use or immunosuppressive treatment	Patients with conditions requiring chronic steroid or immunosuppressive treatment, such as rheumatoid arthritis, multiple sclerosis and lupus, are likely to need additional steroid or immunosuppressive treatments in addition to the study treatment (lenalidomide in combination with dexamethasone or prednisone). Chronic steroid or immunosuppressive agents can compromise the immune system even more, thus putting the patients at increased risk for infections.	No Experience to date has indicated that treatment with lenalidomide has been well tolerated by patients receiving physiological and high doses of dexamethasone. Use of other immunosuppressive medications in the target population is not anticipated to lead to an increased risk of common AEs known to be associated with lenalidomide.
Known hypersensitivity to thalidomide	A possible cross-reaction between lenalidomide and thalidomide has been reported in the literature.	No Section 4.4 of the SmPC includes a warning that cases of allergic reaction/hypersensitivity reactions have been reported in patients treated with lenalidomide. Patients who had previous allergic reactions while treated with thalidomide should be monitored closely, as a possible cross-reaction between lenalidomide and thalidomide has been reported in the literature.

Table 26: Important Exclusion Criteria in Pivotal Clinical Studies (Continued)

Exclusion Criteria	Reason for Exclusion	Is it Considered to be Included as Missing Information? Yes/No, If No, Rationale.
Active central nervous system (CNS) lymphoma	Patients with active CNS lymphoma conditions have significantly worse prognoses and are excluded from the clinical development programme to ensure interpretability of efficacy.	No Patients whose CNS lymphoma had been treated with chemotherapy, radiotherapy or surgery; had remained asymptomatic for 90 days (3 months); and demonstrated no CNS lymphoma were not excluded. Lenalidomide does not cross the blood-brain barrier.
Studies CALGB 100104, IFM 2005-02, MM-020, MM-015, MM-009, MM-010, MDS-003, MDS-004, MCL-002, MCL-001, NHL-003, NHL-002		
Moderate to severe hepatic impairment	Lenalidomide has not formally been studied in patients with impaired hepatic function. No detectable in vitro metabolism of lenalidomide was observed in human liver microsomes, recombinant CYP enzymes, or isolated human hepatocytes, indicating that hepatic metabolism is not a major clearance pathway.	No In PSURs, review of the safety profile in patients with a medical history of hepatic impairment did not provide any unexpected findings. Hepatic metabolism is not a major clearance pathway for lenalidomide. Section 4.2 of the SmPC states that lenalidomide has not been formally studied in patients with impaired hepatic function and there are no specific dose recommendations (for patients with hepatic impairment). Section 5.2 of the SmPC states that population pharmacokinetic analyses included patients with mild hepatic impairment (N = 16, total bilirubin > 1 to ≤ 1.5 x upper limit of normal [ULN] or aspartate aminotransferase [AST] > ULN) and indicate that mild hepatic impairment does not influence lenalidomide clearance (exposure in plasma). There are no data available for patients with moderate to severe hepatic impairment.
Moderate to severe renal insufficiency	Approximately 65% to 85% of lenalidomide is eliminated unchanged through urinary excretion in subjects with normal renal function. The elimination half-life is approximately 3 to 5 hours at clinical doses (5 to 50 mg/day). Steady-state levels are achieved within 4 days. Pharmacokinetic analyses in subjects with impaired renal function indicate that, as renal function decreases, the total drug clearance decreases proportionally, which is reflected by	No Renal excretion is the major clearance pathway for lenalidomide. Recommended dose adjustments in patients with impaired renal function are described in Section 4.2 of the SmPC. No dose adjustments are required for patients with mild renal impairment. Warnings and information regarding the use of lenalidomide in patients with renal insufficiency

Table 26: Important Exclusion Criteria in Pivotal Clinical Studies (Continued)

Exclusion Criteria	Reason for Exclusion	Is it Considered to be Included as Missing Information? Yes/No, If No, Rationale.
	increased AUC. The terminal half-life ($t_{1/2,z}$) of lenalidomide was longer by approximately 6 to 12 hours in subjects with moderate or worse renal insufficiency. However, renal insufficiency did not alter the oral absorption of lenalidomide. The maximum concentration (C_{max}) was similar between healthy subjects and subjects with renal insufficiency.	are provided in Sections 4.4 and 5.2 of the SmPC.
Inadequate marrow reserve Neutropenia (≥ Grade 3)	Study patients may be at risk of significant neutropenia through effects of the study drug.	No Guidelines for dose adjustment for patients with neutropenia and MM, MDS, MCL or FL are outlined in Section 4.2 of the SmPC. Warnings regarding the risk of neutropenia in patients treated with lenalidomide are provided in Sections 4.4 and 4.8 of the SmPC.
Inadequate marrow reserve Thrombocytopenia (≥ Grade 2 or ≥ Grade 3 per indication)	Study patients may be at risk of significant thrombocytopenia through effects of the study drug.	No Guidelines for dose adjustment for patients with thrombocytopenia and MM, MDS, MCL or FL are outlined in Section 4.2 of the SmPC. Warnings regarding the risk of thrombocytopenia in patients treated with lenalidomide are provided in Sections 4.4 and 4.8 of the SmPC.

2. LIMITATIONS OF ADVERSE DRUG REACTION DETECTION IN CLINICAL TRIAL DEVELOPMENT PROGRAMMES

The clinical development programme is unlikely to detect rare adverse reactions. Patients with FL, relapsed or refractory MM, del 5q MDS and MCL have overall a limited survival time meaning that the trial programme may be limited in its ability to assess cumulative effects, and those effects with a long latency. Furthermore, these patients are, to a great extent, elderly with a limited natural life expectancy.

3. LIMITATIONS IN RESPECT TO POPULATIONS TYPICALLY UNDER-REPRESENTED IN CLINICAL TRIAL DEVELOPMENT PROGRAMMES

To ensure patient safety, specific populations of patients were excluded from the clinical studies (Table 27). Thus, experience in these populations is limited.

Table 27: 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.
Patients with renal impairment	**FL studies** In Studies NHL-007 and NHL-008, patients were required to have a baseline CLcr of ≥ 30 mL/min. In Study NHL-007, 13.7% and 10.8% of FL patients in the lenalidomide plus rituximab and rituximab plus placebo arms, respectively, had a baseline CLcr of ≥ 30 mL/min but < 60 mL/min. In Study NHL-008, 20.9% of FL patients had a baseline CLcr of ≥ 30 mL/min but < 60 mL/min. **TE NDMM studies** The TE NDMM studies had entry criteria for renal function, measured by either serum creatinine or CLcr. In Study CALGB 100104, patients were required to have CLcr ≥ 30 mL/min (after ASCT) prior to receiving maintenance therapy. In Study IFM 2005-02, patients were required to have serum creatinine < 160 µmol/L before and after ASCT, and serum creatinine < 250 µmol/L during ASCT. In both TE NDMM studies, there were no starting dose adjustments based on renal function specified for lenalidomide maintenance. The majority of patients in both studies had CLcr ≥ 50 mL/min at post-ASCT. In Study CALGB 100104, 3 patients (1.3%) in the lenalidomide arm (no patients in the placebo arm) and in Study IFM 2005-02, no patients in the lenalidomide arm and only one patient in the placebo arm (0.4%) had severe renal insufficiency (CLcr < 30 mL/min) post-ASCT. The proportions of patients with moderate renal impairment (CLcr ≥ 30 mL/min to < 50 mL/min) were 8.5% and 6.3% in the lenalidomide and placebo arms of Study CALGB 100104, respectively, and 3.1% and 2.5% in the lenalidomide and placebo arms of Study IFM 2005-02, respectively. **TNE NDMM studies** In Study SWOG S0777, patients were required to have a calculated or measured CLcr > 30 cc/min. Across both arms (RVd and Rd), approximately 70% of patients had baseline creatinine values of ≥ 60 mL/min, while 30% entered with a baseline creatinine value of < 60 mL/min and 17.7% of patients entered had a CLcr < 50 mL/min. Approximately half of patients enrolled in TNE NDMM Studies MM-020 and MM-015 had some degree of renal insufficiency (CLcr < 60 mL/min).

Table 27: Exposure of Special Populations Included or Not in Clinical Trial Development Programmes (Continued)

Type of Special Population	Exposure
	RRMM studies In Study MM-009, 22.4% of patients in each treatment arm had relevant medical history/concomitant disease in the renal and urinary disorder system organ class (SOC). In Study MM-010, 12.5% of patients in the lenalidomide/dexamethasone arm and 14.9% of patients in the placebo/dexamethasone arm had relevant medical history/concomitant disease in the renal and urinary disorder SOC. **MDS studies** In total, 17.6% of patients in Study MDS-003, and 11.6%, 5.8% and 6.0% of patients in the lenalidomide 10 mg, 5 mg and placebo groups, respectively, in Study MDS-004 had relevant medical history/concomitant disease in the renal and urinary disorder SOC. **MCL studies** Patients with severe renal impairment (CLcr < 30 mL/min) were excluded from the clinical studies in MCL. In Study MCL-002, 77.6% of all enrolled patients had normal renal function or mild renal impairment at baseline whereas 21.7% had moderate renal impairment (30 mL/min ≤ CLcr < 60 mL/min). **PK study** A multi-centre study (CC-5013-PK-001) has been performed with lenalidomide 25 mg daily as a single oral dose in 5 groups of patients (total 30 patients) with non-malignant conditions and defined by renal function (normal, mild impairment, moderate impairment, severe impairment and end-stage renal disease). Dose adjustment for patients with moderate or severe impaired renal function or end stage renal disease are provided in Section 4.2 the SmPC.
Patients with moderate to severe hepatic impairment	These patients were excluded from the clinical development programme.
Patients with uncontrolled cardiovascular disorders (including congestive heart failure, hypertension , or cardiac arrhythmia) and MI within 6 months prior to enrollment	These patients were excluded from the clinical development programme.
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	**FL studies** In Study NHL-007, patients were required to have documented relapsed, refractory, or progressive disease after previous treatment with at least one prior systemic chemotherapy, immunotherapy or rituximab plus chemotherapy and had to have received at least 2 previous doses of rituximab. Overall, 74.1% of FL patients in Study NHL-007 had advanced disease (Ann Arbor Stage III/IV) and 34.0% had high-risk FLIPI scores. In Study NHL-008, 88.7% of FL patients had advanced disease (Ann Arbor Stage III/IV).

Table 27: Exposure of Special Populations Included or Not in Clinical Trial Development Programmes (Continued)

Type of Special Population	Exposure
Patients with a disease severity different from inclusion criteria in clinical trials (Continued)	**TE NDMM studies** In Studies CALGB 100104 and IFM 2005-02, of the patients treated with lenalidomide, 16.5% and 21.8% of patients, respectively, had ISS Stage III at diagnosis. In Study CALGB 100104, 3 patients (1.3%) in the lenalidomide arm (no patients in the placebo arm) and in Study IFM 2005-02, no patients in the lenalidomide arm and only one patient in the placebo arm (0.4%) had severe renal insufficiency (CLcr < 30 mL/min) post-ASCT. **TNE NDMM studies** In Study SWOG S0777, patients in general had distribution of disease severity that was similar to what is reported and expected in studies of NDMM. Of note, at baseline, 33.1% of patients were ISS Stage III; 12.6% of patients had cytogenic risk classified as high; 3.3% of patients had an ECOG performance status of 3, and 14.5% of patients presented with a high lactate dehydrogenase value (> 280 IU/L). In general, patients in Study MM-020 had advanced-stage disease: of the total study population, 40.6% had ISS Stage III, 9.1% had severe renal insufficiency (CLcr < 30 mL/min), 71.2% had a history of bone disease, and 13.5% had radiation for MM prior to treatment in the study. About a third (33.5%) of the study patients had cytogenetic profiles associated with adverse risk (defined as t[4;14], t[14;16], del[13q] or monosomy 13, del[17p], or 1q gain), while 18.3% of patients overall presented with baseline lactate dehydrogenase values of 200 U/L or higher. In Study MM-015, it is noteworthy that approximately half of the patients in each treatment arm were ISS Stage III; and approximately half had CLcr < 60 mL/min. **RRMM studies** Participants in Studies MM-009 and MM-010 had a history of disease progression after at least one prior antimyeloma regimen (with at least 2 cycles of treatment), measurable levels of serum (> 0.5 mg/dL) and urine (≥ 0.2 g excreted in a 24 hour collection sample) M-paraprotein, and an Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1 or 2. The majority of patients had Stage II or III MM; however, a small but comparable proportion of patients in each treatment group of both studies had Stage I disease (1.8% and 6.3% in the lenalidomide/dexamethasone arm versus 2.3% and 4.6% in the placebo/dexamethasone arm of Studies MM-009 and MM-010, respectively). **MDS studies** In Study MDS-003, all 148 patients had a del 5q cytogenetic abnormality, and the majority had low or INT-1-risk MDS (118/148; 79.7%). Seven (4.7%) and two (1.4%) patients had INT-2 and high-risk MDS, respectively. In Study MDS-004, 93.2% of patients overall had a del 5q cytogenetic abnormality, and the majority had low or INT-1-risk MDS (144/205; 70.2%). Ten (4.9%) patients overall had INT-2 risk-MDS, and a single patient in the lenalidomide 10 mg group had high-risk MDS. IPSS score was missing for 50 of the 205 patients (24.4%). Therefore, limited data are available for the use of lenalidomide in the higher risk group. It should be noted that patients with INT-2 and high-risk MDS have a poor prognosis, with median survival durations of 1.2 and 0.4 years, respectively (Greenberg, 1997).

Table 27: Exposure of Special Populations Included or Not in Clinical Trial Development Programmes (Continued)

Type of Special Population	Exposure
Patients with a disease severity different from inclusion criteria in clinical trials (Continued)	**MCL studies** In Study MCL-002, patients generally had advanced stage disease: 91.3% of all patients randomised had MCL Stage III or IV at diagnosis. Furthermore, 33.5% of patients had high-risk Mantle cell lymphoma International Prognostic Index (MIPI) score at baseline, 42.9% had high tumour burden at baseline, and 19.7% had bulky disease. For 79 patients, data on bone marrow were available at baseline. For 34 (43.0%) of these patients, disease involvement in the bone marrow was positive (ie, the biopsy showed unequivocal cytologic or architectural evidence of malignancy). Few patients (15.0%) had an ECOG performance score of 2 at baseline. Patients with ECOG performance scores of 3 or 4 were excluded.
Population with relevant different ethnic origin	The PK and safety of lenalidomide were compared between healthy Japanese and Caucasian subjects in a Phase 1, randomised, double-blind, placebo-controlled, single-dose study. The concentration-time profiles for the Japanese and Caucasian subjects were similar at all 3 lenalidomide dose levels (5 mg, 10 mg, and 20 mg). There were no statistically significant differences ($p > 0.05$) in the PK parameters between Japanese and Caucasian subjects at each dose level. C_{max} and AUC extrapolated to time infinity increased proportionally with doses from 5 mg to 20 mg in both ethnic groups. No ethnicity-related trends were observed in AEs, clinical laboratory tests, vital signs, and ECGs. In Study NHL-007, patients were predominantly white with 90 (61.6%) and 92 (62.2%) white FL patients receiving treatment with lenalidomide plus rituximab and rituximab plus placebo, respectively. In Study NHL-008, 164 (92.7%) FL patients who received lenalidomide plus rituximab were white. In the TE NDMM Study CALGB 100104, patients were predominantly of white or Caucasian race with 169 (75.4%) and 167 (75.6%) white/Caucasian patients receiving maintenance treatment with lenalidomide and placebo, respectively. Data on race were not collected in Study IFM 2005-02. In the TNE NDMM study SWOG S0777, 79.7% of patients were Caucasian, 13.7% were Black or African-American, 2.3% were Asian, 1.1% were Native Hawaiian or other Pacific Islander, 0.6% were American Indian or Alaska Native, and 2.5% were of Unknown race. Patients were predominantly of white or Caucasian (89.0%) race, non-Hispanic or Latino (92.8%) ethnicity, and recruited in Europe (68.6%) in Study MM-020, and the majority of patients were of white or Caucasian (98.7%) race and non-Hispanic or Latino (99.8%) ethnicity in Study MM-015. In the RRMM studies performed in the USA, Canada, Australia, Europe, Israel and Ukraine, 88.7% of patients in the lenalidomide/dexamethasone arm were categorised as white, 7.6% of these patients were categorised as black, 0.8% were categorised as Hispanic, 1.7% were categorised as Asian/Pacific Islander and 1.1% were categorised as other. The lenalidomide PK in Asian RRMM patients (Studies CC-5013-MM-017 and CC-5013-MM-021) are comparable to that historically observed in Caucasian RRMM patients.

Table 27: Exposure of Special Populations Included or Not in Clinical Trial Development Programmes (Continued)

Type of Special Population	Exposure
Population with relevant different ethnic origin (Continued)	In the del 5q MDS studies, which were performed in the USA, Europe and Israel, the majority of patients were white (96.6% and 98.5% for Studies MDS-003 and MDS-004, respectively). The PK of lenalidomide in Japanese patients with del 5q MDS (Study CC-5013-MDS-007-PK) were comparable to that historically observed in the Caucasian MM or MDS patients. In the studies in MCL, the majority of patients were of white or Caucasian race. In Study MCL-002, 94.9% of all patients randomised were of white race.
Subpopulations carrying relevant genetic polymorphisms	Lenalidomide is not metabolised by the CYP enzymes. Genetic polymorphisms have not been studied in the lenalidomide clinical trial population. A tumour protein (TP) 53 mutation is present in approximately 20% to 25% of lower-risk MDS del 5q patients and is associated with a higher risk of progression to AML. In a post-hoc analysis of a clinical trial of Revlimid in low- or INT-1-risk MDS (Study MDS-004), the estimated 2-year rate of progression to AML was 27.5% in patients with immunohistochemistry (IHC)-p53 positivity and 3.6% in patients with IHC-p53 negativity ($p = 0.0038$) (SmPC, Sections 4.4 and 4.8).
Other	**Paediatric Population:** Lenalidomide is not authorised for use in children in the EU/EEA or elsewhere in the world. Class waivers for MM and all mature B cell neoplasms in paediatrics and product-specific waivers for MCL, MDS and all mature B cell neoplasms in paediatrics have been granted by the Paediatric Committee (PDCO) at the EMA (Decision dated 04 Oct 2017). There is limited experience with lenalidomide from investigator-initiated trials (IITs) in children. Lenalidomide should not be used in the paediatric age group (0 to 17 years) outside of a clinical trial. Data for cumulative paediatric exposure in the EU/EEA Member States from product launch to 26 Dec 2017 (where such data are available) are presented in Part II SV, Section 2. The cumulative paediatric commercial exposure for lenalidomide is 257 patients as of 26 Dec 2017. In total, 17 paediatric patients with relapsed/refractory AML were treated with lenalidomide in the Celgene-sponsored Study CC-5013-AML-002, which was conducted in the US and Canada, and accounts for all known paediatric exposure within the clinical trial setting.

PART II – MODULE SV: POSTAUTHORISATION EXPERIENCE

1. POSTAUTHORISATION EXPOSURE

1.1. Method Used to Calculate Exposure

Exposure to lenalidomide in the US is obtained through the Revlimid REMS® (formerly RevAssist®) Program and for Canada through the RevAid® Program. For other regions, estimates of patient exposures are based on Celgene reported pack level sales by country for the defined period of time. The number of packs per cycle and latest estimates for average duration across indications (represented as the percentage remaining on therapy after 1 month, 2 months, etc.) are factored into the number of total packs sold such that a varied patient consumption is accounted for (eg, some patients will be ending their therapy during the specified period having started their therapy prior to the period, some patients will be initiating their therapy in the beginning of the period, and some will be initiating at the end. All of which is calculated as an "average realised duration" and used as the factor to be applied to total packs sold for calculating patient exposures for the period).

1.2. Exposure

Cumulatively, as of 26 Dec 2017, approximately 637,832 patients have been exposed to commercial lenalidomide. To adjust for IITs, patients who receive lenalidomide in the US through the REMS Program and in Canada through RevAid®, the cumulative total as derived from the various programs (656,639) has been reduced by 18,807 to avoid double counting these exposures. Overall, approximately 36.0% of the commercial exposures (229,900/637,832) occurred in the US, while an estimated 248,762 patients have been exposed to commercial lenalidomide in the EEA, 32,863 patients have been exposed to commercial lenalidomide in Japan; 14,379 in Canada; 8826 in Australia/New Zealand; 6358 in China, and the remaining 96,744 patients exposed to commercial lenalidomide in the rest of the world. These figures include compassionate use or named patient/expanded access programmes in territories where lenalidomide has not been commercially launched.

A summary of worldwide commercial exposure is provided in Table 28.

Table 28: Summary of Worldwide Commercial Exposure

Location	Cumulative
US	229,900
EEA	248,762
Japan	32,863
Canada	14,379
Australia/New Zealand	8826
China	6358
Rest of World	96,744
TOTAL	**637,832**

EEA = European Economic Area; US = United States of America

2. EXPOSURE WITHIN THE EU/EEA MEMBER STATES

As of 26 Dec 2017, lenalidomide has been approved in 31 EU/EEA Member States: Austria, Belgium, Bulgaria, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Liechtenstein, Lithuania, Luxembourg, Malta, Norway, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden, The Netherlands and the UK.

Of the EU/EEA Member States which have launched, information regarding off-label use is available for 23 countries (Table 29 to Table 32) due to the implemented controlled distribution programme. It should be noted that the methodology for monitoring off-label use varies per country, as does the level of detail which can currently be collected.

Factors which may determine the methodology agreed with the NCA to monitor off-label use include local healthcare systems, the role of the physician/pharmacy in the local PPP process and the local prescription process. It is not always possible to obtain information on the postmarketing use of lenalidomide by indication in all EU/EEA Member States. Similarly, it is not possible to obtain patient demographic information, including the childbearing status of the patient, in most Member States.

In some Member States, it is not possible for the MAH to hold specific information which links a specific patient to identifiable information such as demographics, childbearing potential status or indication. In some countries it is considered unacceptable by both the patient and the physician for the pharmacist to hold sensitive information such as childbearing potential status or indication, as the order will go directly from the pharmacist to the distributor, the pharmacist will not be able to provide this level of information with an order. Due to these considerations, the MAH has worked with each NCA to come to an agreement as to how monitoring of off-label use will be evaluated.

As a result, in some Member States the data represents all market exposure, whereas in others a sample has been taken either through a pharmacy self-audit process or survey in order to give an estimation of the proportion of off-label use. In some Member States it has been possible to identify unique patients and hence provide exposure data in terms of patient numbers.

Data on EU/EEA Member States as pertains to cumulative exposure up to 26 Dec 2017 in adults, females of childbearing potential (FCBP), and paediatric use (where such data are available) are presented in Table 29 and Table 30. In the EU/EEA Member States, the most common indications for which lenalidomide has been used up to 26 Dec 2017 are presented in Table 31 and Table 32. Comparisons should be treated with caution, however, as in some cases the data are derived from all patients exposed and in other cases from a sample.

Table 29: EEA Lenalidomide Estimated Patient Exposure by Country from Implemented Controlled Distribution System

Country	Number of Patients (%)															
	Exposure Cumulative Period															
	MM		MDS		MCL		Off-label		Adults		FCBP		Children		Total Exposure	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Austria	4613	78	175	3	71	1	1024	17	NA	NA	0	0	0	0	5883	100
Belgium	7356	94	265	3	4	0	197	3	7429	95	49	1	1	0	7822	100
Croatia	104	97	1	1	0	0	2	2	107	100	0	0	0	0	107	100
Cyprus	111	96	3	3	0	0	2	2	116	100	0	0	0	0	116	100
Czech Republic	2376	93	164	6	2	0	2	0	2533	100	NA	NA	0	0	2544	100
Estonia	218	96	10	4	0	0	0	0	228	100	4	2	0	0	228	100
Greece	4427	90	394	8	10	0	97	2	4928	100	68	1	0	0	4928	100
Hungary	562	81	97	14	0	0	39	6	698	100	5	1	0	0	698	100
Ireland	5532	83	72	1	38	1	1025	15	6665	100	173	3	2	0	6667	100
Italy	18,288	78	1272	5	131	1	3871	16	NA	NA	NA	NA	NA	NA	23,562	100
Latvia	7	100	0	0	0	0	0	0	7	100	0	0	0	0	7	100
Lithuania	86	98	0	0	0	0	2	2	88	100	NA	NA	0	0	88	100
Luxembourg	423	95	15	3	0	0	8	2	398	89	7	2	0	0	446	100
Malta	60	82	0	0	1	1	12	16	60	82	2	3	0	0	73	100
Poland	3650	93	260	7	3	0	28	1	3941	100	141	4	0	0	3941	100
Slovakia	1471	83	63	4	1	0	227	13	NA	NA	NA	NA	NA	NA	1762	100
Slovenia	938	99	8	1	0	0	0	0	946	100	NA	NA	0	0	946	100
UK	12,244	80	325	2	49	0	2630	17	15,224	100	176	1	4	0	15,248	100
Total	62,466	83	3124	4	310	0	9166	12	43,368	58	625	1	7	0	75,066	100

AE = adverse event; AIFA = Agenzia Italiana del Farmaco; del(5q) = deletion 5q; EEA = European Economic Area; FCBP = females of childbearing potential; FNCBP = females not of childbearing potential; MCL = mantle cell lymphoma; MDS = myelodysplastic syndrome; MM = multiple myeloma; NA = not available; RMP = Risk Management Plan; UK = United Kingdom.

Belgium: For cumulative data: age category included 7429 confirmed adult patients, 1 child patient, 390 unknown patients, and 2 inconclusive patients; risk category included 4327 male patients, 3465 female patients, 1 unknown patient, and 29 inconclusive patients.

Croatia:	Cumulative data exposure is from 02 Nov 2016, when lenalidomide AE materials were approved.
Greece:	MDS data include only del(5q) patients. Approval was received for MCL on 27 Jul 2017; MCL was considered off-label use prior to this date. Cumulatively, 394 patients received lenalidomide for MDS, 10 patients for MCL, and 20 patients for MDS other than del(5q) (off-label use).
Hungary:	A patient identification system change in 2016 carries some uncertainty for cumulative data.
Ireland:	Cumulative data included 166 patients of unknown gender.
Italy:	Available data on approved indications originated from the AIFA Registry until 2013. From 2013 and onwards, available data on approved indications originate from sales data. Data regarding age and risk categories are not available.
Latvia:	In the previous reporting period, there was 1 patient given lenalidomide for off-label use. After further clarification, this patient is now included cumulatively in the MM category.
Poland:	The previous method of calculation was based on sales data; however, there has now been a change to the methodology used to collect patient exposure by using only RMP data. Effective for this period and onward, the methodology used will now be based on RMP data. The cumulative period was from 11 Sep 2009 until 26 Dec 2017.
Slovakia:	The cumulative period reflects 09 Apr 2009 to 31 Dec 2017.
UK:	Revlimid UK exposure data provided in this report are based on the reporting period to 26 Dec 2016.

Table 30: EEA Lenalidomide Estimated Exposure by Country based on Surrogates* for Off-label Use

*surrogates: medical inquiries or free of charge supply requests received by Celgene

Country	Number of Patients (%)															
	Exposure Cumulative Period															
	MM		MDS		MCL		Off-label		Adults		FCBP		Children		Total Exposure	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Denmark	1	8	3	23	1	8	8	62	NA	NA	NA	NA	0	0	13	100
Finland	6	38	0	0	1	6	9	56	NA	NA	NA	NA	0	0	16	100
France	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Germany	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Iceland	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Netherlands	NA	NA	NA	NA	NA	NA	224	100	NA	NA	NA	NA	NA	NA	224	100
Norway	2	11	2	11	1	6	13	72	NA	NA	NA	NA	NA	NA	18	100
Portugal	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Spain	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Sweden	4	13	4	13	2	7	20	67	NA	NA	NA	NA	1	3	30	100
Total	13	4	9	3	5	2	274	91	0	0	0	0	1	0	301	100

AML = acute myeloid leukaemia; ASCT = autologous stem cell transplantation; CLL = chronic lymphocytic leukaemia; del(5q) = deletion 5q; EEA = European Economic Area; FCBP = females of childbearing potential; FL = follicular leukaemia; MCL = mantle cell lymphoma; MDS = myelodysplastic syndrome; MM = multiple myeloma; NA = not available; NHL = non-Hodgkin lymphoma; NPP = Named Patient Programme; PC = prostate cancer; PPP = Pregnancy Prevention Programme; PSUR = Periodic Safety Update Report; RM = Risk Management; RVd = lenalidomide plus Velcade (bortezomib) plus dexamethasone; SCT = stem cell transplantation.

Denmark: From the date of launch of lenalidomide in Denmark (03 Dec 2007) until 26 Dec 2017, 13 queries have been received regarding its use in MM maintenance treatment (1), MDS (3), myelofibrosis (2), Richter's syndrome (1), Prurigo Nodulus Hyder (1), dermatological condition (1), chronic myeloproliferative syndrome (1), MCL (1), PC (1), and lymphomas (1).

Finland: From the date of launch of lenalidomide in Finland (26 May 2008) until 26 Dec 2017, 16 queries have been received regarding the use in MM maintenance treatment (3), myelofibrosis (2), CLL (2), AML (2), azacitidine plus lenalidomide combination therapy in AML (1), plasmacytoma (1), MCL (1), allogeneic SCT in MM (1), combination regimens with lenalidomide in MM (lenalidomide plus chemotherapy and lenalidomide plus bendamustine) (1), RVd combination in MM (1), and dermatology (1).

France: No cumulative data are available.

Germany: Germany RM does not dispose on exposure data originating from the implemented controlled distribution system.

Iceland: From the date of launch of lenalidomide in Iceland (05 Mar 2010) until 26 Dec 2017, no queries about off-label use have been received.

Netherlands: Only off-label use data from the NPP is available. Total exposure is based on off-label use only.

Norway: From the date of launch of lenalidomide in Norway (03 Dec 2007) until 26 Dec 2017, 18 queries have been received regarding the use of RVd combination as induction and maintenance/consolidation therapy for myeloma (1), plasma cell leukaemia (2), amyloidosis (2), myelofibrosis (3), consolidation therapy after ASCT for MM (1), MCL (1), FL (1), lenalidomide plus bendamustine plus rituximab combination therapy (1), lenalidomide plus romidepsin combination therapy (1), pre-allogeneic SCT use of lenalidomide plus azacitidine in MDS (1), lenalidomide plus bevacizumab combination therapy (1), use in ovarian cancer (2), and use of lenalidomide high-risk MDS non-del(5q) in combination with azacitidine (1).

Portugal: The lenalidomide PPP in place in Portugal does not collect exposure data.

Spain: Exposure data are not available.

Sweden: From the date of launch of lenalidomide in Sweden (14 Mar 2008) until 26 Dec 2017, 30 queries have been received regarding the use in newly diagnosed MM (1), plasma cell leukaemia (1), malignant B-cell lymphoma (1), MCL (2), low-dose lenalidomide pre-allogeneic SCT (1), MM maintenance (1), MDS (4), amyloidosis (1), AML (2), lenalidomide in combination with radiation therapy (1), PC (1), NHL (2), polycythaemia vera (1), stem cell mobilisation (1), children (1), lenalidomide plus cyclophosphamide combination therapy (1), colon cancer (1), consolidation/maintenance treatment (2), novel treatment combinations in MM (1), lymphoma (1), transplant-eligible patients (1), plasmacytoma (1), and induction and maintenance treatment in ASCT myeloma (1).

Table 31: EEA Lenalidomide Estimated Patient Exposure by Country and Indication from Implemented Controlled Distribution System

Country	Number of Patients (%)															
	Exposure Cumulative Period															
	MM		MDS		MCL		Amyloidosis		Myelofibrosis		CLL		Other		Total Exposure	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Austria	4613	78	175	3	71	1	79	1	75	1	77	1	793	13	5883	100
Belgium	7356	94	265	3	4	0	7	0	11	0	4	0	175	2	7822	100
Croatia	104	97	1	1	0	0	0	0	0	0	0	0	2	2	107	100
Cyprus	111	96	3	3	0	0	1	1	0	0	0	0	1	1	116	100
Czech Republic	2376	93	164	6	2	0	0	0	0	0	0	0	2	0	2544	100
Estonia	218	96	10	4	0	0	0	0	0	0	0	0	0	0	228	100
Greece	4427	90	394	8	10	0	2	0	7	0	4	0	84	2	4928	100
Hungary	562	81	97	14	0	0	0	0	1	0	0	0	38	5	698	100
Ireland	5532	83	72	1	38	1	48	1	37	1	48	1	892	13	6667	100
Italy	18,288	78	1272	5	131	1	366	2	62	0	113	0	3330	14	23,562	100
Latvia	7	100	0	0	0	0	0	0	0	0	0	0	0	0	7	100
Lithuania	86	98	0	0	0	0	0	0	0	0	0	0	2	2	88	100
Luxembourg	423	95	15	3	0	0	0	0	1	0	0	0	7	2	446	100
Malta	60	82	0	0	1	1	1	1	0	0	0	0	11	15	73	100
Poland	3650	93	260	7	3	0	2	0	1	0	3	0	22	1	3941	100
Slovakia	1471	83	63	4	1	0	2	0	56	3	0	0	169	10	1762	100
Slovenia	938	99	8	1	0	0	0	0	0	0	0	0	0	0	946	100
UK	12,244	80	325	2	49	0	121	1	9	0	21	0	2479	16	15,248	100
Total	62,466	83	3124	4	310	0	629	1	260	0	270	0	8007	11	75,066	100

AE = adverse event; AIFA = Agenzia Italiana del Farmaco; CLL = chronic lymphocytic leukaemia; del(5q) = deletion 5q; EEA = European Economic Area; MCL = mantle cell lymphoma; MDS = myelodysplastic syndrome; MM = multiple myeloma; OMF = osteomyelofibrosis; OMS = osteomyelosclerosis; PMF = primary myelofibrosis; UK = United Kingdom.

Austria:	In Austria, a new approach to calculate exposure has been taken whereby synonyms of myelofibrosis have been identified for inclusion in the myelofibrosis category (OMF, OMS, PMF, and primary OMF). This approach has been applied retrospectively, resulting in recategorisation of some patients in the cumulative period.
Croatia:	Cumulative data exposure is from 02 Nov 2016, when lenalidomide AE materials were approved.
Greece:	MDS data include only del(5q) patients. Approval was received for MCL on 27 Jul 2017; MCL was considered off-label use prior to this date. Cumulatively, 7 patients received lenalidomide for myelofibrosis, 2 patients for amyloidosis, and 20 patients for MDS other than del(5q) (off-label use).
Hungary:	A patient identification system change in 2016 carries some uncertainty for cumulative data.
Ireland:	After review of cumulative data it was noted that a patient with polylymphatic leukaemia had been included with CLL patients in error; this has been corrected.
Italy:	Available data on approved indications originated from the AIFA Registry until 2013. From 2013 and onwards, available data on approved indications originate from sales data.
Latvia:	In the previous reporting period, there was 1 patient included in the Other category. After further clarification, this patient is now included cumulatively in the MM category.
Poland:	Patient exposure is based on the order form forwarded by the wholesaler to the vendor [redacted] on behalf of Celgene. The cumulative period was from 11 Sep 2009 until 26 Dec 2017.
Slovakia:	The cumulative period reflects 09 Apr 2009 to 31 Dec 2017.
UK:	Revlimid UK exposure data provided in this report are based on the reporting period to 26 Dec 2016.

Table 32: EEA Lenalidomide Estimated Exposure by Country and Indication based on Surrogates* for Off-label Use

*surrogates: medical inquiries or free of charge supply requests received by Celgene

Country	Number of Patients (%)															
	Exposure Cumulative Period															
	MM		MDS		MCL		Amyloidosis		Myelofibrosis		CLL		Other		Total Exposure	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Denmark	1	8	3	23	1	8	0	0	2	15	0	0	6	46	13	100
Finland	6	38	0	0	1	6	0	0	2	13	2	13	5	31	16	100
France	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Germany	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Iceland	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Netherlands	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	224	100
Norway	2	11	2	11	1	6	2	11	3	17	0	0	8	44	18	100
Portugal	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Spain	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Sweden	4	13	4	13	2	7	1	3	0	0	0	0	19	63	30	100
Total	13	4	9	3	5	2	3	1	7	2	2	1	38	13	301	100

AML = acute myeloid leukaemia; ASCT = autologous stem cell transplantation; CLL = chronic lymphocytic leukaemia; del(5q) = deletion 5q; EEA = European Economic Area; FL = follicular leukaemia; MCL = mantle cell lymphoma; MDS = myelodysplastic syndrome; MM = multiple myeloma; NA = not available; NHL = non-Hodgkin lymphoma; NPP = Named Patient Programme; PC = prostate cancer; PPP = Pregnancy Prevention Programme; PSUR = Periodic Safety Update Report; RM = Risk Management; RVd = lenalidomide plus Velcade (bortezomib) plus dexamethasone; SCT = stem cell transplantation.

Denmark: From the date of launch of lenalidomide in Denmark (03 Dec 2007) until 26 Dec 2017, 13 queries have been received regarding the use in MM maintenance treatment (1), MDS (3), myelofibrosis (2), Richter's syndrome (1), Prurigo Nodulus Hyder (1), dermatological condition (1), chronic myeloproliferative syndrome (1), MCL (1), PC (1), and lymphomas (1).

Finland: From the date of launch of lenalidomide in Finland (26 May 2008) until 26 Dec 2017, 16 queries have been received regarding the use in MM maintenance treatment (3), myelofibrosis (2), CLL (2), AML (2), azacitidine plus lenalidomide combination therapy in AML (1), plasmacytoma (1), MCL (1), allogeneic SCT in MM (1), combination regimens with lenalidomide in MM (lenalidomide plus chemotherapy and lenalidomide plus bendamustine) (1), RVd combination in MM (1), and dermatology (1).

France: No cumulative data are available.

Germany: Germany RM does not dispose on exposure data originating from the implemented controlled distribution system.

Iceland: From the date of launch of lenalidomide in Iceland (05 Mar 2010) until 26 Dec 2017, no queries about off-label use have been received.

Netherlands: Only off-label use data from the NPP is available. Total exposure is based on off-label use only.

Norway: From the date of launch of lenalidomide in Norway (03 Dec 2007) until 26 Dec 2017, 18 queries have been received regarding the use of RVd combination as induction and maintenance/consolidation therapy for myeloma (1), plasma cell leukaemia (2), amyloidosis (2), myelofibrosis (3), consolidation therapy after ASCT for MM (1), MCL (1), FL (1), lenalidomide plus bendamustine plus rituximab combination therapy (1), lenalidomide plus romidepsin combination therapy (1), pre-allogeneic SCT use of lenalidomide plus azacitidine in MDS (1), lenalidomide plus bevacizumab combination therapy (1), use in ovarian cancer (2), and use of lenalidomide high-risk MDS non-del(5q) in combination with azacitidine (1).

Portugal: The lenalidomide PPP in place in Portugal does not collect exposure data.

Spain: Exposure data are not available.

Sweden: From the date of launch of lenalidomide in Sweden (14 Mar 2008) until 26 Dec 2017, 30 queries have been received regarding the use in newly diagnosed MM (1), plasma cell leukaemia (1), malignant B-cell lymphoma (1), MCL (2), low-dose lenalidomide pre-allogeneic SCT (1), MM maintenance (1), MDS (4), amyloidosis (1), AML (2), lenalidomide in combination with radiation therapy (1), PC (1), NHL (2), polycythaemia vera (1), stem cell mobilisation (1), children (1), lenalidomide plus cyclophosphamide combination therapy (1), colon cancer (1), consolidation/maintenance treatment (2), novel treatment combinations in MM (1), lymphoma (1), transplant-eligible patients (1), plasmacytoma (1), and induction and maintenance treatment in ASCT myeloma (1).

PART II – MODULE SVI: ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

1. POTENTIAL FOR MISUSE FOR ILLEGAL PURPOSES

Lenalidomide has not been systematically studied in humans for its potential for abuse, tolerance or physical dependence. Based on its pharmacological properties, there is no anticipated risk of abuse or misuse for illegal purposes. To date, no safety signal has been identified relating to the misuse or abuse of lenalidomide.

PART II – MODULE SVII: IDENTIFIED AND POTENTIAL RISKS

1. IDENTIFICATION OF SAFETY CONCERNS IN THE INITIAL RMP SUBMISSION

The summary of the safety concerns in the initial RMP submission (Version 5.0) at time of authorisation (14 Jun 2007) is presented in Table 33. A description of the changes to the list of safety concerns in the approved RMPs is presented in Annex 8.

Table 33: Summary of Safety Concerns in the Initial RMP Submission

Important Identified Risks	Neutropenia and thrombocytopenia Infection Bleeding events Thrombosis/thromboembolism
Important Potential Risks	Foetal exposure Peripheral neuropathy Cardiac failure Cardiac arrhythmias QT prolongation Hypersensitivity Rash Hypothyroidism Renal failure
Missing Information	Long-term use Change in death rate Change in rate of progression of MDS to AML Use in renal failure

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 diseases being treated) include low grade abdominal pain, dyspepsia, nausea, dry mouth, stomatitis, dysphagia, toothache, vomiting, low grade colitis and low grade caecitis, fatigue, asthenia, pyrexia, oedema, influenza-like syndrome, chest pain, chills, cough, dyspnoea, rhinorrhoea, ataxia, balance impaired, headache, tremor, dysgeusia, lethargy, tinnitus and dizziness, muscle spasms, bone pain, musculoskeletal pain (including back pain and pain in extremity) and connective tissue pain and discomfort, arthralgia, myalgia, muscular weakness, joint swelling, insomnia, altered mood, loss of libido, haematuria, urinary retention, urinary incontinence, hyperhidrosis, skin hyperpigmentation, erythema, night sweats, skin discoloration, photosensitivity reaction, decreased appetite, weight decreased, C-reactive protein increased, hypomagnesemia, iron overload, and low grade hypertension.

Adverse reactions such as low grade blurred vision, reduced visual acuity, deafness, erectile dysfunction and higher grades of cataract and depression could have an impact on the quality of life; however, the clinical impact of these reactions is considered minimal in relation to the severity of the underlying life-threatening malignancy being treated. Other reactions such as haemolysis, autoimmune haemolytic anaemia, acquired hemophilia, acquired fanconi syndrome,

somnolence, hyperthyroidism and hypothyroidism are not considered important because only low grades were reported with the lenalidomide treatment group. Low grade events are not considered to have significant impact on the benefit-risk profile of lenalidomide in the target population.

Adverse reactions of higher grade with acceptable clinical impact on patients treated for life-threating oncologic diseases include renal tubular necrosis, gout, vasculitis, ischaemia, peripheral ischaemia, hemolytic anaemia, hypokalaemia, hypocalcaemia, hyperglycaemia, hyperuricaemia, hypophosphataemia, dehydration, syncope, rhabdomyolysis, pancreatitis, gastrointestinal perforations (including diverticular, intestinal and large intestine perforations), diabetes mellitus, hypotension, and respiratory distress. Some of the above reactions may have serious consequences but occur with a low frequency, such as rhabdomyolysis. These reactions are not considered to impact the benefit-risk profile of lenalidomide in the target population. The most current product information does not advise on specific clinical actions to be taken to minimise the risk and no additional risk minimisation measures are in place for these reactions. They are not considered to be important for the target population. These ADRs are included in Section 4.8 of the SmPC.

Haematological toxicities such as febrile neutropenia, anaemia, leucopenia, lymphopenia, and pancytopenia are already well known to health care professionals (HCPs). The HCPs have appropriate measures in place as part of routine clinical practice for prevention and treatment of these haematological toxicities. These reactions are included in Section 4.8 of the SmPC.

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

Important Identified Risks

Important Identified Risk	Risk-benefit Impact
Teratogenicity	Lenalidomide is a chemical analogue of thalidomide, a known human teratogen that causes severe life-threatening birth defects. In addition, lenalidomide induced malformations in the offspring of pregnant monkeys similar to those described with thalidomide. If lenalidomide is taken during pregnancy, a teratogenic effect of lenalidomide in humans is expected. Please see Section 3.1.1 for further details. Lenalidomide is contraindicated in pregnant women. Lenalidomide is subject to controlled distribution due to potential off-label use to treat malignancies in younger populations than the target population, and FCBP have to meet all the conditions of the PPP, which is intended to prevent the risk of embryofoetal exposure and thus reduce the potential teratogenic effects of lenalidomide exposure. The teratogenic effects in humans can be potentially serious or life-threatening to the foetus or unborn baby.

Important Identified Risk	Risk-benefit Impact
Serious Infection due to Neutropenia	In the FL studies, lenalidomide plus rituximab treatment was associated with a higher frequency of neutropenia AEs compared to rituximab plus placebo. In Study NHL-007, of the 50.7% lenalidomide-rituximab treated patients with ≥ Grade 3 neutropenia, 2.7% of the patients had concurrent serious infection. In Study NHL-008, of the 31.6% lenalidomide-rituximab treated patients with ≥ Grade 3 neutropenia, 10.7% of the patients had concurrent serious infection. Overall, in pooled Studies NHL-007 and NHL-008, of the 45.8% lenalidomide-rituximab treated patients with treatment-emergent neutropenia, 9.5% and 7.4%, experienced concurrent treatment-emergent Grade 3 or 4 and serious infection, respectively (Table 36). In NDMM, lenalidomide maintenance after ASCT is associated with a higher frequency of Grade 4 neutropenia compared to placebo maintenance. The combination of lenalidomide with dexamethasone in NDMM patients is associated with a lower frequency of Grade 4 neutropenia compared with MPT. In patients treated with lenalidomide in Study IFM 2005-02, of the 14.1% of patients with ≥ Grade 3 infection, only one-fourth (25.6%) of the patients had concurrent neutropenia and both of the patients (0.7%) who had ≥ Grade 4 infection had concurrent neutropenia (IFM 2005-02 CSR, Table 14.3-60 and Table 14.3-62). The combination of lenalidomide with melphalan and prednisone in NDMM patients is associated with a higher frequency of Grade 4 neutropenia compared with MPp+p. There was a higher frequency of Grade 4 febrile neutropenia observed. In patients treated with lenalidomide in NDMM Study MM-020, of the 29.3% of patients with ≥ Grade 3 infection, one-fifth (20.5%) of the patients had concurrent neutropenia (any grade); and of the 6.8% of patients with ≥ Grade 4 infection, less than one-fourth (22.2%) of the patients had concurrent neutropenia of any grade (MM-020 CSR, Table 14.3.2.3.22.2). The combination of lenalidomide with dexamethasone in MM patients is associated with a higher incidence of Grade 4 neutropenia. In MDS and MCL, lenalidomide is associated with a higher incidence of Grade 3 or 4 neutropenia. Severe/serious infections in the context of neutropenia may put the patient at an unacceptable risk of death and are considered important. Please see Section 3.1.2 for further details.
SPM	In NDMM patients receiving lenalidomide in combination with bortezomib and dexamethasone, the haematologic SPM incidence rate was 0.00 to 0.16 per 100 person-years and the incidence rate of solid tumour SPM 0.21 to 1.04 per 100 person-years. In clinical trials of newly diagnosed MM patients not eligible for transplant, a 4.9-fold increase in incidence rate of haematologic SPM (cases of AML, MDS) has been observed in patients receiving lenalidomide in combination with melphalan and prednisone until progression (1.75 per 100 person-years) compared with melphalan in combination with prednisone (0.36 per 100 person-years). A 2.12-fold increase in incidence rate of solid tumour SPM has been observed in patients receiving lenalidomide (9 cycles) in combination with melphalan and prednisone (1.57 per 100 person-years) compared with melphalan in combination with prednisone (0.74 per 100 person-years).

Important Identified Risk	Risk-benefit Impact
SPM (Continued)	The increased risk of SPM associated with lenalidomide is relevant also in the context of NDMM after stem cell transplantation. The incidence rate of haematologic malignancies, most notably AML, MDS and B-cell malignancies (including Hodgkin's lymphoma), was 1.31 per 100 person-years for the lenalidomide arms and 0.58 per 100 person-years for the placebo arms (1.02 per 100 person-years for patients exposed to lenalidomide after ASCT and 0.60 per 100 person-years for patients not-exposed to lenalidomide after ASCT). The incidence rate of solid tumour SPM was 1.36 per 100 person-years for the lenalidomide arms and 1.05 per 100 person-years for the placebo arms (1.26 per 100 person-years for patients exposed to lenalidomide after ASCT and 0.60 per 100 person-years for patients not-exposed to lenalidomide after ASCT). In clinical trials in previously treated myeloma patients with lenalidomide/dexamethasone compared to controls, mainly comprising of basal cell or squamous cell skin cancers. In clinical trials other than MM, SPM risk has been lower (MDS, MCL). In a relapsed/refractory study which included FL patients, no increased risk of SPM was observed in the lenalidomide/rituximab arm compared to the placebo/rituximab arm. Haematologic SPM of AML occurred in 0.29 per 100 person-years in the lenalidomide/rituximab arm compared with 0.29 per 100 person-years in patients receiving placebo/rituximab. The incidence rate of haematologic plus solid tumour SPMs was 0.87 per 100 person-years in the lenalidomide/rituximab arm, compared to 1.17 per 100 person-years in patients receiving placebo/rituximab. The diagnosis of a new malignancy is one of the most serious events experienced by a cancer survivor, and the identification of SPM and their treatment are critical. Please see Section 3.1.3 for further details.
Important Identified Risk Related to Indication/Target Population	
For MCL and FL: Tumour Flare Reaction (TFR)	In Study NHL-007, the proportion of FL patients experiencing at least one TFR event was higher among lenalidomide plus rituximab-treated patients than patients treated with rituximab plus placebo (risk ratio = 19.3 [95% CI: 2.6-143.9]). Tumour flare reaction AEs were reported for 7 lenalidomide plus rituximab-treated patients in Study NHL-008. In pooled Studies NHL-007 and NHL-008, TFR SAEs were reported for 2/323 (0.6%) lenalidomide plus rituximab-treated patients, both of which resolved. No TFR SAEs had an outcome of death. Less than 2% of lenalidomide plus rituximab-treated patients experienced Grade 3 or 4 AEs of TFR and TFR AEs leading to dose interruption. No patients experienced TFR AEs leading to dose discontinuation or reduction. TFR has been reported in MCL patients receiving lenalidomide. In Study MCL-002, approximately 10% of lenalidomide-treated patients experienced TFR compared with 0% in the control arm. The majority of the events occurred in Cycle 1, all were assessed as treatment-related, and the majority of the reports were Grade 1 or 2. Patients with high MIPI at diagnosis or bulky disease (at least one lesion $\geq$ 7 cm in the longest diameter) at baseline may be at risk of TFR. A Postauthorisation Safety Study (PASS) is being carried out to quantify and characterise the event of TFR by tumour burden and the proportion of early deaths by tumour burden in RRMCL patients receiving lenalidomide in a 'real world' setting. Please see Section 3.1.4 for further details.

Important Potential Risks

Important Potential Risk	Risk-benefit Impact
Cardiac Failure	In Study NHL-007, no cardiac failure events occurred in the lenalidomide plus rituximab arm. In Study NHL-008, cardiac failure AEs were reported in one (0.6%) lenalidomide plus rituximab-treated patient. In Studies NHL-007 and NHL-008, no cardiac failure SAEs were reported and no patients died due to an event of cardiac failure. Cardiac failure events occurred at a similar frequency in Arm MPT and Arm Rd18 (5.0% and 5.2%, respectively) but occurred with higher frequency in Arm Rd (8.8%) in TNE NDMM Study MM-020. When adjusted for treatment duration, the incidence of events was similar between Arm Rd (6.19 events per 100 PY,) Arm Rd18 (5.62), and Arm MPT (6.19). The incidence rate of events was highest and similar across arms during the first 6 months of treatment indicating that more events occurred in the first 6 months of treatment. Deaths due to cardiac disorders on study treatment were low and similar in Arms Rd, Rd18 and MPT. A PASS is being conducted to further characterise this safety concern in the recently added target population of TNE NDMM patients by investigating the aetiology of cardiovascular events in a 'real world' setting. Please see Section 3.1.5 for further details.
Cardiac Arrhythmias	In Study NHL-007, the proportion of patients experiencing at least one cardiac arrhythmia event was slightly higher in the lenalidomide plus rituximab arm than the rituximab plus placebo arm (8.8% and 11.6%, respectively; risk ratio = 1.3 [95% CI: 0.6-2.7]). Deaths due to cardiac arrhythmia were low: there was one death (0.7%) reported for a lenalidomide plus rituximab-treated patient in Study NHL-007 (PT: arrhythmia). In Study NHL-008, cardiac arrhythmia AEs were reported for 6.8% lenalidomide plus rituximab treated patients. One patient in this study died due to an event of cardiac arrhythmia (PT: cardio-respiratory arrest). Cardiac arrhythmia events occurred more frequently in Arm Rd compared with Arm Rd18 and MPT (25.0% versus 17.4% and 22.7%, respectively) in TNE NDMM Study MM-020. When adjusted for treatment duration, the incidence of events was higher in Arm MPT than Arm Rd and Arm Rd18. Grade 3 or 4 cardiac arrhythmias and SAEs of cardiac arrhythmias also occurred with generally similar frequencies across all arms. A PASS is being conducted to further characterise this safety concern by investigating the incidence and mortality associated with cardiovascular events and to utilise extensive risk factor information among TNE NDMM patients treated with a lenalidomide-containing regimen in a 'real world' setting. Please see Section 3.1.6 for further details.

Important Potential Risk	Risk-benefit Impact
Ischaemic Heart Disease (Including Myocardial Infarction)	In Study NHL-007, IHD events occurred at a low frequency in both the rituximab plus placebo and lenalidomide plus rituximab arms (1.4% and 0.7%, respectively). In Study NHL-008, IHD events were reported for 4.0% of lenalidomide plus rituximab-treated patients. There were no deaths due to IHD in the FL studies. Myocardial infarction has been reported in patients receiving lenalidomide, particularly in those with known risk factors. The overall frequency of myocardial infarction/ischaemic heart disease (MI/IHD) was slightly higher in Study MM-015 than in Study MM-020. In Study MM-020, an imbalance in the incidence of MI/IHD between the two lenalidomide-containing arms (Rd/Rd18) was observed during the first 6 months of treatment. Further investigation into the potential risk factors for MI/IHD did not yield an explanation for the difference in frequency of MI/IHD between arms with identical treatment during the first 6 months of the study. Therefore, such a difference may have resulted from unmeasured confounders before or after baseline, or due to some combination of different risk factors that have not yet been fully understood. Fatal outcomes have been observed although these were of low frequency. A PASS is being conducted to further characterise this safety concern by investigating the incidence and mortality associated with cardiovascular events and to utilise extensive risk factor information among TNE NDMM patients treated with a lenalidomide-containing regimen in a 'real world' setting. Please see Section 3.1.7 for further details.
Off-label Use	The risk of off-label use is monitored through the MDS PASS. Further characterisation of this risk is warranted and, therefore, this risk remains important. Please see Section 3.1.8 for further details.

Missing Information

None.

2. NEW SAFETY CONCERNS AND RECLASSIFICATION WITH A SUBMISSION OF AN UPDATED RMP

There are no changes to the Safety Concerns proposed.

3. DETAILS OF IMPORTANT IDENTIFIED RISKS, IMPORTANT POTENTIAL RISKS, AND MISSING INFORMATION

This section presents information on identified and potential risks that require further characterisation or evaluation. Sections 3.1.1 to 3.1.7 provide the clinical data for the respective indications.

Main and Supporting Studies

MM indication:

- NDMM-TE/TNE (RVd initial/induction therapy): Study SWOG S0777;
- NDMM-TE (maintenance post-autologous stem cell transplant): Studies CALGB 100104 and IFM 2005-02;
- NDMM-TNE: Studies MM-020 and MM-015.

RRMM indication: Studies MM-009 and MM-010.

Del 5q MDS indication: Studies MDS-003 and MDS-004.

MCL indication: Studies MCL-002, MCL-001, NHL-002 and NHL-003.

FL indication: Studies NHL-007 and NHL-008

Study MCL-003 (described in Section 1.1, Part II Module SIII) was stopped prematurely for reasons other than safety concerns after only nine patients had been enrolled (four in the lenalidomide arm, five in the placebo arm). No data from this study have been presented in the RMP.

RMP Search Strategy for Adverse Events Presentation

The RMP search criteria have been defined for each study based on the MedDRA version as noted in Table 34. 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. The MedDRA PTs for each of the Important Identified Risks and Important Potential Risks are shown in the respective tables in Section 3.1.

Table 34: RMP Search Criteria

Study	RMP Search Criteria[a]	MedDRA Version Used to Code AEs in Clinical Database
SWOG S0777	15.1	15.1
IFM 2005-02	15.1	15.1
CALGB 100104	15.1	15.1
GIMEMA[b]	15.1	15.1
MM-015	15.1	10.0
MM-020	15.1	15.1

Table 34: RMP Search Criteria (Continued)

Study	RMP Search Criteria[a]	MedDRA Version Used to Code AEs in Clinical Database
MM-009	13.0[c]	13.0
MM-010	13.0[c]	13.0
MDS-003	13.0	5.1
MDS-004	13.0	5.1
MCL-001	16.1	16.1
MCL-002	16.1	16.1
NHL-002	16.1	16.1
NHL-003	16.1	16.1
NHL-007	21.0	21.0
NHL-008	21.0	21.0

[a] For the risk of SPM, the RMP search criteria for each study were consistent to the MedDRA version used to code AEs in the clinical database.
[b] The GIMEMA study was only included for the SPM-related risks.
[c] For the RRMM studies MM-009 and MM-010, the search criteria for the important identified risks of Serious Infection due to Neutropenia, and the important potential risks of Cardiac Failure, Cardiac Arrhythmias, and Ischaemic Heart Disease (Including Myocardial Infarction) were defined in MedDRA Versions 5.1 and/or 11.0.

In Sections 3.1.1 to 3.1.7, the definition of "risk" of each event of interest is based on cumulative incidence (ie, the proportion of patients experiencing each event, or group of events), and also relative risk, where indicated.

SPM Search Strategy

A search for SPM from the clinical and safety databases was performed by retrieving and manually reviewing all MedDRA PTs in the Neoplasms Benign, Malignant, and Unspecified (Including Cysts and Polyps) SOC. Events deemed to not represent an SPM were excluded. Thus, events in the high level group terms (HLGTs) of metastases and neoplasm-related morbidities (eg, tumour lysis syndrome, tumour flare, and cancer pain); reports of most neoplasms clearly identifiable as benign except for meningioma, which was considered to be a solid tumour malignancy because the clinical course is not benign; events of disease progression of the underlying indication (eg, MM in a study investigating treatment for MM); and reports of pre-existing SPM were not included as SPM events in presentations or analyses in this RMP.

Data Collection

TEAEs:

Typically all AEs in Celgene-sponsored clinical studies are collected for 28 days post discontinuation of active treatment and 30 days post discontinuation of active treatment in the cooperative studies (CALGB 100104, IFM 2005-02 and RVd study SWOG S0777).

SPM:

Collection of SPM in clinical trials is continuing for the duration of the studies, from the time of signing the Informed Consent Document up to the time all patients have been followed for at least 5 years (a maximum of 6 years for SWOG S0777) from randomisation or have died. Due to the long-term nature of the SPM data collection and the different follow up times in the studies, these events are better understood through incidence rates rather than frequency only. For this reason, both frequencies and incidence rates have been included for the SPM risk assessment. For each SPM category, the incidence rate per 100 person-years was calculated as: (the number of patients with any SPM in the SPM category/total person-years)*100.

Data Presentation

It is important to note that pooling across indications (TE and TNE NDMM, RRMM, MDS, MCL and FL) for this section was not performed because of the basic differences in the pathophysiology of the indications, patient populations, treatment regimens, dose/dose intensity and schedules (cycle length) and route of administration across the indications. Treatment regimen for RVd as initial treatment in NDMM: 25 mg lenalidomide QD orally on Days 1 to 14 of a 21-day cycle for up to eight 3-week cycles with 1.3 mg/m^2 bortezomib IV on Days 1, 4, 8 and 11 and 20 mg dexamethasone QD orally on Days 1, 2, 4, 5, 8, 9, 11, and 12 (SWOG S0777); lenalidomide 25 mg QD orally 21/28 days cyclic regimen with dexamethasone or lenalidomide 10 mg QD orally 21/28 days cyclic regimen with melphalan and prednisone induction followed by lenalidomide maintenance with 10 mg QD orally 21/28 days cyclic regimen for TNE NDMM; lenalidomide maintenance 10 mg QD orally 28/28 days continuous regimen for TE NDMM; lenalidomide 25 mg QD orally 21/28 days cyclic regimen for RRMM, and lenalidomide 10 mg QD orally 21/28 days cyclic regimen, 10 mg QD orally 28/28 days cyclic regimen or 5 mg QD orally 28/28 days continuous regimen for MDS.

Pooling of Studies

Pooling was not performed for the MM indication primarily due to the different patient populations (TE versus TNE), disease setting, study designs, study treatment regimen (monotherapy, doublet versus triplet), dose/dose intensity and cycle length:

- In TE NDMM Study CALGB 100104, patients received maintenance treatment with either lenalidomide or placebo until disease progression. The starting dose of lenalidomide was 10 mg/day for the first 3 months, increased to 15 mg/day if tolerated. A conservative approach was applied to determine the adverse reactions from CALGB 100104. The adverse reactions included events reported post-HDM/ASCT as well as events from the maintenance treatment period.
- In TE NDMM Study IFM 2005-02, patients received maintenance treatment with either lenalidomide or placebo until relapse. The starting dose of lenalidomide was 10 mg/day for the first 3 months, increased to 15 mg if tolerated. With the exception of the SPM risks (SPM safety analysis population), data are presented for the maintenance period only in Study IFM 2005-02, and include AEs reported during the start of the maintenance period.
- The TNE RVd NDMM Study SWOG S0777 compared initial (induction) treatment with RVd versus Rd followed by continued Rd for all patients.

- The TNE NDMM Study MM-020 compared 3 regimens: lenalidomide with low-dose dexamethasone given until disease progression (Rd), or Rd given for eighteen 28-day cycles (Rd18 = 72 weeks); versus MPT given for twelve 6-week cycles (72 weeks).
- The TNE NDMM Study MM-015 compared the combination of melphalan/prednisone with or without lenalidomide during 9 cycles of induction followed by a maintenance phase comparing lenalidomide with placebo.

Pooling within the MDS indication (MDS-003 and MDS-004 studies), was not done because of the differences in the duration of exposure to lenalidomide and dosing. The median duration of exposure was 52.5 weeks for the 10 mg dose in MDS-003, and 50.3 weeks for the 10 mg dose, 18 weeks for the 5 mg dose, and 16 weeks for the placebo arm in MDS-004. Unless otherwise indicated, the data presented from Study MDS-004 are from the double-blind phase (N = 69 patients each in the 10 mg and 5 mg lenalidomide groups; N = 67 in the placebo group), and so do not include open-label phase results (during which placebo-treated patients could cross over to lenalidomide 5 mg) or the follow-up phase of Study MDS-004. The double-blind phase was 52 weeks including the first 16 weeks of which the patients in the placebo arm who did not achieve a minor response by Week 16 were given the option to cross over to the 5 mg lenalidomide arm. Details of the clinical study design for MDS-003 and MDS-004 are found in Part II Module SIII.

It is worth noting that in Study MCL-002, as of the 07 Mar 2014 data cutoff, the median treatment duration in the lenalidomide arm (24.3 weeks; range: 0.4, 241.9) was longer than in the control arm (13.1 weeks; range: 0.1, 157.9). This longer time on treatment was partially due to the fact that three of the investigator's choice drugs in the control arm (cytarabine, gemcitabine and fludarabine) were administered up to a maximum of 6 cycles (per protocol, based on standard of care), while lenalidomide was administered until PD or unacceptable toxicity.

3.1. Presentation of the Important Identified Risks and Important Potential Risks

3.1.1. Important Identified Risk: Teratogenicity

Information concerning the risk of teratogenicity is summarised in Table 35.

Table 35: Important Identified Risk: Teratogenicity

Teratogenicity
Potential Mechanisms No mechanism by which lenalidomide may cause teratogenicity has been established.
Evidence Source(s) and Strength of Evidence: Lenalidomide is structurally related to thalidomide, which is known to cause serious birth defects and death of the foetus. In nonclinical studies, lenalidomide induced malformations similar to those described with thalidomide. Therefore, a teratogenic effect of lenalidomide is expected and lenalidomide is contraindicated during pregnancy.
Characterisation of the Risk Not applicable (N/A). There were no cases of pregnancy in Studies SWOG S0777, CALGB 100104, IFM 2005-02, MM-020, MM-015, MM-009, MM-010, MDS-003, MDS-004, MCL-002, MCL-001, NHL-002, NHL-003, NHL-007 or NHL-008.

Table 35: Important Identified Risk: Teratogenicity (Continued)

Teratogenicity
As of 26 Dec 2017, there have been a total of 13 confirmed reports of possible maternal exposure during pregnancy from clinical trials, of which 5 were reports from non-US trials [redacted] (1), [redacted] (1), [redacted] (2) and [redacted] (1)). Five of the pregnancies were in female patients receiving lenalidomide and 8 pregnancies were in the female partners of male patients receiving lenalidomide. Two of the 5 reports of pregnancy in female patients on lenalidomide arose from a Celgene-sponsored study for complex regional pain syndrome. The remaining 3 reports in female patients receiving lenalidomide were from investigator-led studies (two in MM and one in Hodgkin's lymphoma). Of the 8 reports of pregnancy in the female partner of a male patient receiving lenalidomide, two reports arose from a Celgene-sponsored study for complex regional pain syndrome, two reports arose from an investigator-led study in MM and one report arose from an investigator-led study in chronic lymphocytic leukaemia (CLL). The remaining 3 reports of pregnancy in female partners of male patients receiving lenalidomide were in a follicular lymphoma study.
Risk Groups and Risk Factors The 'at risk' group comprises FCBP or female partners of male patients treated with lenalidomide and there are no risk factors.
Preventability To avoid any risk of foetal exposure to lenalidomide, the drug is contraindicated in women who are pregnant and in FCBP unless all of the conditions of the PPP are met (SmPC, Section 4.3). Women of childbearing potential should use an effective method of contraception (SmPC, Sections 4.4 and 4.6). Male patients taking lenalidomide should use condoms throughout treatment duration, during dose interruption and for 1 week after cessation of treatment if their partner is pregnant or of childbearing potential and not using effective contraception, even if the man has had a vasectomy (SmPC, Sections 4.4 and 4.6) and should not donate semen throughout treatment duration, during dose interruption and for 1 week after cessation of treatment. It is not known whether lenalidomide is excreted in human milk. Therefore, breastfeeding should be discontinued during therapy with lenalidomide (SmPC, Section 4.6).
Impact on the Risk-benefit Balance of the Product Lenalidomide 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 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 Lenalidomide is an analogue of a known human teratogenic compound. It was shown to be present in the semen of healthy male subjects in Phase 1 studies and a developmental toxicity study in monkeys indicated that lenalidomide produced malformations in the monkeys' offspring. If lenalidomide is taken during pregnancy, a teratogenic effect of lenalidomide in humans is expected (SmPC, Sections 4.4, 4.6 and 4.8).
Data Source: Clinical trials, RRMM PASS, spontaneous reports. **MedDRA Terms** *FL Studies (NHL-007 and NHL-008)* MedDRA v21.0 PTs: pregnancy, pregnancy of partner, pregnancy test positive, abortion, abortion induced, abortion spontaneous, congenital anomaly and human chorionic gonadotropin (hCG) positive. *NDMM RVd (SWOG S0777)* MedDRA v15.1 PTs: pregnancy, pregnancy of partner, pregnancy test positive, abortion, abortion induced, abortion spontaneous, congenital anomaly and hCG positive.

Table 35: Important Identified Risk: Teratogenicity (Continued)

Teratogenicity
TE NDMM (CALGB 100104 and IFM 2005-02)
MedDRA v15.1 PTs: pregnancy, pregnancy of partner, pregnancy test positive, abortion, abortion induced, abortion spontaneous, congenital anomaly and hCG positive.
TNE NDMM (MM-020 and MM-015)
MedDRA v15.1 PTs: pregnancy, pregnancy of partner, pregnancy test positive, abortion, abortion induced, abortion spontaneous, miscarriage, congenital anomaly and blood hCG positive.
RRMM (MM-009 and MM-010)
MedDRA v13.0 PTs: pregnancy, pregnancy of partner, pregnancy test positive, abortion, abortion induced, abortion spontaneous, miscarriage, congenital anomaly and blood hCG positive.
Del 5q MDS (MDS-003 and MDS-004)
MedDRA v13.0 PTs: pregnancy, pregnancy of partner, pregnancy test positive, abortion, abortion induced, abortion spontaneous, miscarriage, congenital anomaly and blood hCG positive.
MCL (MCL-001, MCL-002, NHL-002 and NHL-003)
MedDRA v16.1 PTs: pregnancy, pregnancy of partner, pregnancy test positive, abortion, abortion induced, abortion spontaneous, congenital anomaly and hCG positive.

3.1.2. Important Identified Risk: Serious Infection due to Neutropenia

Information concerning the risk of Serious Infection due to Neutropenia is summarised in Table 36.

Table 36: Important Identified Risk: Serious Infection due to Neutropenia

Serious Infection due to Neutropenia
Potential Mechanisms The pathogenesis of lenalidomide-induced neutropenia has not been elucidated.
Evidence Source(s) and Strength of Evidence: In clinical trials, neutropenia has been reported as a consequence of lenalidomide treatment; ≥ Grade 4 and ≥ Grade 3 infections have occurred in the context of neutropenia (any grade).

Table 36: Important Identified Risk: Serious Infection due to Neutropenia (Continued)

Serious Infection due to Neutropenia

Characterisation of the Risk

Frequency with 95% CI

FL Studies:

Neutropenia/Infection	**NHL-007**		**NHL-008**	**Pooled NHL-007 and NHL-008**
	PBO+Rit	**Len+Rit**	**Len+Rit**	**Len+Rit**
Total number of patients	148	146	177	323
Patients with ≥ 1 SAE				
Neutropenia	0	6	9	15
Infection	5	14	20	34
Patients with ≥ 1 AE				
Neutropenia	33	85	63	148
Infection	68	92	90	182
Incidence (% of patients) with ≥ 1 AE (95% CI)				
Neutropenia	22.3 (15.9 to 29.9)	58.2 (49.8 to 66.3)	35.6 (28.6 to 43.1)	-
Infection	45.9 (37.7 to 54.3)	63.0 (54.6 to 70.8)	50.8 (43.2 to 58.4)	-

Overall, in pooled Studies NHL-007 and NHL-008, neutropenia AEs were reported for 148 lenalidomide plus rituximab-treated patients and infection AEs were reported for 182 lenalidomide plus rituximab-treated patients.

In Study NHL-007, the proportion of FL patients experiencing at least one neutropenia event was higher among lenalidomide plus rituximab-treated patients than patients treated with rituximab plus placebo (risk ratio = 2.6 [95% CI: 1.7 to 3.9]). The proportion of FL patients experiencing at least one infection event was higher among lenalidomide plus rituximab-treated patients than patients treated with rituximab plus placebo (risk ratio = 1.4 [95% CI: 1.0 to 1.9]).

In Study NHL-008, 35.6% and 50.8% FL patients who received lenalidomide plus rituximab experienced at least one AE of neutropenia or infection, respectively.

To further elucidate the relationship between neutropenia and infection, a stratified analysis of infection in neutropenic patients was performed.

Table 36: Important Identified Risk: Serious Infection due to Neutropenia (Continued)

Serious Infection due to Neutropenia

Infection Events in Patients with Concurrent Infection After Treatment-emergent Neutropenia (Studies NHL-007 and NHL-008)

AE Category [a,b]	Statistic [c]	NHL-007				NHL-008 Len+Rit		Pooled NHL-007 and NHL-008 Len+Rit	
		PBO+Rit		Len+Rit					
		M/N or n/M (%)	95% CI [c]	M/N or n/M (%)	95% CI [c]	M/N or n/M (%)	95% CI [c]	M/N or n/M (%)	95% CI [c]
Total Neutropenia (Any Grade)	**M/N (%)**	**33/148 (22 3)**	**(15.9, 29.9)**	**85/146 (58.2)**	**(49.8, 66.3)**	**63/177 (35.6)**	**(28.6, 43.1)**	**148/323 (45.8)**	**(40.3, 51.4)**
With concurrent infection (Grade 3 or 4)	n/M (%)			5/85 (5.9)	(1.9, 13.2)	9/63 (14.3)	(6.7, 25.4)	14/148 (9.5)	(5.3, 15.4)
Without concurrent infection (Grade 3 or 4)	n/M (%)			80/85 (94.1)	(86.8, 98.1)	54/63 (85.7)	(74.6, 93.3)	134/148 (90.5)	(84.6, 94.7)
With concurrent infection (serious)	n/M (%)			3/85 (3.5)	(0.7, 10.0)	8/63 (12.7)	(5.6, 23.5)	11/148 (7.4)	(3.8, 12.9)
Without concurrent infection (serious)	n/M (%)			82/85 (96.5)	(90.0, 99.3)	55/63 (87.3)	(76.5, 94.4)	137/148 (92.6)	(87.1, 96.2)
Total Neutropenia ≥ Grade 3	**M/N (%)**	**19/148 (12.8)**	**(7.9, 19.3)**	**74/146 (50.7)**	**(42.3, 59.0)**	**56/177 (31.6)**	**(24.9, 39.0)**	**130/323 (40.2)**	**(34.9, 45.8)**
With concurrent infection (Grade 3 or 4)	n/M (%)			3/74 (4.1)	(0.8, 11.4)	7/56 (12.5)	(5.2, 24.1)	10/130 (7.7)	(3.8, 13.7)
Without concurrent infection (Grade 3 or 4)	n/M (%)			71/74 (95.9)	(88.6, 99.2)	49/56 (87.5)	(75.9, 94.8)	120/130 (92.3)	(86.3, 96.2)
With concurrent infection (serious)	n/M (%)			2/74 (2.7)	(0.3, 9.4)	6/56 (10.7)	(4.0, 21.9)	8/130 (6.2)	(2.7, 11.8)
Without concurrent infection (serious)	n/M (%)			72/74 (97.3)	(90.6, 99.7)	50/56 (89.3)	(78.1, 96.0)	122/130 (93.8)	(88.2, 97.3)
Total Neutropenia ≥ Grade 4	**M/N (%)**	**5/148 (3.4)**	**(1.1, 7.7)**	**32/146 (21.9)**	**(15.5, 29.5)**	**30/177 (16.9)**	**(11.7, 23.3)**	**62/323 (19.2)**	**(15.0, 23.9)**
With concurrent infection (Grade 3 or 4)	n/M (%)			3/32 (9.4)	(2.0, 25.0)	1/30 (3.3)	(0.1, 17.2)	4/62 (6.5)	(1.8, 15.7)
Without concurrent infection (Grade 3 or 4)	n/M (%)			29/32 (90.6)	(75.0, 98.0)	29/30 (96.7)	(82.8, 99.9)	58/62 (93.5)	(84.3, 98.2)
With concurrent infection (serious)	n/M (%)			2/32 (6.3)	(0.8, 20.8)	1/30 (3.3)	(0.1, 17.2)	3/62 (4.8)	(1.0, 13.5)
Without concurrent infection (serious)	n/M (%)			30/32 (93.8)	(79.2, 99.2)	29/30 (96.7)	(82.8, 99.9)	59/62 (95.2)	(86.5, 99.0)

[a] Definition of concurrent infection: the start date of any infection is within 2 weeks after the start date, but before or on the end date of neutropenia. Neutropenia and infection are considered as concurrent if either of them had both missing start and end date or both of them had missing start date. Otherwise, if neutropenia start date is missing, infection is concurrent if its start date is before neutropenia end date; if neutropenia end date is missing, infection is considered as concurrent if its start date is within 2 weeks after the neutropenia start date; if infection start date is missing, it is considered as concurrent if its end date is on or after the neutropenia start date.

[b] Graded using CTCAE version 4.03 or higher.

[c] N = number of subjects in the designated population; M = number of subjects with neutropenia in specific AE grade; n=number of subjects with concurrent infection. Confidence interval is 95% Clopper-Pearson CI for the percentage.

Table 36: Important Identified Risk: Serious Infection due to Neutropenia (Continued)

Serious Infection due to Neutropenia

NDMM RVd Study:

Neutropenia/Infection	SWOG S0777	
	Arm B (RVd)	Arm A (Rd)
Total number of patients	262	256
Patients with ≥ 1 SAE		
Neutropenia	3	6
Infection	28	17
Patients with ≥ 1 AE		
Neutropenia	78	101
Infection	92	74
Incidence (% of patients) with ≥ 1 AE (95% CI)		
Neutropenia	29.8 (24.3 to 35.7)	39.5 (33.4 to 45.7)
Infection	35.1 (29.3 to 41.2)	28.9 (23.4 to 34.9)

In Study SWOG S0777, the proportion of patients experiencing at least one neutropenia event was smaller among patients treated with RVd than patients treated with Rd (risk ratio = 0.75 [95% CI: 0.59-0.96]). The proportion of patients experiencing at least one infection event was greater among patients treated with RVd than patients treated with Rd (risk ratio = 1.21 [95% CI: 0.94-1.56]).

TE NDMM Studies:

Neutropenia/Infection	CALGB 100104 Maintenance		IFM 2005-02 Maintenance	
	Len	Placebo	Len	Placebo
Total number of patients	224	221	293	280
Patients with ≥ 1 SAE				
Neutropenia	15	2	17	1
Infection	36	11	40	10
Patients with ≥ 1 AE				
Neutropenia	179	100	178	34
Infection	122	84	235	219
Incidence (% of patients) with ≥ 1 AE (95% CI)[a]				
Neutropenia	79.9 (74.1 to 85.0)	45.2 (38.6 to 52.1)	60.8 (54.9 to 66.4)	12.1 (8.6 to 16.6)
Infection	54.5 (47.7 to 61.1)	38.0 (31.6 to 44.8)	80.2 (75.2 to 84.6)	78.2 (72.9 to 82.9)

[a] Incidence was not adjusted for time on treatment.

In Study CALGB 100104, the proportion of patients experiencing at least one neutropenia event was greater among lenalidomide-treated patients than patients treated with placebo (risk ratio = 1.77 [95% CI: 1.51-2.07]; $p < 0.001$). The proportion of patients experiencing at least one infection event was greater among lenalidomide-treated patients than patients treated with placebo (risk ratio = 1.43 [95% CI: 1.17-1.76]; $p < 0.001$). Of note, "ANC" and "febrile neutropenia" (CTCAE) were preprinted terms on the CRF in Study CALGB 100104 (EU SCS, Section 1.2.1.2.1).

Table 36: Important Identified Risk: Serious Infection due to Neutropenia (Continued)

Serious Infection due to Neutropenia

In Study IFM 2005-02, the proportion of patients experiencing at least one neutropenia event was greater among lenalidomide-treated patients than patients treated with placebo (risk ratio = 5.00 [95% CI: 3.60-6.95]; p < 0.001). The proportion of patients experiencing at least one infection event was similar among lenalidomide-treated patients and patients treated with placebo (risk ratio = 1.03 [95% CI: 0.94-1.12]; p = 0.558).

To further elucidate the relationship between neutropenia and infection a stratified analysis of infection in neutropenic and non-neutropenic patients was performed in Study IFM 2005-02. This relationship could not be analysed for Study CALGB 100104, as the start dates for regular AEs were not collected in the study; only the reporting periods were collected and they are either 3- or 6-month intervals.

Infection Events in Patients with Neutropenia (Study IFM 2005-02)

Infection Events	Number (%) of Patients with Neutropenia (N = 119)		Number (%) of Patients without Neutropenia (N = 454)	
	Len N = 105	Placebo N = 14	Len N = 188	Placebo N = 266
With infection	78 (74.3)	10 (71.4)	157 (83.5)	209 (78.6)
Without infection	27 (25.7)	4 (28.6)	31 (16.5)	57 (21.4)

These data demonstrate that in the presence of neutropenia, no notable trend in infection risk is noted in lenalidomide-treated patients compared with placebo in the TE NDMM Study IFM 2005-02.

TNE NDMM Studies:

Neutropenia/Infection	MM-020			MM-015		
	Rd	Rd18	MPT	MPR+R	MPR+p	MPp+p
Total number of patients	532	540	541	150	152	153
Patients with ≥ 1 SAE						
Neutropenia	16	12	21	14	6	1
Infection	163	129	89	23	20	19
Patients with ≥ 1 AE						
Neutropenia	190	181	338	128	122	81
Infection	399	378	305	96	87	98
Incidence (% of patients) with ≥ 1 AE (95% CI)[a]						
Neutropenia	35.7 (31.6 to 40.0)	33.5 (29.5 to 37.7)	62.5 (58.2 to 66.6)	85.3 (78.6 to 90.6)	80.3 (73.0 to 86.3)	52.9 (44.7 to 61.1)
Infection	75.0 (71.1 to 78.6)	70.0 (65.9 to 73.8)	56.4 (52.1 to 60.6)	64.0 (55.8 to 71.7)	57.2 (49.0 to 65.2)	64.1 (55.9 to 71.6)

[a] Incidence was not adjusted for time on treatment.

In Study MM-020, the proportion of patients experiencing at least one neutropenia event was lower among lenalidomide-treated patients than patients treated with control (risk ratio = 0.55 [95% CI: 0.50-0.62]; p < 0.001). The proportion of patients experiencing at least one infection event was greater among lenalidomide-treated patients than patients treated with control (risk ratio = 1.29 [95% CI: 1.18-1.40]; p < 0.001).

In Study MM-015, the proportion of patients experiencing at least one neutropenia event was greater among lenalidomide-treated patients than patients treated with control (risk ratio = 1.56 [95% CI: 1.34-1.83]; p < 0.001). The proportion of patients experiencing at least one infection event was lower among lenalidomide-treated patients than patients treated with control (risk ratio = 0.95 [95% CI: 0.81-1.10]; p = 0.467).

Table 36: Important Identified Risk: Serious Infection due to Neutropenia (Continued)

Serious Infection due to Neutropenia

To further elucidate the relationship between neutropenia and infection a stratified analysis of infection in neutropenic and non-neutropenic patients was performed.

Infection Events in Patients with Neutropenia (Study MM-020)

Infection Events	Number (%) of Patients with Neutropenia (N = 463)			Number (%) of Patients without Neutropenia (N = 1150)		
	Rd N = 119	Rd18 N = 111	MPT N = 233	Rd N = 413	Rd18 N = 429	MPT N = 308
With infection	85 (71.4)	72 (64.9)	100 (42.9)	314 (76.0)	306 (71.3)	205 (66.6)
Without infection	34 (28.6)	39 (35.1)	133 (57.1)	99 (24.0)	123 (28.7)	103 (33.4)

Infection Events in Patients with Neutropenia (Study MM-015)

Infection Events	Number (%) of Patients with Neutropenia (N = 245)			Number (%) of Patients without Neutropenia (N = 210)		
	MPR+R N = 101	MPR+p N = 96	MPp+p N = 48	MPR+R N = 49	MPR+p N = 56	MPp+p N = 105
With infection	57 (56.4)	44 (45.8)	22 (45.8)	39 (79.6)	43 (76.8)	75 (71.4)
Without infection	44 (43.6)	52 (54.2)	26 (54.2)	10 (20.4)	13 (23.2)	30 (28.6)

These data demonstrate that in the presence of neutropenia, no notable trend in infection risk is noted in lenalidomide-treated patients compared with control in the TNE NDMM studies.

RRMM Studies:

Neutropenia/Infection	MM-009 and MM-010	
	Len/Dex	PBO/Dex
Total number of patients	353	350
Patients with ≥ 1 SAE		
Neutropenia	11	1
Infection	81	59
Patients with ≥ 1 AE		
Neutropenia	157	23
Infection	243	200
Incidence (% of patients) with ≥ 1 AE (95% CI)[a]		
Neutropenia	44.5 (39.2 to 49.8)	6.6 (4.2 to 9.7)
Infection	68.8 (63.7 to 73.6)	57.1 (51.8 to 62.4)

[a] Incidence between arms was not adjusted for actual time on treatment (mean treatment duration 44 weeks [Len/Dex] versus 23 weeks [PBO/Dex]).

In the RRMM clinical studies, the risk of patients experiencing at least one event of neutropenia was greater among lenalidomide/dexamethasone-treated patients (157/353; 44.5%) than that observed among placebo/dexamethasone-treated patients (23/350; 6.6%). The risk ratio for neutropenia of lenalidomide versus placebo is 6.77 (95% CI: 4.38–9.71; $p < 0.0001$).

The risk of experiencing at least one episode of infection was comparable for lenalidomide/dexamethasone-treated and placebo/dexamethasone-treated patients (243/353 [68.8%] and 200/350 [57.1%], respectively). The risk ratio is 1.21 (95% CI: 1.07–1.35; $p = 0.001$).

Table 36: Important Identified Risk: Serious Infection due to Neutropenia (Continued)

Serious Infection due to Neutropenia

To further elucidate the relationship between neutropenia and infection in patients in the RRMM studies, a stratified analysis of the risk of infection in the presence or absence of neutropenia in this population was performed and is presented in the table below.

Infection Events in Patients with and without Neutropenia (Studies MM-009 and MM-010)

Infection Events	Number (%) of Patients with Neutropenia N = 180		Number (%) of Patients without Neutropenia N = 523	
	Len/Dex N = 157	PBO/Dex N = 23	Len/Dex N = 196	PBO/Dex N = 327
With infection	129 (82.2)	17 (73.9)	114 (58.2)	183 (56.0)
Without infection	28 (17.8)	6 (26.1)	82 (41.8)	144 (44.0)

Among neutropenic patients in the lenalidomide/dexamethasone arm, the risk of infection was 82.2% (129/157); among neutropenic patients in the placebo/dexamethasone arm, the risk was 73.9% (17/23). The risk ratio contrasting infection risk between these two groups was 1.11 (95% CI: 0.86–1.43; p = 0.36).

There were 196 patients in the lenalidomide/dexamethasone arm without neutropenia and 327 patients in the placebo/dexamethasone arm without neutropenia. The risk of infection within these two arms was 58.2% and 56.0%, respectively. The risk ratio was 1.04 (95% CI: 0.89–1.21; p = 0.63).

The Breslow-Day test for interaction of the risk ratio between strata was 0.91 (p = 0.34), indicating no significant statistical difference. After controlling for the effect of neutropenia, there is no increased risk of infection among lenalidomide-treated patients (adjusted risk ratio 1.05; 95% CI: 0.92–1.21, p = 0.45). However, the greater risk of infection may be understood by the greater proportion of patients with neutropenia.

Del 5q MDS Studies:

Neutropenia/Infection	MDS-003[a] Len (10 mg)	MDS-004[b]		
		Len (10 mg)	Len (5 mg)	PBO[c]
Total number of patients	148	69	69	67
Patients with ≥ 1 SAE				
Neutropenia	17	5	6	0
Infection	35[d]	9[e]	8[f]	3[g]
Patients with ≥ 1 AE				
Neutropenia	101	53	54	12
Infection	117	45	41	23
Incidence (% of patients) with ≥ 1 AE (95% CI)				
Neutropenia	68.2 (60.1 to 75.6)	76.8 (65.1 to 86.1)	78.3 (66.7 to 87.3)	17.9 (9.6 to 29.2)
Infection	79.1 (71.6 to 85.3)	65.2 (52.8 to 76.3)	59.4 (46.9 to 71.1)	34.3 (23.2 to 46.9)

[a] Median time on treatment was 52.5 weeks.
[b] Median time on treatment was 50.3 weeks in the 10 mg group, 18.0 weeks in the 5 mg group and 16.0 weeks in the PBO group.
[c] Data in PBO group is from the first 16 weeks of the double-blind phase.
[d] Includes PTs of pneumonia NOS (15), sepsis NOS (6), and bacteraemia, cellulitis, infection NOS and urinary tract infection NOS (2 each). All other PTs reported for ≤ 1 patient.
[e] Includes PTs of pneumonia (2), and bronchopneumonia, anal abscess, cellulitis, erysipelas, gastroenteritis, pyelonephritis, septic shock and urinary tract infection (1 each).
[f] Includes PTs of pneumonia (2), and erysipelas, infection, lower respiratory tract infection, respiratory tract infection, staphylococcal sepsis, urinary tract infection and urosepsis (1 each).
[g] Includes PTs of arthritis bacterial, bronchopneumonia and pneumonia (1 each).

Table 36: Important Identified Risk: Serious Infection due to Neutropenia (Continued)

Serious Infection due to Neutropenia

In Study MDS-004, the risk of neutropenia was comparable in the lenalidomide 10 mg and 5 mg groups (53/69; 76.8% and 54/69; 78.3%, respectively) and greater than in the placebo group (12/67; 17.9%). For the combined group (5 mg and 10 mg) versus placebo, the risk ratio is 4.33 (95% CI: 2.57–7.28).

The risk of infection was similar in the lenalidomide 10 mg and 5 mg groups (45/69; 65.2% and 41/69; 59.4%, respectively), and greater than in the placebo group (23/67; 34.3%). For the combined group (5 mg and 10 mg) versus placebo, the risk ratio is 1.81 (95% CI: 1.27–2.59).

A stratified analysis of infection with and without neutropenia in this population is presented below.

Infection Events in Patients with and without Neutropenia (Study MDS-004)

Infection Events	**Number (%) of Patients with Neutropenia N = 137**			**Number (%) of Patients without Neutropenia N = 68**		
	Len (10 mg) N = 62	**Len (5 mg) N = 59**	**PBO N = 16**	**Len (10 mg) N = 7**	**Len (5 mg) N = 10**	**PBO N = 51**
With infection	40 (64.5)	35 (59.3)	5 (31.3)	5 (71.4)	6 (60.0)	18 (35.3)
With related infection	27 (43.5)	23 (39.0)	2 (12.5)	0	0	0

Temporally related infection was defined as infection that occurred within 2 weeks of an AE of neutropenia.

It can be concluded that the risk of infection with lenalidomide is probably related to the risk of neutropenia in this population.

MCL Studies:

Neutropenia/Infection	**MCL-002**		**All MCL Lenalidomide Patients (MCL-002, MCL-001, NHL-002, NHL-003)**
	Len	**Control**	
Total number of patients	167	83	373
Patients with ≥ 1 SAE			
Neutropenia	11	2	25
Infection	22	7	63
Patients with ≥ 1 AE			
Neutropenia	89	29	201
Infection	90	31	211
Incidence (% of patients) with ≥ 1 AE (95% CI)			
Neutropenia	53.3 (45.4 to 61.0)	34.9 (24.8 to 46.2)	53.9 (48.7 to 59.0)
Infection	53.9 (46.0 to 61.6)	37.3 (27.0 to 48.7)	56.6 (51.4 to 61.7)

In Study MCL-002, the proportion of patients experiencing at least one neutropenia event was greater among lenalidomide-treated patients than patients treated with control (risk ratio = 1.53 [95% CI: 1.10-2.11]; p = 0.011).

The proportion of patients experiencing at least one infection event was also greater among lenalidomide-treated patients than patients treated with control (risk ratio = 1.44 [95% CI: 1.06-1.97]; p = 0.021).

To further elucidate the relationship between neutropenia and infection a stratified analysis of infection in neutropenic and non-neutropenic patients was performed.

Table 36: Important Identified Risk: Serious Infection due to Neutropenia (Continued)

Serious Infection due to Neutropenia

Infection Events in Patients with Neutropenia

	Number (%) of Patients with Neutropenia			Number (%) of Patients without Neutropenia		
	MCL-002		All MCL Len Patients (MCL-002, MCL-001, NHL-002, NHL-003)	MCL-002		All MCL Len Patients (MCL-002, MCL-001, NHL-002, NHL-003)
	Len N = 89	Control N = 29	Len N = 201	Len N = 78	Control N = 54	Len N = 172
With infection	27 (30.3)	5 (17.2)	54 (26.9)	28 (35.9)	18 (33.3)	75 (43.6)
Without infection	62 (69.7)	24 (82.8)	147 (73.1)	50 (64.1)	36 (66.7)	97 (56.4)

These data demonstrate that in the presence of neutropenia, no notable trend in infection risk is noted in lenalidomide-treated patients compared with infection events in the absence of neutropenia in the studies in MCL.

Seriousness/Outcomes

FL Studies:

SAE outcomes reported in the FL studies are summarised below.

Neutropenia/Infection	NHL-007		NHL-008	Pooled NHL-007 and NHL-008
	PBO+Rit	Len+Rit	Len+Rit	Len+Rit
Total number of patients	148	146	177	323
Patients with ≥ 1 SAE				
Neutropenia	0	6 (4.1)	9 (5.1)	15 (4.6)
Infection	5 (3.4)	14 (9.6)	20 (11.3)	34 (10.5)
Death				
Neutropenia	0	0	0	0
Infection	0	0	0	0
Resolved				
Neutropenia	0	6 (4.1)	9 (5.1)	15 (4.6)
Infection	5 (3.4)	14 (9.6)	16 (9.0)	30 (9.3)
Resolved with Sequelae				
Neutropenia	0	0	0	0
Infection	0	0	3 (1.7)	3 (0.9)
Not Recovered/Not Resolved				
Neutropenia	0	0	0	0
Infection	0	0	0	0
Ongoing at Time of Death				
Neutropenia	0	0	0	0
Infection	0	0	1 (0.6)	1 (0.3)

Table 36: Important Identified Risk: Serious Infection due to Neutropenia (Continued)

Serious Infection due to Neutropenia

In Study NHL-007, neutropenia SAEs were reported for 6/146 (4.1%) lenalidomide plus rituximab-treated patients (PTs reported were febrile neutropenia and neutropenia) and 0/148 rituximab plus placebo-treated patients. No neutropenia SAEs had an outcome of death. Infection SAEs were reported for 14/146 (9.6%) lenalidomide plus rituximab-treated patients and for 5/148 (3.4%) rituximab plus placebo-treated patients. No infection SAEs had an outcome of death.

In Study NHL-008, neutropenia SAEs were reported for 9/177 (5.1%) lenalidomide plus rituximab-treated patients (PTs reported were febrile neutropenia and neutropenia). No neutropenia SAEs had an outcome of death. Infection SAEs were reported for 20/177 (11.3%) lenalidomide plus rituximab-treated patients (PTs reported in 2 or more patients were pneumonia, sepsis and cellulitis). No infection SAEs had an outcome of death.

NDMM RVd Study

SAE outcomes reported in Study SWOG S0777 are summarised below.

Outcome	**SWOG S0777**	
	Arm B (RVd)	**Arm A (Rd)**
Total number of patients	262	256
Patients with ≥ 1 SAE		
Neutropenia	3 (1.1)	6 (2.3)
Infection	28 (10.7)	17 (6.6)
Death		
Neutropenia	0	0
Infection	0	0
Recovered/Resolved		
Neutropenia	1 (0.4)	4 (1.6)
Infection	8 (3.1)	4 (1.6)
Recovered/Resolved with Sequelae		
Neutropenia	0	0
Infection	2 (0.8)	1 (0.4)
Recovering/Resolving		
Neutropenia	1 (0.4)	0
Infection	13 (5.0)	9 (3.5)
Not Recovered/Not Resolved		
Neutropenia	1 (0.4)	2 (0.8)
Infection	3 (1.1)	3 (1.2)
Ongoing at Death		
Neutropenia	0	0
Infection	1 (0.4)	0
Unknown		
Neutropenia	0	0
Infection	1 (0.4)	0

In Study SWOG S0777, neutropenia SAEs were experienced by 3/262 (1.1%) patients treated with RVd and 6/256 (2.3%) patients treated with Rd (PTs reported were febrile neutropenia and neutropenia). Infection SAEs

Table 36: Important Identified Risk: Serious Infection due to Neutropenia (Continued)

Serious Infection due to Neutropenia

were reported in 28/262 (10.7%) patients treated with RVd (PTs reported in 2 or more patients were urinary tract infection, lung infection, sepsis and Enterocolitis infectious) and 17/256 (6.6%) patients treated with Rd (PTs reported in 2 or more patients were urinary tract infection and lung infection). No neutropenia or infection SAEs had an outcome of death in Study SWOG S0777.

TE NDMM Studies:

SAE outcomes reported in the TE NDMM studies are summarised below.

Outcome	CALGB 100104 Maintenance		IFM 2005-02 Maintenance	
	Len	Placebo	Len	Placebo
Total number of patients	224	221	293	280
Patients with ≥ 1 SAE				
Neutropenia	15 (6.7)	2 (0.9)	17 (5.8)	1 (0.4)
Infection	36 (16.1)	11 (5.0)	40 (13.7)	10 (3.6)
Death				
Neutropenia	0	0	0	0
Infection	1 (0.4)	0	0	0
Recovered/Resolved				
Neutropenia	5 (2.2)	0	12 (4.1)	0
Infection	11 (4.9)	4 (1.8)	16 (5.5)	3 (1.1)
Recovering/Resolving				
Neutropenia	3 (1.3)	0	4 (1.4)	0
Infection	15 (6.7)	2 (0.9)	6 (2.0)	0
Not Recovered/Not Resolved				
Neutropenia	6 (2.7)	0	0	0
Infection	6 (2.7)	0	0	0
Recovered with Sequelae				
Neutropenia	1 (0.4)	0	0	0
Infection	3 (1.3)	2 (0.9)	1 (0.3)	0
Missing				
Neutropenia	0	2 (0.9)	1 (0.3)	1 (0.4)
Infection	0	3 (1.4)	17 (5.8)	7 (2.5)
Ongoing at Death				
Neutropenia	0	0	0	0
Infection	0	0	0	0

In Study CALGB 100104, neutropenia SAEs were reported for 15/224 (6.7%) lenalidomide-treated patients (PTs reported were febrile neutropenia, neutropenia and neutropenic infection). No neutropenia SAEs had an outcome of death in Study CALGB 100104. Infection SAEs were reported for 36/224 (16.1%) lenalidomide-treated patients in Study CALGB 100104. PTs reported in the lenalidomide group in 2 or more patients were appendicitis, infection, lung infection, meningitis, upper respiratory tract infection, and urinary tract infection. An infection SAE (PT: sepsis) had an outcome of death in 1 (0.4%) lenalidomide-treated patient in Study CALGB 100104.

Table 36: Important Identified Risk: Serious Infection due to Neutropenia (Continued)

Serious Infection due to Neutropenia

In Study IFM 2005-02, neutropenia SAEs were reported for 17/293 (5.8%) lenalidomide-treated patients (PTs reported were febrile neutropenia and neutropenia). Infection SAEs were reported for 40/293 (13.7%) lenalidomide-treated patients. PTs reported in the lenalidomide group in 2 or more patients were bacterial sepsis, bronchitis, bronchopneumonia, gastroenteritis, herpes zoster, influenza, pneumonia, pneumonia pneumococcal and staphylococcal sepsis. No neutropenia and infection SAEs had an outcome of death in Study IFM 2005-02.

TNE NDMM Studies:

SAE outcomes reported in the TNE NDMM studies are summarised below.

Outcome	MM-020			MM-015		
	Rd	Rd18	MPT	MPR+R	MPR+p	MPp+p
Total number of patients	532	540	541	150	152	153
Patients with ≥ 1 SAE						
Neutropenia	16 (3.0)	12 (2.2)	21 (3.9)	14 (9.3)	6 (3.9)	1 (0.7)
Infection	163 (30.6)	129 (23.9)	89 (16.5)	23 (15.3)	20 (13.2)	19 (12.4)
Death						
Neutropenia	0	1 (0.2)	1 (0.2)	0	0	0
Infection	21 (3.9)	12 (2.2)	10 (1.8)	3 (2.0)	1 (0.7)	0
Recovered/Resolved						
Neutropenia	14 (2.6)	10 (1.9)	14 (2.6)	11 (7.3)	3 (2.0)	0
Infection	111 (20.9)	92 (17.0)	61 (11.3)	14 (9.3)	15 (9.9)	0
Not Recovered/Not Resolved						
Neutropenia	0	0	1 (0.2)	1 (0.7)	0	0
Infection	3 (0.6)	4 (0.7)	1 (0.2)	0	0	0
Recovered with Sequelae						
Neutropenia	1 (0.2)	0	1 (0.2)	0	0	0
Infection	14 (2.6)	5 (0.9)	6 (1.1)	6 (4.0)	1 (0.7)	1 (0.7)
Missing						
Neutropenia	1 (0.2)	0	1 (0.2)	1 (0.7)	2 (1.3)	1 (0.7)
Infection	9 (1.7)	9 (1.7)	6 (1.1)	0	3 (2.0)	18 (11.8)
Ongoing at Death						
Neutropenia	0	1 (0.2)	3 (0.6)	1 (0.7)	1 (0.7)	0
Infection	5 (0.9)	7 (1.3)	4 (0.7)	0	0	0
Recovering/Resolving						
Neutropenia	0	0	0	0	0	0
Infection	0	0	1 (0.2)	0	0	0

In Study MM-020, SAEs of neutropenia were reported more frequently in the MPT arm of the study compared with the Rd and Rd18 arms (MPT: 3.9% versus Rd: 3.0%, Rd18: 2.2%). (PTs were febrile neutropenia, neutropenia and neutropenic sepsis). Neutropenia (neutropenic sepsis) was Grade 5 (fatal) in 3 patients: 1 in each treatment arm of the study. In Study MM-015, SAEs of neutropenia were reported more frequently in the lenalidomide-containing arms of the study (MPR+R: 9.3%; MPR+p: 3.9%) compared with placebo-treated

Table 36: Important Identified Risk: Serious Infection due to Neutropenia (Continued)

Serious Infection due to Neutropenia

patients (MPp+p: 0.7%). Among patients receiving induction with melphalan, prednisone and lenalidomide, the frequency of these events was higher in patients receiving continuous treatment with lenalidomide following induction than in patients receiving placebo.

No neutropenia SAEs had an outcome of death in Study MM-015.

In Study MM-020, infection SAEs were experienced by more patients in the lenalidomide arms: 163/532 (30.6%) and 129/540 (23.9%) patients in Arm Rd and Arm Rd18, respectively, compared with 89/541 (16.5%) patients in Arm MPT. PTs reported for 5 or more patients overall (in descending order of frequency) were pneumonia (135 patients), sepsis (33), bronchitis (20), upper respiratory tract infection, respiratory tract infection and lobar pneumonia (17 each), urinary tract infection and lung infection (16 each), septic shock and lower respiratory tract infection (15 each), cellulitis (13), influenza (10), infection and bronchopneumonia (9 each), pneumonia pneumococcal (7), bacteraemia (6), and staphylococcal sepsis, pyelonephritis, herpes zoster, gastroenteritis, erysipelas and arthritis bacterial (5 each). Infection SAEs with an outcome of death were reported for 21 (3.9%), 12 (2.2%) and 10 (1.8%) patients, respectively. In Study MM-015, infection SAEs were experienced by slightly fewer patients in the control arm: 23/150 (15.3%), 20/152 (13.2%) and 19/153 (12.4%) patients in the MPR+R, MPR+p and MPp+p arms, respectively. PTs reported for more than 2 patients overall were bronchitis, lower respiratory tract infection, pneumonia, sepsis, and urinary tract infection). A total of 3 (2.0%), 1 (0.7%) and 0 patients with infection SAEs in the MPR+R, MPR+p and MPp+p arms, respectively, had outcomes of death.

RRMM Studies:

The SAEs reported in the RRMM studies are summarised below.

Outcome	**Number (%) of Patients[a]**	
	MM-009 and MM-010	
	Len/Dex N = 353	**PBO/Dex N = 350**
Patients with ≥ 1 SAE		
Neutropenia	11 (3.1)	1 (0.3)
Infection	81 (22.9)	59 (16.9)
Death		
Neutropenia	0	0
Infection	1 (0.3)	3 (0.9)
Resolved/Recovered with/without Sequelae (MM-009 and MM-010)		
Neutropenia	8 (2.3)	1 (0.3)
Infection	21 (5.9)	14 (4)
Not Recovered/Not Resolved (MM-009 and MM-010)		
Neutropenia	1 (0.3)	0
Infection	1 (0.3)	0
Unknown/Missing (MM-009 and MM-010)		
Neutropenia	4 (1.1)	0
Infection	68 (19.2)	44 (12.5)

[a] Patients may be counted more than once.

A total of 14 serious neutropenia events were experienced by 11/353 (3.1%) lenalidomide/dexamethasone-treated patients. These SAEs were febrile neutropenia (6 patients), neutropenia (5 patients), and neutropenic sepsis (one patient). A total of 116 infection SAEs were experienced by 81 (22.9%) lenalidomide/dexamethasone-treated patients. SAEs of pneumonia NOS were experienced by 34 patients, all other SAEs were experienced by 4 or fewer patients. A total of 4 patients were reported with both SAEs of infection and leucopenia/neutropenia.

Table 36: Important Identified Risk: Serious Infection due to Neutropenia (Continued)

Serious Infection due to Neutropenia

Of the 14 neutropenia SAEs experienced by lenalidomide/dexamethasone-treated patients, all 14 were of Grade 3 or 4 intensity and 12 were considered to be related to treatment. In 13 of the 14 SAEs, the dose of lenalidomide was reduced or interrupted, or treatment was permanently discontinued. A neutropenia SAE was reported in 1 out of 350 (0.3%) placebo/dexamethasone-treated patients.

Of the 116 infection SAEs experienced by lenalidomide/dexamethasone-treated patients, 98 were of Grade 3 or 4 intensity and 41 were considered to be related to treatment. In 61 of the 116 SAEs, the dose of lenalidomide was reduced or interrupted, or treatment was permanently discontinued. One patient died as a result of septic shock not related to lenalidomide/dexamethasone. Infection SAEs were experienced by 59 out of 350 (16.9%) placebo/dexamethasone-treated patients.

Del 5q MDS Studies:

The outcomes of the SAEs reported in Studies MDS-003 and MDS-004 are summarised below.

Outcome	Number (%) of Patients[a]			
	MDS-003[b] Len (10 mg) N = 148	MDS-004[c]		
		Len (10 mg) N = 69	Len (5 mg) N = 69	PBO[d] N = 67
Patients with ≥ 1 SAE				
Neutropenia	17 (11.5)	5 (7.2)	6 (8.7)	0
Infection	35 (23.6)[e]	9 (13.0)[f]	8 (11.6)[g]	3 (4.5)[h]
Death				
Neutropenia	0	0	0	0
Infection	4 (2.7)	1 (1.4)	0	0
Not Recovered/Not Resolved				
Neutropenia	2 (1.4)	0	0	0
Infection	2 (1.4)	1 (1.4)	0	0
Resolved/Recovered with/without Sequelae				
Neutropenia	12 (8.1)	5 (7.2)	5 (7.2)	0
Infection	27 (18.2)	7 (10.1)	6 (8.7)	2 (3.0)
Unknown/Missing				
Neutropenia	3 (2.0)	1 (1.4)	1 (1.4)	0
Infection	7 (4.7)	1 (1.4)	2 (2.9)	1 (1.5)

[a] Patients may be counted more than once.
[b] Median time on treatment was 52.5 weeks.
[c] Median time on treatment was 50.3 weeks in the 10 mg group, 18.0 weeks in the 5 mg group and 16.0 weeks in the PBO group.
[d] Data in PBO group is from the first 16 weeks of the double-blind phase.
[e] Includes PTs of pneumonia NOS (15), sepsis NOS (6), and bacteraemia, cellulitis, infection NOS and urinary tract infection NOS (2 each). All other PTs reported for ≤ 1 patient.
[f] Includes PTs of pneumonia (2), and bronchopneumonia, anal abscess, cellulitis, erysipelas, gastroenteritis, pyelonephritis, septic shock and urinary tract infection (1 each).
[g] Includes PTs of pneumonia (2), and erysipelas, infection, lower respiratory tract infection, respiratory tract infection, staphylococcal sepsis, urinary tract infection and urosepsis (1 each).
[h] Includes PTs of arthritis bacterial, bronchopneumonia and pneumonia (1 each).

In Study MDS-004, neutropenia-related SAEs were PT neutropenia in 4 patients each in the lenalidomide groups, and the PT of febrile neutropenia, which was experienced by 1 and 2 patients in the lenalidomide 10 mg and 5 mg groups, respectively. All of the neutropenia SAEs were considered related to treatment.

Table 36: Important Identified Risk: Serious Infection due to Neutropenia (Continued)

Serious Infection due to Neutropenia

In Study MDS-004, treatment-related SAEs of infection included cellulitis in the lenalidomide 10 mg group and erysipelas, infection, lower respiratory tract infection and pneumonia in the lenalidomide 5 mg group. One patient in the lenalidomide 10 mg group died due to septic shock (respiratory origin).

In Study MDS-003, 4 patients experienced infection SAEs that resulted in death. These SAEs were sepsis in 2 patients, which were considered not related to study medication, and Klebsiella sepsis and pneumonia in 1 patient each, which were considered treatment related.

MCL Studies:

SAE outcomes reported in the studies in MCL are summarised below.

Outcome	MCL-002		All MCL Lenalidomide Patients (MCL-002, MCL-001 NHL-002, NHL-003)
	Len	Control	
Total number of patients	167	83	373
Patients with ≥ 1 SAE			
Neutropenia	11 (6.6)	2 (2.4)	25 (6.7)
Infection	22 (13.2)	7 (8.4)	63 (16.9)
Death			
Infection	0	0	5 (1.3)
Ongoing at Death			
Neutropenia	2 (1.2)	0	2 (0.5)
Infection	1 (0.6)	0	4 (1.1)
Recovered with Sequelae			
Neutropenia	1 (0.6)	0	1 (0.3)
Infection	3 (1.8)	0	7 (1.9)
Recovered/Resolved			
Neutropenia	8 (4.8)	2 (2.4)	22 (5.9)
Infection	17 (10.2)	7 (8.4)	44 (11.8)
Unknown			
Neutropenia	0	0	0
Infection	1 (0.6)	0	3 (0.8)

In Study MCL-002, neutropenia SAEs were experienced more frequently by lenalidomide-treated patients (11/167 [6.6%]) than by patients in the control group (2/83 [2.4%]); PTs reported in the lenalidomide group were febrile neutropenia, neutropenia and neutropenic sepsis). No patients experienced SAEs of neutropenia that had an outcome of death.

In the combined MCL Studies MCL-002, MCL-001, NHL-002 and NHL-003, neutropenia SAEs were experienced by 25/373 (6.7%) lenalidomide-treated patients (PTs reported were febrile neutropenia, neutropenia and neutropenic sepsis). No patients experienced SAEs of neutropenia that had an outcome of death.

In Study MCL-002, infection SAEs were experienced by more patients in the lenalidomide group (22/167 [13.2%]) than in the control group (7/83 [8.4%]). PTs reported in the lenalidomide group in 2 or more patients were pneumonia, bronchitis, urinary tract infection, lower respiratory tract infection, and lung infection. No patients experienced SAEs of infection that had an outcome of death.

In the combined MCL Studies MCL-002, MCL-001, NHL-002 and NHL-003, infection SAEs were experienced by 63/373 (16.9%) lenalidomide-treated patients. PTs reported in 2 or more patients were pneumonia, bronchitis,

Table 36: Important Identified Risk: Serious Infection due to Neutropenia (Continued)

Serious Infection due to Neutropenia

urinary tract infection, cellulitis, lower respiratory tract infection, pneumonia bacterial, pneumonia streptococcal, sepsis, staphylococcal sepsis, bronchopneumonia, bronchopulmonary aspergillosis, bacteraemia, clostridium difficile colitis, lung infection, respiratory tract infection, septic shock, staphylococcal bacteraemia and urosepsis. A total of 5 (1.3%) patients experienced SAEs of infection that had an outcome of death.

Severity and Nature of Risk

FL Studies:

Details of AEs pertaining to neutropenia and infection that were reported in the FL studies are summarised below.

Neutropenia/Infection	**NHL-007**		**NHL-008**	**Pooled NHL-007 and NHL-008**
	PBO+Rit	**Len+Rit**	**Len+Rit**	**Len+Rit**
Total number of patients	148	146	177	323
All AEs				
Neutropenia	33 (22.3)	85 (58.2)	63 (35.6)	148 (45.8)
Infection	68 (45.9)	92 (63.0)	90 (50.8)	182 (56.3)
Grade 3 or 4				
Neutropenia	19 (12.8)	74 (50.7)	56 (31.6)	130 (40.2)
Infection	7 (4.7)	22 (15.1)	23 (13.0)	45 (13.9)
AEs Leading to Dose Discontinuation				
Neutropenia	0	5 (3.4)	10 (5.6)	15 (4.6)
Infection	0	1 (0.7)	5 (2.8)	6 (1.9)
AEs Leading to Dose Interruption				
Neutropenia	13 (8.8)	59 (40.4)	32 (18.1)	91 (28.2)
Infection	12 (8.1)	29 (19.9)	30 (16.9)	59 (18.3)
AEs Leading to Dose Reduction				
Neutropenia	4 (2.7)	28 (19.2)	38 (21.5)	66 (20.4)
Infection	0	0	5 (2.8)	5 (1.5)

In Study NHL-007, a greater proportion of FL patients treated with lenalidomide plus rituximab than those treated with rituximab plus placebo experienced Grade 3 or 4 AEs of neutropenia (50.7% versus 12.8%), and neutropenia AEs leading to dose interruption (40.4% versus 8.8%), dose reduction (19.2% versus 2.7%) and study treatment discontinuation (3.4% versus 0%). A greater proportion of patients treated with lenalidomide plus rituximab than those treated with rituximab plus placebo experienced Grade 3 or 4 AEs of infection (15.1% versus 4.7%), and infection AEs leading to dose interruption (19.9% versus 8.1%). Less than 1% of patients treated with lenalidomide plus rituximab experienced infection AEs leading to study treatment discontinuation. No patients in either treatment arm experienced infection AEs leading to dose reduction.

In Study NHL-008, Grade 3 or 4 AEs of neutropenia were reported for 31.6% lenalidomide plus rituximab-treated patients, and neutropenia AEs leading to dose interruption, dose reduction and study treatment discontinuation were reported for 18.1%, 21.5% and 5.6% lenalidomide plus rituximab-treated patients, respectively. Grade 3 or 4 AEs of infection were reported for 13.0% lenalidomide plus rituximab-treated patients, and infection AEs leading to dose interruption, dose reduction and study treatment discontinuation were reported for 16.9%, 2.8% and 2.8% lenalidomide plus rituximab-treated patients, respectively.

Table 36: Important Identified Risk: Serious Infection due to Neutropenia (Continued)

Serious Infection due to Neutropenia

NDMM RVd Study:

Details of AEs pertaining to neutropenia and infection that were reported in Study SWOG S0777 are summarised below.

Neutropenia/Infection	SWOG S0777	
	Arm B (RVd)	**Arm A (Rd)**
Total number of patients	262	256
All AEs		
Neutropenia	78 (29.8)	101 (39.5)
Infection	92 (35.1)	74 (28.9)
Grade 3 or 4		
Neutropenia	27 (10.3)	45 (17.6)
Infection	36 (13.7)	24 (9.4)
AEs Leading to Dose Withdrawn Permanently		
Neutropenia	NC	NC
Infection	NC	NC
AEs Leading to Dose Interruption		
Neutropenia	NC	NC
Infection	NC	NC
AEs Leading to Dose Reduction		
Neutropenia	NC	NC
Infection	NC	NC

NC = not collected.

In Study SWOG S0777, the incidences of Grade 3 or 4 AEs of neutropenia (10.3% versus 17.6%) and infection (13.7% versus 9.4%) were comparable for patients in the RVd and Rd arms. Adverse events leading to study treatment withdrawal, interruption and dose reduction were not collected in this study.

Table 36: Important Identified Risk: Serious Infection due to Neutropenia (Continued)

Serious Infection due to Neutropenia

TE NDMM Studies:

Details of AEs pertaining to neutropenia and infection that were reported in the TE NDMM studies are summarised below.

Neutropenia/Infection	CALGB 100104 Maintenance		IFM 2005-02 Maintenance	
	Len	Placebo	Len	Placebo
Total number of patients	224	221	293	280
All AEs				
Neutropenia	179 (79.9)	100 (45.2)	178 (60.8)	34 (12.1)
Infection	122 (54.5)	84 (38.0)	235 (80.2)	219 (78.2)
Grade 3 or 4				
Neutropenia	140 (62.5)	78 (35.3)	158 (53.9)	22 (7.9)
Infection	66 (29.5)	34 (15.4)	40 (13.7)	13 (4.6)
AEs Leading to Dose Withdrawn Permanently[a]				
Neutropenia	5 (2.2)	0	8 (2.7)	0
Infection	4 (1.8)	0	5 (1.7)	2 (0.7)
AEs Leading to Dose Interruption[a]				
Neutropenia	NC	NC	72 (24.6)	1 (0.4)
Infection	NC	NC	52 (17.7)	20 (7.1)
AEs Leading to Dose Reduction[a]				
Neutropenia	NC	NC	42 (14.3)	2 (0.7)
Infection	NC	NC	4 (1.4)	2 (0.7)

NC = not collected per study design.

[a] In Study CALGB 100104, actions taken due to AEs (eg, treatment discontinued, dose reduced, dose interrupted) were not collected on the CRF. AEs leading to treatment discontinuation were derived retrospectively from the Off Treatment Notice form.

In Study CALGB 100104, greater proportions of patients treated with lenalidomide than those treated with placebo experienced Grade 3 or 4 AEs of neutropenia (62.5% versus 35.3%) and infection (29.5% versus 15.4%). AEs of neutropenia and infection led to permanent withdrawal of study treatment in 2.2% and 1.8% of patients treated with lenalidomide, respectively; there were no AEs of neutropenia or infection leading to permanent withdrawal of study treatment in patients treated with placebo.

In Study IFM 2005-02, greater proportions of patients treated with lenalidomide than those treated with placebo experienced Grade 3 or 4 AEs of neutropenia (53.9% versus 7.9%), and neutropenia AEs leading to dose interruption (24.6% versus 0.4%), dose reduction (14.3% versus 0.7%) and study treatment withdrawal (2.7% versus 0%). Greater proportions of patients treated with lenalidomide than those treated with placebo experienced Grade 3 or 4 AEs of infection (13.7% versus 4.6%), and infection AEs leading to dose interruption (17.7% versus 7.1%). Less than 2% of patients in both treatment arms experienced infection AEs leading to dose reduction or study treatment withdrawal.

There was no evidence of an increased frequency of onset of neutropenia or infection over time across studies (EU SCS, Section 2.1.11).

Table 36: Important Identified Risk: Serious Infection due to Neutropenia (Continued)

Serious Infection due to Neutropenia

TNE NDMM Studies

Details of AEs pertaining to neutropenia and infection that were reported in the TNE NDMM studies are summarised below.

Neutropenia/Infection	MM-020			MM-015		
	Rd	Rd18	MPT	MPR+R	MPR+p	MPp+p
Total number of patients	532	540	541	150	152	153
All AEs						
Neutropenia	190 (35.7)	181 (33.5)	338 (62.5)	128 (85.3)	122 (80.3)	81 (52.9)
Infection	399 (75.0)	378 (70.0)	305 (56.4)	96 (64.0)	87 (57.2)	98 (64.1)
Grade 3 or 4						
Neutropenia	152 (28.6)	147 (27.2)	252 (46.6)	114 (76.0)	102 (67.1)	48 (31.4)
Infection	154 (28.9)	118 (21.9)	93 (17.2)	17 (11.3)	22 (14.5)	15 (9.8)
AEs Leading to Dose Withdrawn Permanently						
Neutropenia	7 (1.3)	2 (0.4)	13 (2.4)	4 (2.7)	6 (3.9)	2 (1.3)
Infection	23 (4.3)	15 (2.8)	6 (1.1)	4 (2.7)	1 (0.7)	1 (0.7)
AEs Leading to Dose Interruption						
Neutropenia	119 (22.4)	104 (19.3)	268 (49.5)	95 (63.3)	76 (50.0)	31 (20.3)
Infection	164 (30.8)	113 (20.9)	67 (12.4)	28 (18.7)	30 (19.7)	15 (9.8)
AEs Leading to Dose Reduction						
Neutropenia	15 (2.8)	7 (1.3)	57 (10.5)	23 (15.3)	14 (9.2)	3 (2.0)
Infection	10 (1.9)	4 (0.7)	5 (0.9)	1 (0.7)	1 (0.7)	0

In Study MM-020, more patients in the MPT arm of the study experienced Grade 3 or 4 neutropenia compared with the Rd and Rd18 arms of the study (MPT: 46.6% versus Rd: 28.6% and Rd18: 27.2%). Neutropenia AEs led to lenalidomide withdrawal or dose reduction for ≤ 2.8% of patients in the lenalidomide treatment arms. In patients in Arm MPT, neutropenia AEs led to dose withdrawal in 2.4% of patients and to dose reduction in 10.5% of patients. Neutropenia led to dose interruption for 22.4%, 19.3% and 49.5% of patients in Arms Rd, Rd18 and MPT, respectively. In Study MM-015, more patients in the lenalidomide-containing arms of the study experienced Grade 3 or 4 neutropenia (MPR+R: 76.0%; MPR+p: 67.1%) compared with placebo-treated patients (MPp+p: 31.4%). Among patients receiving induction with melphalan, prednisone and lenalidomide, the frequency of these events was higher in patients receiving continuous treatment with lenalidomide following induction than in patients receiving placebo. Neutropenia AEs led to lenalidomide withdrawal and dose reduction for < 4% and < 16.0% of patients, respectively, in each of the 3 treatment arms. Neutropenia led to dose interruption for 63.3%, 50.0% and 20.3% of patients in the MPR+R, MPR+p and MPp+p arms, respectively.

In Study MM-020, Grade 3 or 4 AEs of infection were reported for more patients in Arm Rd and Arm Rd18 (28.9% and 21.9% of patients, respectively) than patients in Arm MPT (17.2% of patients). Infection AEs led to treatment withdrawal and dose reduction for ≤ 4.3% of patients in all treatment arms. Infection led to dose interruption for 30.8%, 20.9% and 12.4% of patients in Arms Rd, Rd18 and MPT, respectively. In Study MM-015, Grade 3 or 4 infection AEs were reported for 11.3% and 14.5% of patients in the MPR+R and MPR+p arms,

Table 36: Important Identified Risk: Serious Infection due to Neutropenia (Continued)

Serious Infection due to Neutropenia

and 9.8% of patients in the MPp+p arm. Infection AEs led to lenalidomide withdrawal or dose reduction for ≤ 30% of patients in each treatment arm. Infection AEs led to dose interruption for 18.7%, 19.7% and 9.8% of patients in the MPR+R, MPR+p and MPp+p arms, respectively.

RRMM Studies:

Details of neutropenia and infection AEs reported in the RRMM studies are summarised below.

Neutropenia/Infection	Number (%) of Patients	
	MM-009 and MM-010	
	Len/Dex N = 353	PBO/Dex N = 350
All AEs		
Neutropenia	157 (44.5)	23 (6.6)
Infection	243 (68.8)	200 (57.1)
Grade 3 or 4		
Neutropenia	130 (36.8)	12 (3.4)
Infection	88 (24.9)	57 (16.3)
AEs Leading to Discontinuation		
Neutropenia	12 (3.4)[a]	2 (0.6)
Infection	7 (2.0)[b]	10 (2.9)[c]
AEs Leading to Dose Interruption		
Neutropenia	89 (25.2)[d]	13 (3.7)
Infection	79 (22.4)[e]	38 (10.9)[f]
AEs Leading to Dose Reduction		
Neutropenia	16 (4.5)	0
Infection	11 (3.1)[g]	1 (0.3)[h]

[a] Includes PT of febrile neutropenia (1).
[b] Includes PTs of pneumonia NOS (3), sepsis NOS (2), all other PTs experienced by 1 patient each.
[c] Includes PTs of pneumonia NOS (4), all other PTs experienced by 1 patient each.
[d] Includes PT of febrile neutropenia (6).
[e] Includes PTs of pneumonia NOS (20), upper respiratory tract infection NOS (12), urinary tract infection NOS (5), all other PTs experienced by ≤ 4 patients.
[f] Includes PTs of pneumonia NOS, respiratory tract infection NOS, all other PTs experienced by 3 patients or less
[g] Includes PT of oral fungal infection NOS (2). All other PTs reported for ≤ 1 patient.
[h] Includes PT of pneumonia NOS (1).

A total of 130/353 (36.8%) and 88/353 (24.9%) lenalidomide/dexamethasone-treated patients experienced a Grade 3 or 4 neutropenia and infection AE, respectively. Of the neutropenia Grade 3 or 4 events, neutropenia (PT) was the most commonly reported event (125 patients). Of note, Grade 3 or 4 febrile neutropenia and granulocytopenia were reported in only 8 (2.3%) patients and 1 (0.3%) patient, respectively. Infection AEs reported included pneumonia NOS (32 patients), sepsis NOS and urinary tract infection NOS (6 patients each). For placebo/dexamethasone-treated patients, 23/350 (6.6%) experienced a neutropenia AE, with 12/350 (3.4%) experiencing a Grade 3 or 4 AE. A total of 200/350 (57.1%) placebo/dexamethasone-treated patients experienced an infection AE, with 57/350 (16.3%) experiencing a Grade 3 or 4 AE.

Table 36: Important Identified Risk: Serious Infection due to Neutropenia (Continued)

Serious Infection due to Neutropenia

Del 5q MDS Studies:

Details of neutropenia and infection AEs reported in Studies MDS-003 and MDS-004 are summarised below.

Neutropenia/Infection	Number (%) of Patients			
	MDS-003[a] Len (10 mg) N = 148	MDS-004[b]		
		Len (10 mg) N = 69	Len (5 mg) N = 69	PBO[c] N = 67
All AEs				
Neutropenia	101 (68.2)	53 (76.8)	54 (78.3)	12 (17.9)
Infection	117 (79.1)	45 (65.2)	41 (59.4)	23 (34.3)
Grade 3 or 4				
Neutropenia	99 (66.9)	52 (75.4)	51 (73.9)	10 (14.9)
Infection	46 (31.1)	11 (15.9)	6 (8.7)	3 (4.5)
AEs Leading to Discontinuation				
Neutropenia	6 (4.1)	1 (1.4)	1 (1.4)	0
Infection	4 (2.7)	1 (1.4)[d]	1 (1.4)[e]	0
AEs Leading to Dose Interruption				
Neutropenia	38 (25.7)	16 (23.2)	8 (11.6)	0
Infection	0	1 (1.4)[f]	0	1 (1.5)[g]
AEs Leading to Dose Reduction				
Neutropenia	0	23 (33.3)	20 (29.0)[h]	0
Infection	0	2 (2.9)[i]	1 (1.4)[j]	0

[a] Median time on treatment was 52.5 weeks.
[b] Median time on treatment was 50.3 weeks in the 10 mg group, 18.0 weeks in the 5 mg group and 16.0 weeks in the PBO group.
[c] Data in PBO group is from the first 16 weeks of the double-blind phase.
[d, g] Includes PT of pneumonia (both 1)
[e] Includes PT of rash pustular (1)
[f] Includes PT of gastroenteritis (1)
[h] Includes PT of febrile neutropenia (2)
[I] Includes PTs of cellulitis and nasopharyngitis (1 each)
[j] Includes PT of lower respiratory tract infection (1)

In Study MDS-004, the risk of Grade 3 or 4 neutropenia and infection AEs was higher in the lenalidomide groups than the placebo group. Similarly, the risks of neutropenia leading to treatment interruption or dose reduction were higher in the lenalidomide groups than the placebo group.

Table 36: Important Identified Risk: Serious Infection due to Neutropenia (Continued)

Serious Infection due to Neutropenia

MCL Studies:

Neutropenia/Infection	MCL-002		All MCL Lenalidomide Patients (MCL-002, MCL-001, NHL-002, NHL-003) (N = 373)
	Len (N = 167)	Control (N = 83)	
All AEs			
Neutropenia	89 (53.3)	29 (34.9)	201 (53.9)
Infection	90 (53.9)	31 (37.3)	211 (56.6)
Grade 3 or 4			
Neutropenia	78 (46.7)	28 (33.7)	173 (46.4)
Infection	27 (16.2)	8 (9.6)	67 (18.0)
AEs Leading to Discontinuation			
Neutropenia	2 (1.2)	1 (1.2)	10 (2.7)
Infection	2 (1.2)	2 (2.4)	5 (1.3)
AEs Leading to Dose Interruption			
Neutropenia	42 (25.1)	9 (10.8)	87 (23.3)
Infection	31 (18.6)	6 (7.2)	55 (14.7)
AEs Leading to Dose Reduction			
Neutropenia	13 (7.8)	6 (7.2)	28 (7.5)
Infection	0	0	5 (1.3)
AEs Leading to Dose Reduction and Interruption			
Neutropenia	41 (24.6)	2 (2.4)	83 (22.3)
Infection	2 (1.2)	1 (1.2)	7 (1.9)

In Study MCL-002, Grade 3 or 4 neutropenia AEs were reported in a greater proportion of patients in the lenalidomide group (46.7%) than the control group (33.7%). The proportions of patients with neutropenia leading to study treatment being permanently withdrawn, or the dose reduced were the same (1.2% and 1.2%) and similar (7.8% versus 7.2%), respectively, in both treatment groups. A greater proportion of patients in the lenalidomide group than in the control group experienced neutropenia AEs leading to dose interruption (25.1% versus 10.8%, respectively) and to dose reduction and interruption (24.6% versus 2.4%). This might be attributed to the strict dose-modification protocol requirements and the longer treatment duration for the lenalidomide arm compared to the control arm.

In Study MCL-002, Grade 3 or 4 infection AEs were reported in a greater proportion of patients in the lenalidomide group (16.2%) than the control group (9.6%). The proportions of patients with infection AEs leading to study treatment being permanently withdrawn were similar in the lenalidomide and control groups (1.2% versus 2.4%, respectively), whereas a greater proportion of patients in the lenalidomide group than the control group experienced infection AEs leading to dose interruption (18.6% versus 7.2%). The proportions of patients with infection AEs leading to dose reduction and interruption were the same (1.2%) in both groups. No patients had their dose reduced as a result of infection AEs.

Risk Groups and Risk Factors

Haematologic malignancies by themselves or by virtue of their therapeutic strategies, chemotherapy, radiation or haematopoietic stem cell transplant put patients at risk of infections (Khayr 2012). The introduction of stem cell transplantation and novel anti-myeloma agents has improved the outcome of patients with MM. These advances have transformed MM into a chronic condition, with multiple relapses and salvage therapies, all of which results

Table 36: Important Identified Risk: Serious Infection due to Neutropenia (Continued)

Serious Infection due to Neutropenia
in cumulative immunosuppression and higher risk of infection. For example, application of stem cell transplantation has broadened the spectrum of infection to include those caused by Clostridium difficile, cytomegalovirus, and opportunistic moulds. Risk factors include myeloma-related innate immunodeficiency, which involves various arms of the immune system and includes B-cell dysfunction (manifested as hypogammaglobulinemia). Polyclonal hypogammaglobulinemia has been classically associated with infection by encapsulated bacteria, such as Streptococcus pneumoniae and Haemophilus influenzae. Myeloma and treatment-associated organ dysfunctions and comorbidities also increase the risk of infection. These dysfunctions and comorbidities include (1) renal failure (cast nephropathy, hypercalcemia, deposition disease, and others), respiratory compromise, caused by collapse of thoracic vertebra and opiate therapy (which may depress the central nervous system) given to patients with painful fractures (3) severe alimentary mucosal damage (caused by chemotherapy, radiation therapy, or graft-versus-host disease) (4) hyperglycemia induced by dexamethasone (5) transfusional iron overload and (6) the multisystem involvement by myeloma-associated deposition diseases (AL-amyloidosis and light chain deposit disease). Indeed, levels of CD4+ T cells, particularly naive and activated subsets, decrease significantly with increasing cycles of chemotherapy, a decrease strongly associated with opportunistic infections. Finally, myeloma typically affects an older population, with a median age of 62 to 73 years. These patients frequently experience an age-related decline in physiologic reserve of various organs and from other age-related conditions, including frailty, geriatric syndromes, cognitive dysfunction, and social isolation, all of which may increase the risk of infection (Nucci, 2009). Lenalidomide treatment in combination with dexamethasone in MM patients with at least one prior therapy is associated with a higher incidence of Grade 4 neutropenia compared to placebo-dexamethasone treated patients (SmPC, Section 4.4). The combination of lenalidomide with melphalan and prednisone in clinical trials of NDMM patients is associated with a higher incidence of Grade 4 neutropenia than MPp+p treated patients (SmPC, Section 4.4). The proportion of patients who experienced Grade 3 or 4 myelosuppression in one study of lenalidomide-treated patients with MM was significantly higher for patients who had prior high-dose chemotherapy and stem cell transplantation, compared with those that did not (Richardson, 2006b). Impairment of antibody response, neutropenia, treatment with glucocorticoids, and reduction of normal Ig all increase the likelihood of infection. While a much greater proportion of lenalidomide/dexamethasone patients experienced neutropenia relative to placebo/dexamethasone patients, this increased risk did not translate into an infection risk of the same magnitude in either the total study population or in the study population restricted to Grade 3 or 4 toxicities. Lenalidomide treatment in MDS patients is associated with a higher incidence of Grade 3 or 4 neutropenia compared with patients on placebo (SmPC, Section 4.4). In patients with MDS, those experiencing neutropenia while receiving lenalidomide may be at increased risk for infections.
Preventability The major dose-limiting toxicities of lenalidomide include neutropenia. Neutropenia can be managed with dose reduction (Richardson, 2006b). Dosing recommendations in the event of neutropenia can be found in Section 4.2 of the SmPC. The use of growth factors in the management of neutropenia should be considered (SmPC, Section 4.2 and 4.4). Monitoring of lenalidomide-treated patients, particularly in the initial weeks of treatment, is important to reduce the risk of myelosuppression-related complications (List, 2006). Patients should be advised to promptly report febrile episodes and dose reductions may be required (SmPC, Section 4.4). A complete blood cell count, including white blood cell count with differential count, platelet count, haemoglobin, and haematocrit should be performed at baseline, every week for the first 8 weeks of lenalidomide treatment and monthly thereafter to monitor for cytopenias. In MCL patients, the monitoring scheme should be every 2 weeks in Cycles 3 and 4, and then monthly thereafter. In FL patients, the monitoring scheme should be weekly for the first 3 weeks of Cycle 1 (28 days), every 2 weeks during Cycles 2 through 4, and then at the start of each cycle thereafter (SmPC, Section 4.4). Hepatitis B virus status should be established before initiating treatment with lenalidomide. For patients who test positive for HBV infection, consultation with a physician with expertise in the treatment of hepatitis B is

Table 36: Important Identified Risk: Serious Infection due to Neutropenia (Continued)

Serious Infection due to Neutropenia
recommended. Patients previously infected with HBV should be closely monitored for signs and symptoms of active HBV infection throughout therapy (SmPC, Section 4.4). In patients with repeated infectious complications, long-term administration of antibiotic or antiviral medication or use of IV Ig may be recommended (as recommended by Ludwig, 2007).
Impact on the Risk-benefit Balance of the Product Infections in the presence of neutropenia may contribute significantly to morbidity and mortality.
Public Health Impact Severe neutropenia is more prevalent in del 5q MDS patients, than in non-del 5q MDS and MM patients (Kurtin, 2006). In one study of relapsed MM patients, infections were reported in a higher proportion of lenalidomide-treated patients (67.8%), compared to the placebo group (44.0%) (Weber, 2007). Neutropenia is associated with lenalidomide treatment, and is a very common ADR of lenalidomide treatment (SmPC, Section 4.8). All lenalidomide-treated patients should be monitored for myelosuppression to reduce the risk of myelosuppression-related complications. Infections should be treated aggressively in MM patients, as these contribute significantly to morbidity and mortality (Ludwig, 2007). These infections may necessitate treatment with antibiotics and/or G-CSF for neutropenic infection. The majority of patients with MDS die from bleeding or infection due to bone marrow failure (Silverman, 2000). All lenalidomide-treated patients should be monitored for events of infection.
Data Source: Studies NHL-007 and NHL-008 (13 Aug 2018), Study SWOG S0777 (01 Dec 2016); Study CALGB 100104 (01 Mar 2015); Study IFM 2005-02 (01 Mar 2015); Study MM-020 (24 May 2013); Study MM-015 (30 Apr 2013); Integrated Summary of Safety (Dec 2005) for Studies MM-009 and MM-010; Study MDS-003 CSR; Study MDS-004 CSR; Study MCL-001 (20 Mar 2013); Study MCL-002 (07 Mar 2014); Study NHL-002 (23 Jun 2008); Study NHL-003 (27 Apr 2011). **MedDRA Terms** *FL (NHL-007 and NHL-008)* MedDRA v21.0 PTs listed within the Higher Level Term (HLT) for Neutropenias, and the PTs of neutrophil count decreased and neutrophil percentage decreased are collectively referred to as neutropenia. PTs listed within the MedDRA v21.0 SOC of Infections and infestations are collectively referred to as infection. *NDMM RVd Study (SWOG S0777)* The MedDRA v15.1 PTs listed within the HLT for Neutropenias, and the PTs of neutrophil count decreased and neutrophil percentage decreased are collectively referred to as neutropenia. PTs listed within the MedDRA v15.1 SOC of Infections and infestations are collectively referred to as infection. *TE NDMM (CALGB 100104 and IFM 2005-02)* The MedDRA v15.1 PTs listed within the HLT for Neutropenias, and the PTs of neutrophil count decreased and neutrophil percentage decreased are collectively referred to as neutropenia. PTs listed within the MedDRA v15.1 SOC of Infections and infestations are collectively referred to as infection. *TNE NDMM (MM-020 and MM-015)* The MedDRA v15.1 PTs listed within the HLT for Neutropenias, and the PTs of neutrophil count decreased and neutrophil percentage decreased are collectively referred to as neutropenia. PTs listed within the MedDRA v15.1 SOC of Infections and infestations are collectively referred to as infection. *RRMM (MM-009 and MM-010)* The MedDRA v11.0 PTs listed within the HLT for Neutropenias, and the PTs of neutrophil count decreased and neutrophil percentage decreased, as well as the MedDRA v5.1 PT of neutropenia aggravated are collectively referred to as neutropenia. The MedDRA v11.0 and MedDRA v5.1 SOC of Infections and infestations are collectively referred to as infection.

Table 36: Important Identified Risk: Serious Infection due to Neutropenia (Continued)

Serious Infection due to Neutropenia
Del 5q MDS (MDS-003 and MDS-004) The MedDRA v13.0 PTs listed within the HLT for Neutropenias, and the PTs of neutrophil count decreased and neutrophil percentage decreased are collectively referred to as neutropenia. PTs listed within the MedDRA v13.0 SOC of Infections and infestations are collectively referred to as infection. *MCL (MCL-001, MCL-002, NHL-002 and NHL-003)* PTs listed within the MedDRA v16.1 HLT for Neutropenias and PTs of neutrophil count decreased and neutrophil percentage decreased are collectively referred to as neutropenia. PTs listed within the MedDRA v16.1 SOC of Infections and infestations are collectively referred to as infection.

3.1.3. Important Identified Risk: Second Primary Malignancies

Second primary malignancies are identified risks with the use of lenalidomide particularly when lenalidomide is given in combination with oral melphalan or following HDM supported by ASCT or after a prior alkylating therapy. The data from NDMM trials suggest there may be an increased incidence of invasive SPM, especially haematologic SPM, when lenalidomide or thalidomide are given in combination with oral melphalan or as maintenance therapy following HDM supported by ASCT.

The SPM that have been observed include invasive (haematologic [AML, B-cell malignancies, other haematologic malignancies] and solid tumours) and non-invasive (non-melanoma skin cancer [NMSC]) that are identified risks with lenalidomide. Studies NHL-007 and NHL-008 (FL), Study SWOG S0777 (NDMM RVd), Studies IFM 2005-02, CALGB 100104 and GIMEMA (TE NDMM), Studies MM-020 and MM-015 (TNE NDMM), Studies MM-009 and MM-010 (RRMM), Studies MDS-003 and MDS-004 (MDS) and Studies MCL-001, MCL-002, NHL-002 and NHL-003 (MCL) were included in the analysis of these risks. Information concerning this identified risk is summarised in Table 37 using the following data cutoff dates:

FL Studies

- NHL-007: 22 Jun 2018.
- NHL-008: 01 May 2017.

NDMM RVd Study

- SWOG S0777: 01 Dec 2016.

TE NDMM Studies

- IFM 2005-02: 01 Mar 2015.
- CALGB 100104: 01 Mar 2015.
- GIMEMA: 01 Mar 2015.

TNE NDMM Studies

- MM-020: 24 May 2013.
- MM-015: 30 Apr 2013.

RRMM Studies

- MM-009: 23 Jul 2008.
- MM-010: 02 Mar 2008.

MDS Studies

- MDS-003: 27 Aug 2008.
- MDS-004: 26 Nov 2012.

MCL Studies

- MCL-001: 21 Mar 2014.
- MCL-002: 07 Mar 2014.
- NHL-002: 23 Jun 2008.
- NHL-003: 25 Mar 2013.

Table 37: Important Identified Risk: Second Primary Malignancies

Second Primary Malignancies
Potential Mechanisms No mechanism whereby lenalidomide may cause SPM has been identified. While none of the following may be exclusive there may be several explanations why patients with MM might develop secondary haematopoietic and lymphatic 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. • **Heredity** • **Shared aetiologic factors** Human herpes virus-8 (HHV-8) infection in the case of Kaposi sarcoma. EBV infection in the case of PTLD. Exposure to environmental agents.
Evidence Source(s) and Strength of Evidence: Patients treated with lenalidomide may be at increased risk of developing new cancers. The reason for this is not clear, but further investigations are being undertaken.

Table 37: Important Identified Risk: Second Primary Malignancies (Continued)

Second Primary Malignancies
Characterisation of the Risk
Frequency with 95% CI (Invasive SPM [Haematologic Malignancies]) The frequency of haematologic malignancies is summarised in Table 38 for the NDMM RVd study, Table 39 for the NDMM studies, Table 40 for the RRMM studies, and Table 41 for the MDS and lymphoma studies. The risk of SPM associated with lenalidomide is dependent on tumour type and context. In randomised Phase 3 study NHL-007 in FL, there was no increased risk of SPM for lenalidomide plus rituximab compared to rituximab plus placebo. **FL Studies:** Study NHL-007 AML was experienced by 1 (0.29 events per 100 person-years) patient in both the lenalidomide plus rituximab and rituximab plus placebo arms. The AML malignancies were PT acute myeloid leukaemia in both patients. No patients in either treatment arm experienced MDS, B-cell or other haematologic malignancies. Study NHL-008 Other haematologic malignancies were experienced by 1 (0.55 events per 100 person-years) lenalidomide plus rituximab-treated patient. The event of other haematologic malignancies was PT leukaemia granulocytic. No lenalidomide plus rituximab-treated patients experienced AML, MDS or B-cell malignancies. **NDMM RVd Study** Study SWOG S0777 There were no reports of AML in the RVd and Rd arms of Study SWOG S0777. MDS (PT: Myelodysplastic syndrome) was reported in 2 (0.16 events per 100 person-years) patients in the RVd arm and 1 (0.09 events per 100 person-years) patient in the Rd arm. B-cell malignancies were reported in 2 (0.8 events per 100 person-years) patients in the Rd arm (PTs: B-cell type acute leukaemia and diffuse large B-cell lymphoma) and no patients in the RVd arm. There were no reports of other haematologic malignancies in the RVd and Rd arms. **TE NDMM Studies** Study IFM 2005-02 In Study IFM 2005-02, AML was experienced by 6 (0.36 events per 100 person-years) and 3 (0.18 events per 100 person-years) patients in the lenalidomide and placebo arms, respectively. B-cell malignancies were experienced by 11 (0.67 events per 100 person-years) and 2 (0.12 events per 100 person-years) patients in the lenalidomide and placebo arms, respectively. The AML malignancies were acute myeloid leukaemia in 2 (0.7%) patients in the lenalidomide group and 3 (1.0%) patients in the placebo group, and MDS to AML reported in 4 (1.3%) patients in the lenalidomide group. The B-cell malignancies were Hodgkin's disease (4 [1.3%] patients in the lenalidomide group and 1 [0.3%] patient in the placebo group); B-cell type acute leukaemia (3 [1.0%] patients in the lenalidomide group); DLBCL (3 [1.0%] patients in the lenalidomide group) and acute lymphocytic leukaemia (1 [0.3%] patient each in the lenalidomide and placebo groups). MDS was experienced by 4(0.24 events per 100 person-years) patients in the lenalidomide arm and 3 (0.18 events per 100 person-years) patients in the placebo arm. The MDS events were myelodysplastic syndrome in 4 (1.3%) patients in the lenalidomide arm and 2 (0.7%) patients in the placebo group, and refractory anaemia with an excess of blasts in 1 (0.3%) patient in the placebo arm. Other haematologic malignancies were experienced by 1 (0.06 events per 100 person-years) patient in the lenalidomide arm and 1 (0.06 events per 100 person-years) patient in the placebo arm (events of acute biphenotypic leukaemia and TCL, respectively).

Table 37: Important Identified Risk: Second Primary Malignancies (Continued)

Second Primary Malignancies
Study CALGB 100104 In Study CALGB 100104, in the lenalidomide group, the haematologic malignancies of AML and B-cell malignancies were reported for 7 (0.59 events per 100 person-years) and 4 (0.33 events per 100 person-years) patients, respectively. B-cell malignancies were reported in 3 (0.29 events per 100 person-years) patients in the placebo group. The AML malignancies were acute myeloid leukaemia in 5 (2.2%) patients, and MDS to AML and erythroleukaemia each reported in 1 (0.4%) patient in the lenalidomide group. The B-cell malignancies were B-cell type acute leukaemia, reported in 1 (0.4%) patient in the lenalidomide group and 3 (1.4%) patients in the placebo group, and acute lymphocytic leukaemia, B precursor type acute leukaemia and Hodgkin's disease, reported in 1 (0.4%) patient each in the lenalidomide group. Four patients in both the lenalidomide group and the placebo group experienced MDS (0.33 and 0.39 events per 100 person-years, respectively). Other haematologic malignancies were experienced by 1 (0.10 events per 100 person-years) patient in the placebo arm (malignant histiocytosis). Study GIMEMA There were no reports of AML, MDS, other haematologic malignancies or B-cell malignancies in Study GIMEMA. **TNE NDMM Studies** Study MM-020 In Study MM-020, AML was experienced by 1 (0.07 events per 100 person-years), 1 (0.07 events per 100 person-years) and 6 (0.46 events per 100 person-years) patients in Arms Rd, Rd18 and MPT, respectively. There were no reports of B-cell malignancies in Study MM-020. MDS was experienced by 1 (0.07 events per 100 person-years) patient each in Arm Rd and Arm Rd18, and 6 (0.45 events per 100 person-years) patients in Arm MPT. No patients had other haematologic malignancies in Study MM-020. Study MM-015 In Study MM-015, AML was experienced by 5 (0.96 events per 100 person-years), 5 (0.98 events per 100 person-years) and 1 (0.18 events per 100 person-years) patients in Arms MPR+R, MPR+p and MPp+p, respectively. There were no reports of B-cell malignancies in Study MM-015. MDS was experienced by 3 (0.58 events per 100 person-years), 2 (0.39 events per 100 person-years) and 1 (0.18 events per 100 person-years) patients in Arms MPR+R, MPR+p and MPp+p, respectively. Other haematologic malignancies were experienced by 1 (0.19 events per 100 person-years) patient in Arm MPR+R. This other haematologic malignancy was T-cell type acute leukaemia. **RRMM Studies** Studies MM-009 and MM-010 There were no reports of AML or B-cell malignancies in Studies MM-009 and MM-010. MDS was reported in 2 (0.6%) patients in the lenalidomide/dexamethasone group. **Del 5q MDS Studies** For Study MDS-004, the analysis of B-cell malignancies and AML include the double-blind phase of 52 weeks including the first 16 weeks of which the patients in the placebo arm who did not achieve a minor response by Week 16 were given the option to cross over to the 5 mg lenalidomide arm. In MDS, AML is considered disease progression; however, it is also viewed as an important potential risk when taking lenalidomide that will be monitored closely. Study MDS-004 There were no reports of B-cell malignancies in Study MDS-004. AML was reported for 17 (6.50 events per 100 person-years) patients in the lenalidomide 10 mg group, 26 (11.16 events per 100 person-years) patients in the lenalidomide 5 mg group and 27 (12.35 events per 100 person-years) patients in the placebo group (27 patients included 23 patients who crossed over to lenalidomide 5 mg after 16 weeks of placebo treatment).

Table 37: Important Identified Risk: Second Primary Malignancies (Continued)

Second Primary Malignancies
Study MDS-003 B-cell lymphoma was reported for 1 (0.21 events per 100 person-years) patient and AML was reported for 37 (7.86 events per 100 person-years) patients in Study MDS-003. The only other haematologic malignancy reported was MM (1 [0.21 events per 100 patient-years] patient). **MCL Studies** Study MCL-002 There were no reports of AML in Study MCL-002. In Study MCL-002, B-cell malignancies were experienced by 1 (0.36 events per 100 person-years) patient (0.6%) in the lenalidomide group and 1 (0.77 events per 100 person-years) patient (1.2%) in the control group. The B-cell malignancies were acute lymphocytic leukaemia in the patient in the lenalidomide group and DLBCL in the patient in the control group. MDS was experienced by 1 (0.36 events per 100 person-years) patient (0.6%) in the lenalidomide group and no patients in the control group. No patients had other haematologic malignancies in Study MCL-002. Study MCL-001 In Study MCL-001, AML (PT: myeloproliferative disorder) was experienced by 1 (0.48 events per 100 person-years) patient (0.7%) treated with lenalidomide. There were no reports of B-cell malignancies in Study MCL-001. MDS was experienced by 1 (0.48 events per 100 person-years) lenalidomide-treated patient (0.7%). No patients had other haematologic malignancies in Study MCL-001. Study NHL-002 There were no reports of AML, MDS, other haematologic malignancies, or B-cell malignancies in Study NHL-002. Study NHL-003 In Study NHL-003, AML (PT: acute myeloid leukaemia) was reported in 1 (0.5%) patient treated with lenalidomide. There were no reports of B-cell malignancies in Study NHL-003. MDS was reported in 1 (0.5%) patient treated with lenalidomide. There were no reports of other haematologic malignancies in Study NHL-003. **Frequency with 95% CI (Invasive SPM [Solid Tumours])** The frequency of solid tumours is summarised in Table 38 for the RVd study, Table 39 for the NDMM studies, Table 40 for the RRMM studies, and Table 41 for the MDS and lymphoma studies. **FL Studies:** Study NHL-007 Solid tumours were reported for 2 (0.58 events per 100 person-years) and 3 (0.89 events per 100 person-years) patients in the lenalidomide plus rituximab and rituximab plus placebo arms, respectively. Solid tumours in the lenalidomide plus rituximab arm were carcinoid tumour of the gastrointestinal tract and squamous cell carcinoma of lung (1 [0.7%] patient each). Solid tumours in the rituximab plus placebo arm were invasive ductal breast carcinoma, malignant melanoma and transitional cell cancer of the renal pelvis and ureter localised (1 [0.7%] patient each). Study NHL-008 Solid tumours were reported for 1 (0.55 events per 100 person-years) lenalidomide plus rituximab-treated patient. This was an event of transitional cell carcinoma (1 [0.6%] patient). **NDMM RVd Study** Study SWOG S0777 Solid tumours were reported in 8 (0.66 events per 100 person-years) patients in the RVd arm and 10 (0.90 events per 100 person-years) patients in the Rd arm in Study SWOG S0777. The solid tumours reported in the RVd and Rd arms were all single reports (by PT).

Table 37: Important Identified Risk: Second Primary Malignancies (Continued)

Second Primary Malignancies
TE NDMM Studies Study IFM 2005-02 Solid tumours were reported for 21 (1.28 events per 100 person-years) and 13 (0.78 events per 100 person-years) patients in the lenalidomide and placebo arms, respectively. The most frequently reported solid tumours (experienced by ≥ 2 patients overall) were breast cancer (3 [1.0%] patients in the lenalidomide arm and 1 [0.3%] patient in the placebo arm); hypopharyngeal cancer (2 [0.7%] patients in the lenalidomide arm); malignant melanoma (1 [0.3%] patient in the lenalidomide arm and 2 [0.7%] patients in the placebo arm); prostate cancer (3 [1.0%] patients in the lenalidomide arm and 4 [1.3%] patients in the placebo arm); rectal cancer (1 [0.3%] patient each in the lenalidomide and placebo arms), and renal cell carcinoma (1 [0.3%] patient each in the lenalidomide and placebo arms). Study CALGB 100104 Solid tumours were reported for 17 (1.48 events per 100 person-years) and 10 (0.98 events per 100 person-years) patients in the lenalidomide and placebo groups, respectively. The most frequently reported solid tumours (experienced by ≥ 2 patients overall) were breast cancer (experienced by 3 [1.3%] patients in the lenalidomide group and 1 [0.5%] patient in the placebo group); breast cancer in situ (experienced by 2 [0.9%] patients in the lenalidomide group); endometrial cancer (experienced by 2 [0.9%] patients in the lenalidomide group and 1[0.5%] patient in the placebo group); malignant melanoma (1 [0.4%] patient in the lenalidomide group and 2 [0.9%] patients in the placebo group), and prostate cancer (3 [1.3%] patients in the lenalidomide group only). Study GIMEMA Solid tumours were reported for 5 (2.21 events per 100 person-years) and 2 (0.68 events per 100 person-years) in the lenalidomide and no maintenance groups, respectively. The solid tumours reported in the lenalidomide group were adenocarcinoma sigma, breast cancer, colon adenocarcinoma, K prostate, and left breast carcinoma, each reported in 1 (1.8%) patient. The solid tumours reported in the placebo group were 'breast cancer: carcinoma infiltrante con aspetti lobulare G2', K lung, and 'tumor endometrial cancer: adenocarcinoma endometriale IIstadio G2-3', each reported in 1 (1.3%) patient. **TNE NDMM Studies** Study MM-020 Solid tumours were reported for 15 (1.09 events per 100 person-years), 29 (2.15 events per 100 person-years) and 15 (1.15 events per 100 person-years) patients in Arms Rd, Rd18 and MPT, respectively. The most frequently reported solid tumours (experienced by ≥ 3 patients overall) were prostate cancer (1 [0.2%] patient in Arm Rd, 3 [0.6%] patients in Arm Rd18 and 2 [0.4%] patients in Arm MPT), breast cancer (1 [0.2%] patient in Arm Rd, 3 [0.6%] patients in Arm Rd18 and 1 [0.2%] patient in Arm MPT), lung squamous cell carcinoma Stage 1 (3 [0.6%] patients in Arm Rd18). Study MM-015 Solid tumours were reported for 5 (0.97 events per 100 person-years), 11 (2.16 events per 100 person-years) and 4 (0.74 events per 100 person-years) patients in Arms MPR+R, MPR+p and MPp+p, respectively. The most frequently reported solid tumours (experienced by ≥ 2 patients overall) were breast cancer (2 [1.3%] patients in Arm MPp+p), hepatic neoplasm malignant (reported for 1 [0.7%] patient each in Arms MPR+p and MPp+p), prostate cancer and rectal cancer (both reported for 1 patient [0.7%] each in Arms MPR+R and MPR+p). **RRMM Studies** Solid tumours were reported for 6 (1.7%) patients in the lenalidomide/dexamethasone group. The solid tumours were reported for single patients each (fibrous histiocytoma, breast cancer in situ, bronchioalveolar carcinoma, glioblastoma multiforme, lung adenocarcinoma NOS, prostate cancer NOS and transitional cell carcinoma). In the placebo/dexamethasone group, 2 patients (0.6%) developed a solid tumour (fibrous histiocytoma and malignant melanoma).

Table 37: Important Identified Risk: Second Primary Malignancies (Continued)

Second Primary Malignancies
Analyses were performed to present incidence rates per 100 person-years, with person-years being the time in years from first dose date to last dose date for patients without an SPM, and the time from first dose date to SPM onset for patients with an SPM. The incidence rates of solid tumours were similar for the lenalidomide/dexamethasone and placebo/dexamethasone groups (1.28 versus 0.91 per 100 person-years, respectively). **Del 5q MDS Studies** For Study MDS-004, the analysis of SPM includes data from the open-label phase as well as the double-blind phase (the double-blind phase was 52 weeks including the first 16 weeks of which the patients in the placebo arm who did not achieve a minor response by Week 16 were given the option to cross over to the 5 mg lenalidomide arm). Study MDS-004 In Study MDS-004, solid tumours were reported for 4 (1.52 events per 100 patient-years) patients in the 10 mg lenalidomide group, 4 (1.69 events per 100 patient-years) patients in the 5 mg lenalidomide group and 2 (0.85 events per 100 patient-years) patients in the placebo group (including patients who crossed over from placebo to lenalidomide 5 mg). Two patients (1 patient in the 10 mg lenalidomide group and 1 in the placebo group) had 2 SPM each; therefore a total of 12 AEs of SPM have been reported to date. Two of the 12 events of SPM were diagnosed a few days after the patients were randomised on the study and were not therefore considered related to treatment. Study MDS-003 Solid tumours were reported for 7 (1.49 events per 100 patient-years) patients, and comprised carcinoid tumour of the small bowel, colon cancer, endometrial cancer, lung cancer metastatic, ovarian cancer, thymoma and vulval cancer, which were experienced by single (0.7%) patients each. **MCL Studies** Study MCL-002 Solid tumours were reported in 4 (1.47 events per 100 person-years) patients (2.4%) in the lenalidomide group and 3 (2.37 events per 100 person-years) patients (3.6%) in the control group. The solid tumours reported in the lenalidomide group were adenocarcinoma gastric, liposarcoma, metastatic squamous cell carcinoma and transitional cell carcinoma, each reported in 1 (0.6%) patient. The solid tumours reported in the control group were colon cancer, meningioma benign and metastatic renal cell carcinoma, each reported in 1 (1.2%) patient. Study MCL-001 Solid tumours were reported in 5 (2.46 events per 100 person-years) patients (3.7%) and comprised bladder cancer, colon cancer metastatic, meningioma, metastases to liver, metastatic squamous cell carcinoma and transitional cell carcinoma, each reported in 1 (0.7%) patient. Study NHL-002 Solid tumours were reported in 2 (7.29 events per 100 person-years) patients (4.1%) treated with lenalidomide and comprised breast cancer and small cell lung cancer stage unspecified, each reported in 1 (2.0%) patient. Study NHL-003 Solid tumours were reported in 4 (1.8%) patients treated with lenalidomide in Study NHL-003, and comprised gastric cancer, oesophageal carcinoma, prostate cancer and renal cell carcinoma stage unspecified in 1 (0.5%) patient each. **Frequency with 95% CI (Non-invasive SPM [NMSC])** The frequency of NMSC is summarised in Table 38 for the RVd study, Table 39 for the NDMM studies, Table 40 for the RRMM studies, and Table 41 for the MDS and lymphoma studies.

Table 37: Important Identified Risk: Second Primary Malignancies (Continued)

Second Primary Malignancies
FL Studies: Study NHL-007 Non-melanoma skin cancers were experienced by 3 (0.88 events per 100 person-years) and 2 (0.59 events per 100 person-years) patients in the lenalidomide plus rituximab and rituximab plus placebo arms, respectively. Non-melanoma skin cancers reported in the lenalidomide plus rituximab arm comprised squamous cell carcinoma of skin (2 [1.4%] patients) and basal cell carcinoma (1 [0.7%] patient). Non-melanoma skin cancers reported in the rituximab plus placebo arm comprised basal cell carcinoma and squamous cell carcinoma of skin (1 [0.7%] patient each). Study NHL-008 Non-melanoma skin cancers were experienced by 8 (4.57 events per 100 person-years) lenalidomide plus rituximab-treated patients. The NMSCs reported comprised basal cell carcinoma (5 [2.8%] patients) and squamous cell carcinoma of skin (4 [2.3%] patients). **NDMM RVd Study** Study SWOG S0777 In Study SWOG S0777, NMSC was reported in 11 (0.92 events per 100 person-years) patients in the RVd arm and 7 (0.62 events per 100 person-years) patients in the Rd arm. NMSC reported in the RVd arm comprised basal cell carcinoma (6 [2.3%] patients) and squamous cell carcinoma of skin (8 [3.1%] patients). NMSC reported in the Rd arm were basal cell carcinoma (6 [2.3%] patients) and squamous cell carcinoma of skin (2 [0.8%] patients). **TE NDMM Studies** Study IFM 2005-02 In Study IFM 2005-02, NMSC was experienced by 10 (0.61 events per 100 person-years) and 7 (0.42 events per 100 person-years) patients in the lenalidomide and placebo arms, respectively. NMSC reported in the lenalidomide group comprised basal cell carcinoma (8 [2.6%] patients), squamous cell carcinoma (1 [0.3%] patient), and squamous cell carcinoma of skin (4 [1.3%] patients). NMSC reported in the placebo group comprised basal cell carcinoma (2 [0.7%] patients), keratoacanthoma (1 [0.3%] patient), squamous cell carcinoma (2 [0.7%] patients), and squamous cell carcinoma of skin (2 [0.7%] patients). Study CALGB 100104 In Study CALGB 100104, in the lenalidomide group, NMSC was reported for 12 patients (1.02 events per 100 person-years). A similar incidence was reported in the placebo group (9 patients [0.88 events per 100 person-years]). The NMSC comprised squamous cell carcinoma of skin (9 [4.0%] patients in the lenalidomide group and 5 [2.3%] patients in the placebo group), and basal cell carcinoma (7 [3.1%] patients in the lenalidomide group and 5 [2.3%] patients in the placebo group). Study GIMEMA In Study GIMEMA, NMSC was reported for 1 (0.42 events per 100 person-years) patient treated with lenalidomide (basalioma) and 1 (0.34 events per 100 patient-years) patient not receiving maintenance treatment (‘squamous cell cancer of the skin left leg skin (upon tibia)’). **TNE NDMM Studies** Study MM-020 In Study MM-020, NMSC was experienced by 22 (1.62 events per 100 person-years), 17 (1.25 events per 100 person-years) and 21 (1.62 events per 100 person-years) patients in Arms Rd, Rd18 and MPT, respectively. Study MM-015 In Study MM-015, NMSC was experienced by 4 (0.77 events per 100 person-years), 6 (1.19 events per 100 person-years) and 8 (1.51 events per 100 person-years) patients in Arms MPR+R, MPR+p and MPp+p, respectively.

Table 37: Important Identified Risk: Second Primary Malignancies (Continued)

Second Primary Malignancies
RRMM Studies NMSC was reported for 3.1% of lenalidomide-treated patients, including basal cell carcinoma and squamous cell carcinoma (1.7% of patients each), and Bowen's disease (0.6% of patients). In the placebo/dexamethasone group, 2 patients each (0.6%) developed a NMSC (basal cell carcinoma and squamous cell carcinoma). Analyses were performed to present incidence rates per 100 person-years, with person-years being the time in years from first dose date to last dose date for patients without an SPM, and the time from first dose date to SPM onset for patients with an SPM. The incidence rates of NMSC were 2.40 versus 0.91 per 100 person-years for the lenalidomide/dexamethasone and placebo/dexamethasone groups, respectively. **Del 5q MDS Studies** For Study MDS-004, the analysis of SPM includes data from the open-label as well as the double-blind phase (the double-blind phase was 52 weeks including the first 16 weeks of which the patients in the placebo arm who did not achieve a minor response by Week 16 were given the option to cross over to the 5 mg lenalidomide arm). Study MDS-004 One patient each in the lenalidomide 10 mg (0.38 events per 100 person-years) and 5 mg groups (0.42 events per 100 person-years) developed a NMSC (basal cell carcinoma). No placebo-treated patients experienced a NMSC. Study MDS-003 In Study MDS-003, 6 (1.30 events per 100 person-years) patients developed a NMSC. The NMSC comprised squamous cell carcinoma of skin (3 [2.0%] patients), basal cell carcinoma and squamous cell carcinoma (2 [1.4%] patients each) and keratocanthoma (1 [0.7%] patient). NMSC was experienced by 6 (4.1%) patients in total. **MCL Studies** Study MCL-002 In Study MCL-002, NMSC was reported in 5 (1.88 events per 100 person-years) lenalidomide-treated patients (3.0%) and 1 (0.77 events per 100 person-years) control patient (1.2%). For lenalidomide-treated patients, the NMSC comprised squamous cell carcinoma of skin in 4 (2.4%) patients and basal cell carcinoma, squamous cell carcinoma and squamous cell carcinoma of the oral cavity in 1 (0.6%) patient each. In the control group, the NMSC was squamous cell carcinoma of skin in 1 (1.2%) patient. Study MCL-001 In Study MCL-001, NMSC was experienced by 7 (3.54 events per 100 person-years) patients (5.2%) treated with lenalidomide, and comprised squamous cell carcinoma of skin in 6 (4.5%) patients and basal cell carcinoma in 4 (3.0%) patients. Study NHL-002 There were no reports of NMSC in Study NHL-002. Study NHL-003 In Study NHL-003, NMSC was reported in 6 (2.8%) patients treated with lenalidomide, and comprised squamous cell carcinoma in 3 (1.4%) patients, basal cell carcinoma in 2 (0.9%) patients, basosquamous carcinoma in 1 (0.5%) patient and squamous cell carcinoma of skin in 1 (0.5%) patient.

Table 37: Important Identified Risk: Second Primary Malignancies (Continued)

Second Primary Malignancies
Seriousness/Outcomes (Invasive SPM [Haematologic Malignancies]) The outcome of haematologic malignancies is summarised in Table 42 for the NDMM RVd study, Table 43 for the NDMM studies, Table 44 for the RRMM studies, and Table 45 for the MDS and lymphoma studies. **FL Studies:** Study NHL-007 In Study NHL-007, one lenalidomide plus rituximab-treated patient with an event of AML had an outcome of not recovered/not resolved. One event of AML in the rituximab plus placebo arm had an outcome of death. Study NHL-008 In Study NHL-008, no haematologic malignancies had an outcome of death. One (0.6%) lenalidomide plus rituximab-treated patient with an event of leukaemia granulocytic had an outcome of not recovered/not resolved. **NDMM RVd Study** Study SWOG S0777 In Study SWOG S0777, there were no reports of AML in the RVd and Rd arms, and no reports of B-cell malignancy in the RVd arm. B-cell malignancies with outcomes of not recovered/not resolved were reported in 2 (0.8%) patients in the Rd arm. Outcomes of not recovered/not resolved were recorded for MDS in 2 (0.8%) patients in the RVd arm and 1 (0.4%) patient in the Rd arm. There were no reports of other haematologic malignancies in the RVd and Rd arms. **TE NDMM Studies** Study IFM 2005-02 In the lenalidomide arm of Study IFM 2005-02, AML had an outcome of death in 5 (1.6%) patients and ongoing at death in 1 (0.3%) patient; B-cell malignancy had an outcome of death in 3 (1.0%) patients; and MDS had an outcome of death in 1 patient (0.3%). In the placebo arm, an outcome of death was reported for 3 (1.0%) patients with AML and 1 (0.3%) patient with B-cell malignancy. In the lenalidomide arm, B-cell malignancy had an outcome of recovering/resolving for 2 (0.7%) patients; not recovered/not resolved for 2 (0.7%) patients; and missing for 4 (1.3%) patients. An outcome of not recovered/not resolved was recorded for 3 patients (1.0%) with MDS and 1 (0.3%) patient with other haematologic malignancies. In the placebo arm, outcome was missing for 1 (0.3%) patient with a B-cell malignancy. An outcome of death was recorded for 2 patients (0.7%) with MDS and 1 patient (0.3%) with other haematologic malignancies. Study CALGB 100104 In Study CALGB 100104, an outcome of death was reported for AML in 1 (0.4%) patient in the lenalidomide arm. In the lenalidomide arm, AML had an outcome of not recovered/not resolved for 2 (0.9%) patients, and missing for 4 (1.8%) patients. In the lenalidomide arm, B-cell malignancy had an outcome of not recovered/not resolved for 1 (0.4%) patient, and missing for 3 (1.3%) patients. For patients with MDS in the lenalidomide arm, an outcome of not recovered/not resolved was reported for 1 (0.4%) patient, and the outcome was missing for 3 (1.3%) patients. In the placebo group, B-cell malignancy had an outcome of missing for 2 (0.9%) patients and not recovered/not resolved for 1 (0.5%) patient; MDS had an outcome of death for 1 (0.5%) patient. Study GIMEMA There were no reports of AML or B-cell malignancies in Study GIMEMA. **TNE NDMM Studies** Study MM-020 In Study MM-020, AML had an outcome of death for 2 (0.4%) patients in Arm MPT, not recovered/not resolved for 1 (0.2%) patient each in Arm Rd and Arm Rd18 and 2 (0.4%) patients in Arm MPT and missing for 2 (0.4%) patients in Arm MPT. MDS had an outcome of death in 1 (0.2%) patient in Arm Rd and 1 (0.2%) patient in Arm

Table 37: Important Identified Risk: Second Primary Malignancies (Continued)

Second Primary Malignancies
MPT. Other outcomes for other haematologic malignancies were not recovered/not resolved for 1 (0.2%) and 5 (0.9%) patients with MDS in Arms Rd18 and MPT, respectively. There were no reports of B-cell malignancies in Study MM-020. Study MM-015 AML had an outcome of death for 3 (2.0%) patients each in Arms MPR+R and MPR+p, not recovered/not resolved for 1 (0.7%) patient each in Arms MPR+R and MPp+p, and ongoing at death for 1 (0.7%) patient in Arm MPR+R. MDS had an outcome of death in 1 (0.7%) patient each in Arm MPR+R, Arm MPR+p, and Arm MPp+p. Other outcomes for haematologic malignancies were not recovered/not resolved for 2 (1.3%) patients with MDS in Arm MPR+R and 1 (0.7%) patient in Arm MPR+p, and recovered/resolved for 1 (0.7%) patient with other haematologic cancer in Arm MPR+R. There were no reports of B-cell malignancies in Study MM-015. **RRMM Studies** Studies MM-009 and MM-010 There were no reports of AML or B-cell malignancies in Studies MM-009 and MM-010. The outcomes of the other haematologic malignancies in Studies MM-009 and MM-010 were unknown. **Del 5q MDS Studies** For Study MDS-004, the analysis of SPM includes data from the open-label phase as well as the double-blind phase (the double-blind phase was 52 weeks including the first 16 weeks of which the patients in the placebo arm who did not achieve a minor response by Week 16 were given the option to cross over to the 5 mg lenalidomide arm). Study MDS-004 There were no reports of B-cell malignancies or other haematologic malignancies in Study MDS-004. Of the patients with AML, 14 out of 16 patients in the lenalidomide 10 mg group, 23 out of 24 patients in the lenalidomide 5 mg group and 25 out of 26 patients in the placebo group have died. Study MDS-003 In Study MDS-003, no patients had an outcome of death from B-cell malignancies. The outcome of B-cell malignancy in Study MDS-003 was recovered/resolved. Of the 37 patients with AML, 35 had died at the data cutoff and 2 were alive. The cause of death for the 35 patients is not known. An outcome of not recovered/not resolved was reported for a single patient with other haematologic malignancy. **MCL Studies** Study MCL-002 There were no reports of AML in Study MCL-002. In the lenalidomide group, the outcome of the B-cell malignancy was death in 1 (0.6%) patient, and the outcome of the B-cell malignancy was not recovered/not resolved in 1 (1.2%) patient in the control group. MDS had an outcome of not recovered/not resolved in 1 (0.6%) lenalidomide-treated patient. No patients had other haematologic malignancies. Study MCL-001 In Study MCL-001, AML had an outcome of not recovered/not resolved in 1 (0.7%) lenalidomide-treated patient. There were no reports of B-cell malignancies in Study MCL-001. MDS had an outcome of ongoing at death in 1 (0.7%) lenalidomide-treated patient. No patients had other haematologic malignancies in Study MCL-001. Study NHL-002 There were no reports of AML, MDS, other haematologic malignancies and B-cell malignancies in Study NHL-002.

Table 37: Important Identified Risk: Second Primary Malignancies (Continued)

Second Primary Malignancies
Study NHL-003 In Study NHL-003, AML had an outcome of recovered/resolved in 1 (0.5%) lenalidomide-treated patient. MDS had an outcome of not recovered/not resolved in 1 (0.5%) lenalidomide-treated patient. No patients had other haematologic malignancies in Study NHL-003. **Seriousness/Outcomes (Invasive SPM [Solid Tumours])** The outcome of solid tumours is summarised in Table 42 for the NDMM RVd study, Table 43 for the NDMM studies, Table 44 for the RRMM studies, and Table 45 for the MDS and lymphoma studies. **FL Studies:** Study NHL-007 In Study NHL-007, in the lenalidomide plus rituximab arm an outcome of recovered/resolved and not recovered/not resolved was reported for 1 (0.7%) patient each. In the rituximab plus placebo arm, an outcome of recovered/resolved was reported for 3 (2.0%) patients. Study NHL-008 In Study NHL-008, an outcome of not recovered/not resolved was reported for 1 (0.6%) lenalidomide plus rituximab-treated patient. **NDMM RVd Study** Study SWOG S0777 For patients in the RVd arm with solid tumours, the outcomes were death (1 [0.4%] patient), recovered/resolved (4 [1.5%] patients), recovering/resolving (1 [0.4%] patient) and not recovered/not resolved (2 [0.8%] patients). For patients in the Rd arm with solid tumours, the outcomes were recovered/resolved (4 [1.6%] patients), recovered with sequela (1 [0.4%] patient), not recovered/not resolved (3 [1.2%] patient) and missing (2 [0.8%] patients). **TE NDMM Studies** Study IFM 2005-02 In the lenalidomide arm of Study IFM 2005-02, an outcome of death was recorded for 2 patients (0.7%) with solid tumours. In the placebo arm, an outcome of death was recorded for 1 patient (0.3%) with solid tumours. For patients with solid tumours in the lenalidomide arm, an outcome of recovered/resolved was reported for 6 patients (2.0%), recovering/resolving was reported for 5 (1.6%) patients, not recovered/not resolved was reported for 7 (2.3%) patients, and ongoing at death was reported for 1 (0.3%) patient. Study CALGB 100104 In Study CALGB 100104, an outcome of death was reported for 1 (0.4%) patient with solid tumour in the lenalidomide arm. For patients with solid tumours in the lenalidomide arm, an outcome of not recovered/not resolved was reported for 1 (0.4%) patient, and the outcome was missing for 15 (6.7%) patients. Study GIMEMA In Study GIMEMA, an outcome of death was reported for 1 (1.8%) patient with solid tumour in the lenalidomide group. In the lenalidomide group, outcomes of recovered/resolved, recovering/resolving and not recovered/not resolved were reported for 2 (3.6%), 1 (1.8%) and 1 (1.8%) patients with solid tumour, respectively. In patients not receiving maintenance treatment, outcomes of not recovered/not resolved and recovered/resolved were each reported for 1 (1.3%) patient with solid tumour.

Table 37: Important Identified Risk: Second Primary Malignancies (Continued)

Second Primary Malignancies
TNE NDMM Studies Study MM-020 In Study MM-020, solid tumours had an outcome of death in 3 (0.6%) patients each in Arms Rd and Rd18, and in 5 (0.9%) patients in Arm MPT. Other outcomes for solid tumours were not recovered/not resolved for 5 (0.9%), 5 (0.9%) and 3 (0.6%) patients in Arms Rd, Rd18 and MPT, respectively; recovered/resolved for 3 (0.6%), 9 (1.7%) and 5 (0.9%) patients, respectively; ongoing at death for 1 (0.2%), 2 (0.4%) and 2 (0.4%) patients, respectively; recovered with sequelae for 0, 3 (0.6%) and 0 patients, respectively, and missing for 3 (0.6%), 7 (1.3%) and 0 patients, respectively. Study MM-015 In Arm MPR+R, solid tumour had an outcome of death in 2 (1.3%) patients and in Arm MPR+p, solid tumour had an outcome of death in 4 (2.6%) patients. Other outcomes for solid tumours in Arms MPR+R, MPR+p and MPp+p were not recovered/not resolved for 1 (0.7%), 3 (2.0%) and 0 patients, respectively; ongoing at death for 1 (0.7%), 1 (0.7%) and 0 patients, respectively; and missing for 1 (0.7%), 3 (2.0%) and 4 (2.6%) patients, respectively. **RRMM Studies** Studies MM-009 and MM-010 For solid tumours in the lenalidomide/dexamethasone and placebo/dexamethasone groups the outcomes were unknown for 2 (0.6%) and 0 patients, respectively; recovered/resolved for 1 (0.3%) and 0 patients, respectively; and not recovered/not resolved for 3 (0.8%) and 0 patients, respectively. **Del 5q MDS Studies** Study MDS-004 In Study MDS-004, one (1.4%) patient in the lenalidomide 5 mg group and 1 (1.5%) patient in the placebo group had an outcome of death from a solid tumour. The outcomes in the lenalidomide 10 mg group were recovered/resolved (2 [2.9%] patients), recovered with sequelae (1 [1.4%] patient) and not recovered/resolved (1 [1.4%] patient). The outcomes for the single patients with solid tumours in the lenalidomide 5 mg group and placebo groups were not recovered/resolved. Study MDS-003 In Study MDS 003, the outcome was death for 2 (1.4%) patients, resolved/recovered with/without sequelae for 2 (1.4%) patients and unknown/missing for 3 (2.0%) patients, all due to solid tumours. **MCL Studies** Study MCL-002 Outcomes for solid tumours were recovered/resolved in 2 (1.2%) patients, not recovered/not resolved in 1 (0.6%) patient and recovered with sequelae in 1 (0.6%) patient in the lenalidomide group. Outcomes for solid tumours in the control group were death, not recovered/not resolved and recovered/resolved in 1 (1.2%) patient each. Study MCL-001 Outcomes for solid tumours were not recovered/not resolved in 3 (2.2%) patients, recovered/resolved in 1 (0.7 %) patient, and recovered with sequelae in 1 (0.7%) patient treated with lenalidomide. Study NHL-002 Outcomes for solid tumours were not recovered/not resolved in 2 (4.1%) patients treated with lenalidomide. Study NHL-003 One patient (0.5%) had a fatal outcome for solid tumour; the outcomes for the remaining solid tumours were ongoing at death in 1 (0.5%) patient and missing in 2 (0.9%) patients treated with lenalidomide in Study NHL-003.

Table 37: Important Identified Risk: Second Primary Malignancies (Continued)

Second Primary Malignancies
Seriousness/Outcomes (Non-invasive SPM [NMSC]) The outcome of NMSC is summarised in Table 42 for the NDMM RVd study, Table 43 for the NDMM studies, Table 44 for the RRMM studies, and Table 45 for the MDS and lymphoma studies. **FL Studies:** Study NHL-007 In Study NHL-007, an outcome of recovered/resolved was reported for 2 (1.4%) patients and not recovered/not resolved for 1 (0.7%) patient in the lenalidomide plus rituximab arm. In the rituximab plus placebo arm, an outcome of recovered/resolved was reported for 2 (1.4%) patients with NMSC. Study NHL-008 In Study NHL-008, no NMSC had an outcome of death. All reported events of NMSC had an outcome of recovered/resolved. **NDMM RVd Study** Study SWOG S0777 In Study SWOG S0777, the outcomes of NMSC in the RVd arm were recovered/resolved in 6 (2.3%) patients, recovered with sequela in 3 (1.1%) patients and recovering/resolving in 2 (0.8%) patients. The outcomes of NMSC in the Rd arm were recovered/resolved in 2 (0.8%) patients, not recovered/not resolved in 1 (0.4%) patient and missing in 4 (1.6%) patients. **TE NDMM Studies** Study IFM 2005-02 In the lenalidomide arm of Study IFM 2005-02, an outcome of recovered/resolved and recovering/resolving was reported for 8 (2.6%) and 2 (0.7%) patients with NMSC, respectively. In the placebo arm, NMSC had an outcome of recovered/resolved (5 [1.7%] patients), not recovered/not resolved (1 [0.3%] patient) and recovering/resolving (1 [0.3%] patient). Study CALGB 100104 In Study CALGB 100104, in the lenalidomide arm, NMSC had an outcome of not recovered/not resolved for 3 (1.3%) patients, recovering/resolving for 1 (0.4%) patient, and recovered/resolved for 2 (0.9%) patients. The outcome was missing for 6 (2.7%) patients in the lenalidomide arm. In the placebo arm, NMSC had an outcome of not recovered/not resolved for 1 (0.5%) patient, recovered/resolved for 4 (1.8%) patients, and the outcome was missing for 4 (1.8%) patients. Study GIMEMA In Study GIMEMA, in the lenalidomide group, an outcome of recovered/resolved was reported for 1 (1.8%) patient with NMSC. In patients not receiving maintenance treatment, an outcome of recovered/resolved was reported for 1 (1.3%) patient with NMSC. **TNE NDMM Studies** Study MM-020 In Arms Rd and Rd18, respectively, of Study MM-020, an outcome of recovered/resolved was reported for 18 (3.4%) patients and 13 (2.4%) patients with NMSC, not recovered/not resolved was reported for 1 (0.2%) patient and 2 (0.4%) patients, missing was reported for 2 (0.4%) patients each, and ongoing at death was reported for 1 (0.2%) patient and 0 patients. In Arm MPT, an outcome of recovered/resolved was reported for 17 (3.1%) patients with NMSC, not recovered/not resolved was reported for 2 (0.4%) patients, and missing was reported for 2 (0.4%) patients.

Table 37: Important Identified Risk: Second Primary Malignancies (Continued)

Second Primary Malignancies
Study MM-015 For NMSC in Arms MPR+R, MPR+p and MPp+p, the outcomes were recovered/resolved for 1 (0.7%), 5 (3.3%) and 6 (3.9%) patients, respectively, and not recovered/not resolved for 1 (0.7%), 0 and 0 patients, respectively. The outcomes were missing for 2 (1.3%), 1 (0.7%) and 2 (1.3%) patients in Arms MPR+R, MPR+p and MPp+p, respectively. **RRMM Studies** Studies MM-009 and MM-010 The outcomes of the events of NMSC were recovered/resolved for 2 (0.6%) patients in the lenalidomide-treated patients and 1 [0.3%] patient in the placebo/dexamethasone group. The outcomes for the other events of NMSC were unknown. **Del 5q MDS Studies** For Study MDS-004, the analysis of SPM includes data from the open-label phase as well as the double-blind phase (the double-blind phase was 52 weeks including the first 16 weeks of which the patients in the placebo arm who did not achieve a minor response by Week 16 were given the option to cross over to the 5 mg lenalidomide arm). Study MDS-004 In Study MDS-004, the outcome for all events of NMSC was unknown. Study MDS-003 In Study MDS-003, no patients had an outcome of death from NMSC. The outcome for all events of NMSC was unknown. **MCL Studies** Study MCL-002 The outcomes of the events of NMSC were recovered/resolved in 4 (2.4%) patients and not recovered/not resolved in 1 (0.6%) patient treated with lenalidomide in Study MCL-002. The outcome of the event of NMSC was recovered/resolved in 1 (1.2%) patient treated with control. Study MCL-001 The outcomes of the events of NMSC were recovered/resolved in 6 (4.5%) patients and not recovered/not resolved in 1 (0.7%) patient treated with lenalidomide in Study MCL-001. Study NHL-002 There were no reports of NMSC in Study NHL-002. Study NHL-003 The outcomes of the events of NMSC were recovered/resolved in 3 (1.4%) patients and missing in 3 (1.4%) patients treated with lenalidomide in Study NHL-003.
Severity and Nature of Risk (Invasive SPM [Haematologic Malignancies]) The severity and nature of the haematologic malignancies are summarised in Table 46 for the NDMM RVd study, Table 47 for the NDMM studies, Table 48 for the RRMM studies, and Table 49 for the MDS and lymphoma studies. **FL Studies:** Study NHL-007 In Study NHL-007, the frequency of Grade 3 or 4 events was the same in the lenalidomide plus rituximab versus the rituximab plus placebo arm for AML (1 [0.7%] patient each).

Table 37: Important Identified Risk: Second Primary Malignancies (Continued)

Second Primary Malignancies
Study NHL-008 In Study NHL-008, Grade 3 or 4 T-cell malignancy was reported in 1 (0.6%) lenalidomide plus rituximab-treated patient. **NDMM RVd Study** Study SWOG S0777 There were no reports of AML in the RVd and Rd arms of Study SWOG S0777. Grade 3 or 4 B-cell malignancies were reported in 2 (0.8%) patients in the Rd arm and no patients in the RVd arm. Grade 3 or 4 MDS was reported in 1 (0.4%) patient each in the RVd and Rd arms. There were no reports of other haematologic malignancies in the RVd and Rd arms. **TE NDMM Studies** Study IFM 2005-02 In Study IFM 2005-02, the frequency of Grade 3 or 4 events was higher in the lenalidomide versus the placebo group for B-cell malignancies (9 [2.9%] versus 1 [0.3%] patients). For AML, the frequency of Grade 3 or 4 events was comparable in the lenalidomide and placebo groups (4 [1.3%] versus 2 [0.7%] patients). Other haematologic cancer of Grade 3 or 4 intensity was reported for 1 (0.3%) patient each in the lenalidomide and placebo groups. B-cell malignancies (1 [0.3%] patient in the lenalidomide group versus 0 patients in the placebo group) and AML (2 [0.7%] patients in each of the lenalidomide and placebo groups) led to dose discontinuation in Study IFM 2005-02. No patients experienced B-cell malignancies or AML leading to dose reduction or interruption. No patients experienced other haematologic malignancies leading to discontinuation and dose reduction or interruption. Study CALGB 100104 In Study CALGB 100104, Grade 3 or 4 MDS was reported in 2 (0.9%) lenalidomide-treated patients and 1 (0.5%) placebo-treated patient. In Study CALGB 100104, actions taken due to AEs (eg, treatment discontinued, dose reduced, dose interrupted) were not collected on the CRF. Study GIMEMA There were no reports of AML, MDS, other haematologic malignancies or B-cell malignancies in Study GIMEMA. In Study GIMEMA, AE grade and actions taken due to AEs (eg, treatment discontinued, dose reduced, dose interrupted) were not collected on the CRF. **TNE NDMM Studies** Study MM-020 Grade 3 or 4 AML was reported for 1 (0.2%) patient in Arm Rd, 0 patients in Arm Rd18, and 5 (0.9%) patients in Arm MPT. No events of B-cell malignancy were reported. AML leading to discontinuation was reported for 1 (0.2%) patient in Arm Rd, and no patients in Arms Rd18 and MPT. Grade 3 or 4 events of MDS were reported for 1 (0.2%), 0 and 5 (0.9%) patients in Arms Rd, Rd18 and MPT, respectively. Events leading to discontinuation were MDS in 1 (0.2%) patient in Arm Rd. No events led to dose reduction in any of the arms, and there were no events leading to dose interruption or discontinuation in Arm MPT. Study MM-015 In Study MM-015, Grade 3 or 4 AML was reported for 4 (2.7%) patients in Arm MPR+R, 3 (2.0%) patients in Arm MPR+p, and 1 (0.7%) patient in Arm MPp+p. No events of B-cell malignancy were reported. AML leading to discontinuation was more frequently reported in Arm MPR+R (2.7% [4 patients]), than Arms MPR+p and MPp+p (0 patients each).

Table 37: Important Identified Risk: Second Primary Malignancies (Continued)

Second Primary Malignancies
In Study MM-015, Grade 3 or 4 events of MDS were reported for 3 (2.0%), 1 (0.7%) and 0 patients in Arms MPR+R, MPR+p and MPp+p, respectively. Other haematologic cancer of Grade 3 or 4 intensity was reported for 1 (0.7%) patient in Arm MPR+R. Events leading to discontinuation were MDS in 1 (0.7%) patient each in Arms MPR+R and MPR+p and other haematologic cancer in 1 (0.7%) patient in Arm MPR+R. There were no events leading to dose interruption or reduction in any of the arms. **RRMM Studies** In Studies MM-009 and MM-010, no patients experienced Grade 3 to 5 AML or B-cell malignancies, or AML or B-cell malignancies that led to dose reduction or discontinuation. No patients experienced MDS or other haematologic malignancies that led to dose discontinuation, reduction, or interruption. **Del 5q MDS Studies** Severity of events is unknown for AML as most AML cases were captured during follow-up phase via phone contact. Study MDS-004 There were no reports of B-cell malignancies or other haematologic malignancies in Study MDS-004. Study MDS-003 In Study MDS-003, one (0.7%) patient had a Grade 3 or 4 B-cell malignancy which was resolved. None of the events of B-cell malignancies or other haematologic malignancies reported led to dose discontinuation, interruption or reduction. One (0.7%) patient had a Grade 3 or 4 other haematologic malignancy. None of the other haematologic malignancies led to dose discontinuation, reduction, or interruption. **MCL Studies** Study MCL-002 There were no reports of AML in Study MCL-002. Grade 3 or 4 B-cell malignancy was reported in 1 (0.6%) patient in the lenalidomide group and 1 (1.2%) patient in the control group. B-cell malignancy leading to discontinuation was reported in 1 (0.6%) patient in the lenalidomide group and no patients in the control group. There were no B-cell malignancies leading to dose reduction or interruption in Study MCL-002. Grade 3 or 4 MDS was reported in 1 (0.6%) lenalidomide-treated patient and no patients in the control group. There were no events of MDS leading to discontinuation or dose reduction or interruption in Study MCL-002. No patients had other haematologic malignancies in Study MCL-002. Study MCL-001 In Study MCL-001, Grade 3 or 4 AML was reported in 1 (0.7%) lenalidomide-treated patient. There were no reports of AML leading to discontinuation or dose reduction or interruption. There were no reports of B-cell malignancies in Study MCL-001. There were no Grade 3 or 4 events of MDS. No events of MDS led to discontinuation or dose reduction or interruption. No patients had other haematologic malignancies in Study MCL-001. Study NHL-002 There were no reports of AML, MDS, other haematologic malignancies, or B-cell malignancies in Study NHL-002. Study NHL-003 In Study NHL-003, Grade 3 or 4 AML was reported in 1 (0.5%) lenalidomide-treated patient. AML leading to discontinuation was reported in 1 (0.5%) lenalidomide-treated patient. There were no reports of B-cell malignancies in Study NHL-003. Grade 3 or 4 MDS was reported in 1 (0.5%) lenalidomide-treated patient. There were no events of MDS leading to discontinuation, dose interruption or dose reduction. No patients had other haematologic malignancies in Study NHL-003. **Severity and Nature of Risk (Invasive SPM [Solid Tumours])** The severity and nature of the solid tumours are summarised in Table 46 for the NDMM RVd study, Table 47 for the NDMM studies, Table 48 for the RRMM studies, and Table 49 for the MDS and lymphoma studies.

Table 37: Important Identified Risk: Second Primary Malignancies (Continued)

Second Primary Malignancies
FL Studies: Study NHL-007 In Study NHL-007, the frequency of Grade 3 or 4 solid tumours was lower in the lenalidomide plus rituximab versus the rituximab plus placebo arm (1 [0.7%] patients versus 3 [2.0%] patients). Study NHL-008 In Study NHL-008, Grade 3 or 4 solid tumours were reported in 1 (0.6%) lenalidomide plus rituximab-treated patient. One (0.6%) lenalidomide plus rituximab-treated patient had a solid tumour AE that led to study medication discontinuation. **NDMM RVd Study** Study SWOG S0777 Grade 3 or 4 solid tumours were reported in 5 (1.9%) patients in the RVd arm and 6 (2.3%) patients in the Rd arm in Study SWOG S0777. **TE NDMM Studies** Study IFM 2005-02 In Study IFM 2005-02, the frequency of Grade 3 or 4 events was similar in the lenalidomide and placebo groups for solid tumours (17 [5.6%] versus 10 [3.3%] patients). SPM leading to dose discontinuation were solid tumours (3 [1.0%] patients in the lenalidomide group versus 1 [0.3%] patient in the placebo group). Solid tumours leading to dose interruption were experienced by a single patient (0.3%) in the lenalidomide group. Study CALGB 100104 In Study CALGB 100104, Grade 3 or 4 solid tumours were reported in 1 (0.5%) patient treated with placebo and no lenalidomide-treated patients. Actions taken due to AEs (eg, treatment discontinued, dose reduced, dose interrupted) were not collected on the CRF. Study GIMEMA In Study GIMEMA, AE grade and actions taken due to AEs (eg, treatment discontinued, dose reduced, dose interrupted) were not collected on the CRF. **TNE NDMM Studies** Study MM-020 Grade 3 or 4 solid tumours were reported for 12 (2.3%), 20 (3.7%) and 4 (0.7%) patients in Arms Rd, Rd18 and MPT, respectively. Events leading to discontinuation were solid tumours in 5 (0.9%) patients in Arm Rd and 3 (0.6%) patients in Arm Rd18. Solid tumours led to dose interruption in 2 (0.4%) and 4 (0.7%) patients in Arms Rd and Rd18, respectively. No events led to dose reduction in any of the arms, and there were no events leading to dose interruption or discontinuation in Arm MPT. Study MM-015 Grade 3 or 4 solid tumours were reported for 4 (2.7%), 6 (3.9%) and 2 (1.3%) patients in Arms MPR+R, MPR+p and MPp+p, respectively. Events leading to discontinuation were solid tumours in 2 (1.3%) patients, 3 (2.0%) patients and 1 (0.7%) patient in Arms MPR+R, MPR+p and MPp+p, respectively. There were no events leading to dose interruption or reduction in any of the arms. **RRMM Studies** Studies MM-009 and MM-010 In Studies MM-009 and MM-010, Grade 3 or 4 solid tumours (6 [1.7%] and 1 [0.3%] patients, respectively) were reported. Solid tumours leading to discontinuation or dose interruption were infrequently observed in the lenalidomide/ dexamethasone group (3 [0.8%] or 1 [0.3%] patients overall, respectively) and were not observed in the placebo/ dexamethasone group.

Table 37: Important Identified Risk: Second Primary Malignancies (Continued)

Second Primary Malignancies
Del 5q MDS Studies Study MDS-004 In the lenalidomide 10 mg group of Study MDS-004, 3 (4.3%) patients had a Grade 3 or 4 solid tumour and in the lenalidomide 5 mg group, 1 (1.4%) patient had a Grade 3 or 4 solid tumour. Severity and nature of risk was unknown for 2 patients with solid tumours. None of the solid tumours reported led to dose discontinuation, interruption or reduction. Study MDS-003 In Study MDS-003, 5 (3.4%) patients had a Grade 3 or 4 solid tumour. None of the solid tumours reported led to dose discontinuation, interruption or reduction. **MCL Studies** Study MCL-002 Grade 3 or 4 solid tumours were reported in 3 (1.8%) patients in the lenalidomide group and no patients in the control group in Study MCL-002. Events of solid tumours led to discontinuation in 1 (0.6%) patient in the lenalidomide group and no patients in the control group. There were no events of solid tumours leading to dose reduction or interruption in Study MCL-002. Study MCL-001 In Study MCL-001, Grade 3 or 4 events of solid tumours were reported in 4 (3.0%) lenalidomide-treated patients, with events of solid tumours leading to discontinuation and to dose interruption in 1 (0.7%) patient each. No events of solid tumours led to dose reduction in Study MCL-001. Study NHL-002 In Study NHL-002, Grade 3 or 4 events of solid tumours were reported in 1 (2.0%) lenalidomide-treated patient. No events of solid tumour led to dose discontinuation, interruption or reduction. Study NHL-003 In Study NHL-003, Grade 3 or 4 events of solid tumours were reported in 2 (0.9%) lenalidomide-treated patients, and events of solid tumours led to discontinuation in 2 (0.9%) patients. There were no events of solid tumours that led to dose interruption or dose reduction. **Severity and Nature of Risk (Non-Invasive SPM [NMSC])** The severity and nature of the NMSC are summarised in Table 46 for the NDMM RVd study, Table 47 for the NDMM studies, Table 48 for the RRMM studies, and Table 49 for the MDS and lymphoma studies. **FL Studies:** Study NHL-007 In Study NHL-007, there were no Grade 3 or 4 events of NMSC in the lenalidomide plus rituximab or rituximab plus placebo arms. Study NHL-008 In Study NHL-008, Grade 3 or 4 NMSC were reported in 3 (1.7%) lenalidomide plus rituximab-treated patients. One (0.6%) lenalidomide plus rituximab-treated patient had an AE of NMSC that led to study medication interruption. **NDMM RVd Study** Study SWOG S0777 In Study SWOG S0777, Grade 3 or 4 NMSC was reported in 6 (2.3%) patients in the RVd arm and 2 (0.8%) patients in the Rd arm.

Table 37: Important Identified Risk: Second Primary Malignancies (Continued)

Second Primary Malignancies
TE NDMM Studies Study IFM 2005-02 In Study IFM 2005-02, the frequency of Grade 3 or 4 events was higher in the lenalidomide versus the placebo group for NMSC (8 [2.6%] versus 5 [1.7%] patients). One (0.3%) patient in the placebo group had their study treatment interrupted due to events of NMSC. No patients experienced NMSC leading to discontinuation or dose reduction. Study CALGB 100104 In Study CALGB 100104, Grade 3 or 4 events of NMSC were reported for 1 (0.4%) patient treated with lenalidomide and 2 (0.9%) patients treated with placebo. In Study CALGB 100104, actions taken due to AEs (eg, treatment discontinued, dose reduced, dose interrupted) were not collected on the CRF. Study GIMEMA In Study GIMEMA, AE grade and actions taken due to AEs (eg, treatment discontinued, dose reduced, dose interrupted) were not collected on the CRF. **TNE NDMM Studies** Study MM-020 In Study MM-020, Grade 3 or 4 NMSC was reported for 10 (1.9%), 12 (2.2%) and 3 (0.6%) patients in Arms Rd, Rd18 and MPT, respectively. NMSC leading to discontinuation was reported for 1 (0.2%) patient each in Arms Rd and Rd18, and 0 patients in Arm MPT. One (0.2%) patient in Arm Rd had NMSC leading to dose interruption. Study MM-015 For NMSC, Grade 3 or 4 events were reported for 2 (1.3%), 4 (2.6%) and 5 (3.3%) patients in Arms MPR+R, MPR+p and MPp+p, respectively. Two (1.3%) patients in Arm MPp+p had NMSC leading to dose interruption, and 1 (0.7%) patient in Arm MPR+R had NMSC leading to discontinuation. **RRMM Studies** Studies MM-009 and MM-010 In Studies MM-009 and MM-010, Grade 3 or 4 NMSC was reported in 4 (1.1%) and 1 (0.3%) patients in the lenalidomide and placebo arms, respectively. Three (0.8%) patients in the lenalidomide arm had their dose interrupted due to events of NMSC. **Del 5q MDS Studies** Study MDS-004 In Study MDS-004, there were no Grade 3, 4 or 5 events of NMSC. No events of NMSC led to dose interruption, reduction or discontinuation. Study MDS-003 In Study MDS-003, one (0.7%) patient had a Grade 3 or 4 NMSC. None of the events of NMSC reported led to dose discontinuation, interruption or reduction. **MCL Studies** Study MCL-002 In Study MCL-002, Grade 3 or 4 events of NMSC were reported in 3 (1.8%) lenalidomide-treated patients and 1 (1.2%) patient in the control group. There were no events of NMSC leading to discontinuation or dose reduction or interruption in Study MCL-002. Study MCL-001 In Study MCL-001, Grade 3 or 4 events of NMSC were reported in 5 (3.7%) lenalidomide-treated patients. NMSC led to dose interruption in 1 (0.7%) patient. There were no events of NMSC leading to discontinuation or dose reduction in Study MCL-001.

Table 37: Important Identified Risk: Second Primary Malignancies (Continued)

Second Primary Malignancies
Study NHL-002 There were no reports of NMSC in Study NHL-002. Study NHL-003 In Study NHL-003, Grade 3 or 4 events of NMSC were reported in 5 (2.3%) lenalidomide-treated patients. There were no events of NMSC leading to discontinuation, dose interruption or dose reduction in Study NHL-003. • **Lymphoproliferative disorders in ASCT patients** The development of Post-Transplant Lymphoproliferative Disorders (PTLD) after solid organ transplantation is well recognised (Dierickx, 2011). Most cases are due to EBV-driven tumour formation in B-cells. Other important risks include the use of potent and prolonged immunosuppressive medication, the age of donor (in the case of allogenic transplantation) and recipient, number and severity of rejection episodes and cytokine gene polymorphisms (Dierickx, 2011). In patients with MM a number of prospective, randomised trials have been conducted that compare conventional chemotherapy with high-dose therapy using ASCT. As a result of these studies, ASCT has nowadays become a standard of care in MM (Bensinger, 2009). However, these patients are at risk of developing PTLD. Reports have demonstrated that HSCT patients with PTLD generally have higher concentrations of EBV deoxyribonucleic acid (DNA) in the peripheral blood than patients without PTLD (Weinstock, 2006). • **G-CSF therapy** Guidelines for cancer care support the use of G-CSF prophylaxis in specific therapeutic circumstances (Renwick, 2009). Despite the usefulness of G-CSF therapy, increased risks of AML or MDS associated with G-CSF use have been described. Lyman (2010) provided a systematic review of AML/MDS incidence among 6058 and 6746 patients randomly assigned to receive chemotherapy with and without initial G-CSF support in 25 randomised clinical trials. At mean and median follow-up across studies of 60 and 53 months, respectively, AML/MDS was reported in 22 control patients and 43 G-CSF patients, for an estimated risk ratio of 1.92 (95% CI: 1.19–3.07). Median follow-up time was 54 months. The risk of AML/MDS was significantly increased in studies where G-CSF use was associated with higher total dose of chemotherapy (risk ratio = 2.334; 95% CI: 1.237–4.403). There was no significant difference in the risk ratio for mortality. Even though these findings do not establish a unique causal role associated with the use of G-CSF the median follow-up of about 5 years may be insufficient to provide a final quantification of AML/MDS. • **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 involve risk conferred by shared genetic factors (Lynch, 2008; Varkonyi, 2001).
Risk Groups and Risk Factors: MDS Populations (Haematologic Malignancies) A study to identify prognostic factors for progression to leukaemia (LFS) and OS was reported by Malcovati (2005). Four hundred seventy six patients first diagnosed with de novo MDS between 1992 and 2002 were evaluated. In one of the earliest studies to report the negative effects of developing a transfusion requirement, Malcovati reported an increased risk associated with transfusion burden when analysed as a time-dependent covariate in a combined group of patients with RA, RARS or MDS with del(5q) (HR = 3.46). Further development of the WPSS a learning cohort of 426 Italian MDS patients and a validation cohort of 193 German MDS patients was reported by Malcovati and colleagues (2007). In a multivariable analysis of the Italian patients stratified by WHO subgroups, cytogenetics (HR = 1.48) and transfusion requirement (HR = 2.53) significantly affected OS and risk of AML (HR = 1.3 and HR = 2.4, respectively). These findings were corroborated in the subsequent multivariable analysis of German MDS patients stratified by WHO subgroups, with cytogenetics (HR = 1.84) and transfusion dependency (HR = 1.85) and risk of AML (HR = 2.27 and HR = 2.25, respectively).

Table 37: Important Identified Risk: Second Primary Malignancies (Continued)

Second Primary Malignancies
Mallo (2011) reported the results of a cooperative study designed to assess prognostic factors for OS and progression to AML in 541 patients with de novo MDS and del 5q. In multivariate analyses the most important predictors of both OS and AML progression were number of chromosomal abnormalities ($p < 0.001$ for both outcomes), platelet count ($p < 0.001$ and $p = 0.001$, respectively) and proportion of bone marrow blasts ($p < 0.001$ and $p = 0.016$, respectively). Transfusion burden was not addressed in this study. Kuendgen (2013) assessed the risk of AML progression and death in 295 lenalidomide-treated MDS-003 and MDS-004 patients versus 125 MDS patients with del 5q from a large multicentre registry who had received best supportive care only including ESAs. In the final multivariate Cox proportional hazard models, lenalidomide treatment was not associated with progression to AML (HR 0.939; $p = 0.860$). Significant factors associated with an increased risk of AML progression were complex cytogenetics (del 5q plus > 1 abn; HR 3.627; $p = 0.002$), bone marrow blasts 5% to 10% (HR 2.215; $p = 0.016$), and higher transfusion burden (HR 1.097 [10% increase in risk per unit at baseline]; $p = 0.029$). Higher haemoglobin levels were associated with a reduced risk (HR 0.857; $p = 0.054$). Regarding survival, lenalidomide treatment was associated with a reduced risk of death (HR 0.597; $p = 0.012$). Other factors associated with decreased mortality were higher haemoglobin levels (HR 0.883; $p = 0.028$), higher platelet counts (HR 0.999; $p = 0.035$), and female sex (HR 0.598; $p = 0.002$). Higher transfusion burden (HR 1.056; $p = 0.037$) and age (HR 1.049; $p < 0.001$) increased the risk of death. Mutations in the TP53 gene have been well described as a poor prognostic variable and associated with chemotherapy resistance in a wide variety of malignancies including high-risk MDS and AML (Pospisilova, 2012; Rücker, 2012).
Risk Groups and Risk Factors: MCL Population (Haematologic Malignancies) There is no information available. **Risk Groups and Risk Factors: NMSC** Risk factors for NMSC include: increased sun or ultraviolet radiation exposure; physical factors such as fair skin, red or blond hair, and light eye colour; chemical carcinogens such as, arsenic, tobacco, and oral methoxsalen; ionising radiation; and previous history of NMSC (Diepgen, 2002; Rubin, 2005). • **Prolonged survival as a result of improved therapies** As previously noted, the 5-year relative survival among MM patients has increased from 24.6% among patients first diagnosed in 1975 to 1977 to 44.9% among patients first diagnosed between 2003 and 2009 (Howlader, 2013). 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 second malignancy, including NMSC. • **Immunosuppression associated with transplantation procedures** Immunosuppression is a risk factor for NMSC (Rubin, 2005; Diepgen, 2002). Patients receiving immunosuppressive therapy following solid organ transplantation and those receiving bone marrow transplants have an increased risk of skin cancer. In a small series of patients (n = 43) receiving nonmyeloablated haematopoietic cell transplants, 6 patients developed squamous cell carcinoma (n = 3), basal cell carcinoma (n = 2), or malignant melanoma (n = 2) (Cavalier, 2006). In another study, the most frequently observed secondary malignancies among patients (n = 557) receiving allogeneic bone marrow transplants were NMSC. Out of 31 secondary malignancies, 5 were basal cell carcinoma and 4 were squamous cell carcinoma skin cancers (Hasegawa, 2005).
Preventability The risk of occurrence of haematologic SPM must be taken into account before initiating treatment with Revlimid either in combination with melphalan or immediately following HDM and ASCT. 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). TP53 and the risk of progression to AML is mentioned in Section 4.4 of the SmPC.

Table 37: Important Identified Risk: Second Primary Malignancies (Continued)

Second Primary Malignancies
Impact on the Risk-benefit Balance of the Product SPM may result in significant morbidity and mortality depending on the type of SPM. It impacts the patient's activities of daily living. AML and B-cell malignancies may result in an increase in mortality, and adversely affect quality of life. NMSC is rarely fatal but impacts the patient's activities.
Public Health Impact 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 malignancies now comprising about 16% of incident cancers reported to the National Cancer Institute's (NCI) SEER Program in 2003. Moreover, second tumours may be a cause of mortality among several populations of long-term survivors (Travis, 2006). It should be noted, however, that the risk of dying from MM is considerably higher than the risk of developing a second cancer (Landgren, 2011). NMSC is rarely fatal but has adverse public health effects of high medical cost. The total cost of NMSC care in the US in the Medicare population is $426 million/year. The average cost per episode of NMSC when performed in a physician's office setting was found to be $492 and the cost per episode of care in inpatient and outpatient settings were $5537 and $1043, respectively (Chen, 2001).
Data Source: Studies NHL-007 (22 Jun 2018) and NHL-008 (01 May 2017);Study SWOG S0777 (01 Dec 2016); Study CALGB 100104 (01 Mar 2015); Study IFM 2005-02 (01 Mar 2015); Study GIMEMA (01 Mar 2015); Study MM-020 (24 May 2013); Study MM-015 (30 Apr 2013); Integrated Summary of Safety (Dec 2005) for Studies MM-009 and MM-010; Study MDS-003 CSR; Study MDS-004 CSR; Study MCL-001 (21 Mar 2014); Study MCL-002 (07 Mar 2014); Study NHL-002 (23 Jun 2008); Study NHL-003 (25 Mar 2013). NDMM Day 120 Responses. **MedDRA Terms** AML HLT of Leukaemias acute myeloid, PTs of acute promyelocytic leukaemia differentiation syndrome, acute leukaemia and acute leukaemia in remission. Note: patients with an event of 'MDS to AML' were included in the AML category. B-cell malignancies HLGT of Lymphomas non-Hodgkin's B-cell, HLGT of Lymphomas Hodgkin's disease, HLGT of Lymphomas non-Hodgkin's unspecified histology, HLT of Leukaemias acute lymphocytic, HLT of Leukaemias chronic lymphocytic, and HLT of Lymphomas unclassifiable malignant, and PT of lymphocytic lymphoma. Other haematologic malignancies For Study SWOG S0777, HLGTs of Haematopoietic neoplasms (excl leukaemias and lymphomas), Leukaemias, Lymphomas Hodgkin's disease, Lymphomas non-Hodgkin's B-cell, Lymphomas non-Hodgkin's T-cell, Lymphomas non-Hodgkin's unspecified histology, and Lymphomas NEC. For Studies CALGB 100104, IFM 2005-02, GIMEMA, MM-020, MM-015, MM-009, MM-010, MDS-003, MDS-004, HLGT of Haematopoietic neoplasms (excl leukaemias and lymphomas), HLTs of Leukaemias chronic myeloid, Leukaemias chronic NEC, Leukaemias chronic T-cell, Leukaemias lymphocytic NEC, Leukaemias NEC, HLGT Lymphomas non-Hodgkin's T-cell, HLGT of Plasma cell neoplasms, and HLT of MDS. Solid tumours For Studies SWOG S0777, CALGB 100104, IFM 2005-02, GIMEMA, MM-020, MM-015, MM-009, MM-010, MDS-003, MDS-004, HLGTs of Breast neoplasms malignant and unspecified (incl nipple), Endocrine neoplasms malignant and unspecified, Gastrointestinal neoplasms malignant and unspecified, Hepatobiliary

Table 37: Important Identified Risk: Second Primary Malignancies (Continued)

Second Primary Malignancies
neoplasms malignant and unspecified, Mesotheliomas malignant and unspecified, Miscellaneous and site unspecified neoplasms malignant and unspecified, Nervous system neoplasms malignant and unspecified NEC, 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, Soft tissue neoplasms malignant and unspecified (excl sarcomas), Soft tissue sarcomas; HLTs Skin melanomas, (excl ocular), Ocular neoplasms, Ocular neoplasms malignancy unspecified, ocular neoplasms malignant (excl melanomas). For Study SWOG S0777, additional HLT Ocular melanomas. NMSC NMSC were categorised on the basis of the following MedDRA v21.0 for Studies NHL-007 and NHL-008; MedDRA v13.0 (MedDRA v15.1 for Studies SWOG S0777, CALGB 100104, IFM 2005-02 and GIMEMA); MedDRA v16.1 for Study MCL-002, v15.0 for Study MCL-001, v5.1 for Study NHL-002 and v9.0 for Study NHL-003) HLGT/HLT categories: Skin neoplasms malignant and unspecified (excl. melanoma). For Study SWOG S0777, MedDRA v15.1 additional PT of Queyrat ertythroplasia. If, based on the nature of the PT reported, the malignancy status of a particular entity of tumour was undefined, the SAE and/or the CRF was reviewed in addition and the report was classified accordingly.

Table 38: Frequency and Incidence Rate of Second Primary Malignancies: NDMM RVd

SPM		**SWOG S0777**	
		Arm B (RVd) N = 262	**Arm A (Rd) N = 256**
INVASIVE			
Haematologic Malignancies			
- AML[a]	Patients with ≥ 1 SPM	0	0
	IR[b], 95% CI	0	0
- MDS	Patients with ≥ 1 SPM	2	1
	IR[b], 95% CI	0.16 0.04 to 0.65	0.09 0.01 to 0.63
- B-cell Malignancies	Patients with ≥ 1 SPM	0	2
	IR[b], 95% CI	0	0.18 0.04 to 0.71
- Other haematologic malignancies	Patients with ≥ 1 SPM	0	0
	IR[b], 95% CI	0	0
Solid Tumours	Patients with ≥ 1 SPM	8	10
	IR[b], 95% CI	0.66 0.33 to 1.32	0.90 0.48 to 1.67

Table 38: Frequency and Incidence Rate of Second Primary Malignancies: NDMM RVd (Continued)

SPM		SWOG S0777	
		Arm B (RVd) N = 262	**Arm A (Rd) N = 256**
NON-INVASIVE			
NMSC	Patients with ≥ 1 SPM	11	7
	IR[b], 95% CI	0.92 0.51 to 1.66	0.62 0.30 to 1.31

[a] Includes patients with the event of 'MDS to AML'.
[b] Incidence rates per 100 person-years.
Data cutoff: 01 Dec 2016.
Patients may be counted more than once across SPM subcategories.

Table 39: Frequency and Incidence Rate of Second Primary Malignancies: NDMM Studies

SPM		TE NDMM STUDIES						TNE NDMM STUDIES					
		IFM 2005-02		CALGB 100104		GIMEMA		MM-020			MM-015		
		Len N = 306	Placebo N = 302	Len N = 224	Placebo N = 221	Len N = 56	Control N = 79	Rd N = 532	Rd18 N = 540	MPT N = 541	MPR+R N = 150	MPR+p N = 152	MPp+p N = 153
INVASIVE													
Haematologic Malignancies													
AML[a]	Patients with ≥ 1 SPM	6	3	7	0	0	0	1	1	6	6	5	1
	IR[b], 95% CI	0.36 (0.16 to 0.80)	0.18 (0.06 to 0.55)	0.59 (0.28 to 1.23)	0	0	0	0.07 0.01 to 0.51	0.07 0.01 to 0.51	0.46 0.20 to 1.01	0.96 0.40 to 2.31	0.98 0.41 to 2.36	0.18 0.03 to 1.29
MDS	Patients with ≥ 1 SPM	4	3	4	4	0	0	1	1	6	3[c]	2	1
	IR[b], 95% CI	0.24 0.09 to 0.64	0.18 0.06 to 0.55	0.33 0.13 to 0.89	0.39 0.14 to 1.03	0	0	0.07 0.01 to 0.51	0.07 0.01 to 0.51	0.45 0.20 to 1.01	0.58 0.19 to 1.79	0.39 0.10 to 1.57	0.18 0.03 to 1.29
B-cell Malignancies	Patients with ≥ 1 SPM	11	2	4	3	0	0	0	0	0	0	0	0
	IR[b], 95% CI	0.67 0.37 to 1.21	0.12 0.03 to 0.48	0.33 0.12 to 0.89	0.29 0.09 to 0.89	0	0	0	0	0	0	0	0
Other haematologic malignancies[d]	Patients with ≥ 1 SPM	1	1	0	1	0	0	0	0	0	1	0	0
	IR[b], 95% CI	0.06 0.01 to 0.42	0.06 0.01 to 0.42	0	0.10 0.01 to 0.68	0	0	0	0	0	0.19 0.03 to 1.37	0	0

Table 39: Frequency and Incidence Rate of Second Primary Malignancies: NDMM Studies (Continued)

SPM		TE NDMM STUDIES						TNE NDMM STUDIES					
		IFM 2005-02		CALGB 100104		GIMEMA		MM-020			MM-015		
		Len N = 306	Placebo N = 302	Len N = 224	Placebo N = 221	Len N = 56	Control N = 79	Rd N = 532	Rd18 N = 540	MPT N = 541	MPR+R N = 150	MPR+p N = 152	MPp+p N = 153
Solid Tumours	Patients with ≥ 1 SPM	21	13	17	10	5	2	15	29	15	5	11	4
	IR[b], 95% CI	1.28 0.84 to 1.97	0.78 0.46 to 1.35	1.48 0.92 to 2.37	0.98 0.53 to 1.83	2.21 0.92 to 5.31	0.68 0.17 to 2.70	1.09 0.66 to 1.81	2.15 1.49 to 3.09	1.15 0.69 to 1.90	0.97 0.41 to 2.34	2.16 1.20 to 3.91	0.74 0.28 to 1.96
NON-INVASIVE													
NMSC	Patients with ≥ 1 SPM	10	7	12	9	1	1	22	17	21	4	6	8
	IR[b], 95% CI	0.61 0.33 to 1.14	0.42 0.20 to 0.88	1.02 0.58 to 1.80	0.88 0.46 to 1.70	0.42 0.06 to 2.99	0.34 0.05 to 2.41	1.62 1.07 to 2.46	1.25 0.78 to 2.02	1.62 1.05 to 2.48	0.77 0.29 to 2.06	1.19 0.54 to 2.65	1.51 0.75 to 3.02

[a] For all TE NDMM studies, patients with the event of 'MDS to AML' were included in this category.

[b] Incidence rates per 100 person-years.

[c] Two cases of MDS and one case of chronic myelomonocytic leukaemia.

[d] Other includes 1 case of acute biphenotypic leukaemia in the lenalidomide group and 1 case of T-cell lymphoma in the placebo group (Study IFM 2005-02); 1 case of malignant histiocytosis in the placebo group (Study CALGB 100104); 1 case reported as T cell type acute leukaemia (Study MM-015; Arm MPR+R).

Data cutoff: IFM 2005-02: 01 Mar 2015; CALGB 100104: 01 Mar 2015; GIMEMA: 01 Mar 2015; MM-020: 24 May 2013; MM-015: 30 Apr 2013.

Patients may be counted more than once across SPM subcategories.

Table 40: Frequency and Incidence Rate of Second Primary Malignancies: RRMM Studies

SPM		**MM-009 and MM-010[a]**	
		Len/Dex N = 352	**Placebo/Dex N = 350**
INVASIVE			
Haematologic Malignancies			
- AML	Patients with ≥ 1 SPM	0	0
	IR[a], 95% CI	0.0	0.0
- MDS	Patients with ≥ 1 SPM	2	0
	IR[a], 95% CI	0.6 0.07 to 2.03	0.0
- B-cell Malignancies	Patients with ≥ 1 SPM	0	0
	IR[a], 95% CI	0.0	0.0
- Other haematologic malignancies	Patients with ≥ 1 SPM	0	0
	IR[a], 95% CI	0.0	0.0
Solid Tumours	Patients with ≥ 1 SPM	6	2
	IR[a], 95% CI	1.7 0.63 to 3.66	0.6 0.07 to 2.05
NON-INVASIVE			
NMSC	Patients with ≥ 1 SPM	11	2
	IR[a], 95% CI	3.1, 1.57 to 5.51	0.6, 0.07 to 2.05

[a] Incidence between arms was not adjusted for actual time on treatment (mean treatment duration 44 weeks [Len/Dex] versus 23 weeks [Placebo/Dex])
Data cutoff: MM-009: 23 Jul 2008; MM-010: 02 Mar 2008.
Patients may be counted more than once across SPM subcategories.

Table 41: Frequency and Incidence Rate of Second Primary Malignancies: MDS and Lymphoma Studies

SPM		MDS				Lymphoma							
		MDS-003[a]	MDS-004 (Dose Group as Randomised)[b]			MCL-002		MCL-001	NHL-002	NHL-003	NHL-007[g]		NHL-008
		Len (10 mg) N = 148	Len (10 mg) N = 69	Len (5 mg) N = 69	Placebo N = 67	Len N = 167	Control N = 83	Len N = 134	Len N = 49	Len N = 217	PBO+Rit N = 148	Len+Rit N = 146	Len+Rit N = 177
INVASIVE													
Haematologic Malignancies													
AML	Patients with ≥ 1 SPM	37[c]	17	26	27[d]	0	0	1	0	1	1	1	0
	IR[e], 95% CI	7.86 5.69 to 10.85	6.50 4.04 to 10.46	11.16 7.60 to 16.39	12.35 8.47 to 18.00	0	0	0.7 0.0 to 4.1	0	0.5 0.0 to 2.5	0.29 0.04 to 2.09	0.29 0.04 to 2.06	0
MDS	Patients with ≥ 1 SPM	NA	NA	NA	NA	1	0	1	0	1	0	0	0
	IR[e], 95% CI	NA	NA	NA	NA	0.6 0.0 to 3.3	0	0.7 0.0 to 4.1	0	0.5 0.0 to 2.5	0	0	0
B-cell Malignancies	Patients with ≥ 1 SPM	1[f]	0	0	0	1	1	0	0	0	0	0	0
	IR[e], 95% CI	0.21 0.03 to 1.49	0.0	0.0	0.0	0.6 0.0 to 3.3	1.2 0.0 to 6.5	0	0	0	0	0	0

Table 41: Frequency and Incidence Rate of Second Primary Malignancies: MDS and Lymphoma Studies (Continued)

SPM		MDS				Lymphoma							
		MDS-003[a]	MDS-004 (Dose Group as Randomised)[b]			MCL-002		MCL-001	NHL-002	NHL-003	NHL-007[g]		NHL-008
		Len (10 mg) N = 148	Len (10 mg) N = 69	Len (5 mg) N = 69	Placebo N = 67	Len N = 167	Control N = 83	Len N = 134	Len N = 49	Len N = 217	PBO+ Rit N = 148	Len+ Rit N = 146	Len+ Rit N = 177
Other haematologic malignancies[g]	Patients with ≥ 1 SPM	1	0	0	0	0	0	0	0	0	0	0	1
	IR[e], 95% CI	0.21 0.03 to 1.47	0.0	0.0	0.0	0	0	0	0	0	0	0	0.55 0.08 to 3.93
Solid Tumours	Patients with ≥ 1 SPM	7	4	4[b]	2	4	3	5	2	4	3	2	1
	IR[e], 95% CI	1.49 0.71 to 3.13	1.52 0.57 to 4.04	1.69 0.63 to 4.49	0.85 0.21 to 3.39	2.4 0.7 to 6.0	3.6 0.8 to 10.2	3.7 1.2 to 8.5	4.1 0.5 to 14.0	1.8 0.5 to 4.7	0.89 0.29 to 2.76	0.58 0.15 to 2.32	0.55 0.08 to 3.93
NON-INVASIVE													
NMSC	Patients with ≥ 1 SPM	6	1	1	0	5	1	7	0	6	2	3	8
	IR[e], 95% CI	1.30 0.58 to 2.89	0.38 0.05 to 2.68	0.42 0.06 to 2.98	0.0	3.0 1.0 to 6.8	1.2 0.0 to 6.5	5.2 2.1 to 10.5	0	2.8 1.0 to 5.9	0.59 0.15 to 2.36	0.88 0.28 to 2.74	4.57 2.29 to 9.14

[a] Median time on treatment was 52.5 weeks.
[b] For Study MDS-004, the analysis of SPM includes data from the open label phase as well as the double blind phase.
[c] Patient [redacted] in MDS-003, who was identified as having AML at baseline by the central reviewer, was excluded in AML analyses.
[d] 27 patients included 23 patients who crossed over to lenalidomide 5 mg after 16 weeks of placebo treatment.
[e] Incidence rates per 100 person-years.
[f] B-cell lymphoma (1 patient).
[g] Patients could cross over to lenalidomide 5 mg after 16 weeks of placebo treatment.
Data cutoff: MCL-001: 21 Mar 2014; MCL-002: 07 Mar 2014; NHL-002: 23 Jun 2008; NHL-003: 25 Mar 2013; MDS-003 27 Aug 2008; MDS-004: 26 Nov 2012; NHL-007: 22 Jun 2018; NHL-008: 01 May 2017.
Patients may be counted more than once across SPM subcategories.

Table 42: Outcome of Second Primary Malignancies: NDMM RVd

SPM		SWOG S0777	
		Arm B (RVd) N = 262	Arm A (Rd) N = 256
		n (%)	
INVASIVE			
Haematologic Malignancies			
- AML[a]	Death	0	0
	Recovered with sequela	0	0
- B-cell Malignancies	Death	0	0
	Not recovered/not resolved	0	2 (0.8)
- MDS	Death	0	0
	Not recovered/not resolved	2 (0.8)	1 (0.4)
Solid Tumours	Death	1 (0.4)	0
	Ongoing at death	0	0
	Recovered/resolved	4 (1.5)	4 (1.6)
	Recovered with sequela	0	1 (0.4)
	Recovering/resolving	1 (0.4)	0
	Not recovered/not resolved	2 (0.8)	3 (1.2)
	Missing	0	2 (0.8)
NON-INVASIVE			
NMSC	Death	0	0
	Recovered/resolved	6 (2.3)	2 (0.8)
	Recovered with sequela	3 (1.1)	0
	Recovering/resolving	2 (0.8)	0
	Not recovered/not resolved	0	1 (0.4)
	Missing	0	4 (1.6)

n = number of patients.
[a] Includes patients with the event of 'MDS to AML'.
Data cutoff: 01 Dec 2016.
Patients may be counted more than once across SPM subcategories.

Table 43: Outcome of Second Primary Malignancies: NDMM Studies

SPM		TE NDMM						TNE NDMM					
		IFM 2005-02		CALGB 100104		GIMEMA		MM-020			MM-015		
		Len N = 306	Placebo N = 302	Len N = 224	Placebo N = 221	Len N = 56	Control N = 79	Rd N = 532	Rd18 N = 540	MPT N = 541	MPR+R N = 150	MPR+p N = 152	MPp+p N = 153
		n (%)											
INVASIVE													
Haematologic Malignancies													
- AML[a]	Death	5 (1.6)	3 (1.0)	1 (0.4)	0	0	0	0	0	2 (0.4)	3 (2.0)	3 (2.0)	0
	Not recovered/ not resolved	0	0	2 (0.9)	0	0	0	1 (0.2)	1 (0.2)	2 (0.4)	0	1 (0.7)	1 (0.7)
	Ongoing at death	1 (0.3)	0	0	0	0	0	0	0	0	1 (0.7)	0	0
	Unknown/ missing	0	0	4 (1.8)	0	0	0	0	0	2 (0.4)	1 (0.7)	1 (0.7)	0
- MDS	Death	Death	1 (0.3)	2 (0.7)	0	1 (0.5)	0	1 (0.2)	0	1 (0.2)	1 (0.7)	1 (0.7)	1 (0.7)
	Not recovered/ not resolved	Not recovered /not resolved	3 (1.0)	1 (0.3)	1 (0.4)	0	0	0	1 (0.2)	5 (0.9)	2 (1.3)	1 (0.7)	0
	Recovered/ resolved	Recovered/ resolved	0	0	0	1 (0.5)	0	0	0	0	0	0	0
	Unknown/ missing	Unknown/ missing	0	0	3 (1.3)	2 (0.9)	0	0	0	0	0	0	0
- B-cell Malignancies	Death	3 (1.0)	1 (0.3)	0	0	0	0	0	0	0	0	0	0
	Recovering/ resolving	2 (0.7)	0	0	0	0	0	0	0	0	0	0	0
	Not recovered/ not resolved	2 (0.7)	0	1 (0.4)	1 (0.5)	0	0	0	0	0	0	0	0
	Unknown/ missing	4 (1.3)	1 (0.3)	3 (1.3)	2 (0.9)	0	0	0	0	0	0	0	0

Table 43: Outcome of Second Primary Malignancies: NDMM Studies (Continued)

SPM		TE NDMM						TNE NDMM					
		IFM 2005-02		CALGB 100104		GIMEMA		MM-020			MM-015		
		Len N = 306	Placebo N = 302	Len N = 224	Placebo N = 221	Len N = 56	Control N = 79	Rd N = 532	Rd18 N = 540	MPT N = 541	MPR+R N = 150	MPR+p N = 152	MPp+p N = 153
- Other haematologic malignancies	Death	0	1 (0.3)	0	0	0	0	0	0	0	0	0	0
	Recovered/ resolved	0	0	0	0	0	0	0	0	0	1 (0.7)	0	0
	Not recovered/ not resolved	1 (0.3)	0	0	0	0	0	0	0	0	0	0	0
	Unknown/ missing	0	0	0	1 (0.5)	0	0	0	0	0	0	0	0
Solid Tumours	Death	2 (0.7)	1 (0.3)	1 (0.4)	0	1 (1.8)	0	3 (0.6)	3 (0.6)	5 (0.9)	2 (1.3)	4 (2.6)	0
	Recovered with sequelae	0	1 (0.3)	0	0	0	0	0	3 (0.6)	0	0	0	0
	Recovered/ resolved	6 (2.0)	3 (1.0)	0	1 (0.5)	2 (3.6)	1 (1.3)	3 (0.6)	9 (1.7)	5 (0.9)	0	0	0
	Recovering/ resolving	5 (1.6)	3 (1.0)	0	0	1 (1.8)	0	0	0	0	0	0	0
	Not recovered/ not resolved	7 (2.3)	4 (1.3)	1 (0.4)	0	1 (1.8)	1 (1.3)	5 (0.9)	5 (0.9)	3 (0.6)	1 (0.7)	3 (2.0)	0
	Ongoing at death	1 (0.3)	1 (0.3)	0	0	0	0	1 (0.2)	2 (0.4)	2 (0.4)	1 (0.7)	1 (0.7)	0
	Unknown/ missing	0	0	15 (6.7)	9 (4.1)	0	0	3 (0.6)	7 (1.3)	0	1 (0.7)	3 (2.0)	4 (2.6)

Table 43: Outcome of Second Primary Malignancies: NDMM Studies (Continued)

SPM		TE NDMM						TNE NDMM					
		IFM 2005-02		CALGB 100104		GIMEMA		MM-020			MM-015		
		Len N = 306	Placebo N = 302	Len N = 224	Placebo N = 221	Len N = 56	Control N = 79	Rd N = 532	Rd18 N = 540	MPT N = 541	MPR+R N = 150	MPR+p N = 152	MPp+p N = 153
NON-INVASIVE													
NMSC	Death	0	0	0	0	0	0	0	0	0	0	0	0
	Recovered/ resolved	8 (2.6)	5 (1.7)	2 (0.9)	4 (1.8)	1 (1.8)	1 (1.3)	18 (3.4)	13 (2.4)	17 (3.1)	1 (0.7)	5 (3.3)	6 (3.9)
	Recovering/ resolving	2 (0.7)	1 (0.3)	1 (0.4)	0	0	0	0	0	0	0	0	0
	Not recovered/not resolved	0	1 (0.3)	3 (1.3)	1 (0.5)	0	0	1 (0.2)	2 (0.4)	2 (0.4)	1 (0.7)	0	0
	Ongoing at death	0	0	0	0	0	0	1 (0.2)	0	0	0	0	0
	Missing	0	0	6 (2.7)	4 (1.8)	0	0	2 (0.4)	2 (0.4)	2 (0.4)	2 (1.3)	1 (0.7)	2 (1.3)

n = number of patients. Patients may be counted more than once across SPM subcategories.
[a] For all TE NDMM studies, patients with the event of 'MDS to AML' were included in this category.
Data cutoff: IFM 2005-02: 01 Mar 2015; CALGB 100104: 01 Mar 2015; GIMEMA: 01 Mar 2015.

Table 44: Outcome of Second Primary Malignancies: RRMM

SPM		**MM-009 and MM-010**[a]	
		Len/Dex N = 352	**Len/Dex N = 352**
		n (%)	
INVASIVE			
Haematologic Malignancies			
- MDS	Unknown	2 (0.6)	0
Solid Tumours	Recovered/resolved	1 (0.3)	0
	Recovering/resolving	0	0
	Not recovered/not resolved	3 (0.8)	0
	Unknown	2 (0.6)	2 (0.6)
NON-INVASIVE			
NMSC	Death	0	0
	Recovered/resolved	2 (0.6)	1 (0.3)
	Recovering/resolving	0	0
	Not recovered/not resolved	0	0
	Unknown	9 (2.5)	1 (0.3)

n = number of patients.
[a] Incidence between arms was not adjusted for actual time on treatment (mean treatment duration 44 weeks [Len/Dex] versus 23 weeks [Placebo/Dex])
Data cutoff: MM-009: 23 Jul 2008; MM-010: 02 Mar 2008.

Table 45: Outcome of Second Primary Malignancies: MDS and Lymphoma Studies

SPM		MDS				Lymphoma							
		MDS-003[a]	MDS-004 (Dose Group as Randomised)[b]			MCL-002		MCL-001	NHL-002	NHL-003	NHL-007		NHL-008
		Len (10 mg) N = 148	Len (10 mg) N = 69	Len (5 mg) N = 69	Placebo[c] N = 67	Len N = 167	Control N = 83	Len N = 134	Len N = 49	Len N = 217	PBO+ Rit N = 148	Len+ Rit N = 146	Len+ Rit N = 177
		n (%)											
INVASIVE													
Haematologic Malignancies													
AML	Patient died[d]	35 (23.8)	14 (20.3)	23 (33.3)	25 (37.3)	NA	NA	NA	NA	NA	1 (0.7)	0	0
	Patient alive[d]	2 (1.4)	2 (2.9)	1 (1.4)	1 (1.5)	NA	NA	NA	NA	NA	0	1 (0.7)	0
	Not recovered/not resolved	NA	NA	NA	NA	0	0	1 (0.7)	0	0	0	1 (0.7)	0
	Recovered/resolved	NA	NA	NA	NA	0	0	0	0	1 (0.5)	0	0	0
MDS	Not recovered/not resolved	NA	NA	NA	NA	1 (0.6)	0	0	0	1 (0.5)	0	0	0
	Ongoing at death	NA	NA	NA	NA	0	0	1 (0.7)	0	0	0	0	0
B-cell Malignancies	Death	0	0	0	0	1 (0.6)	0	0	0	0	0	0	0
	Resolved/recovered with/without sequelae	1 (0.7)	0	0	0	0	0	0	0	0	0	0	0
	Not recovered/not resolved	0	0	0	0	0	1 (1.2)	0	0	0	0	0	0
	Unknown/missing	0	0	0	0	0	0	0	0	0	0	0	0

Table 45: Outcomes of Second Primary Malignancies: MDS and Lymphoma Studies (Continued)

SPM		MDS				Lymphoma							
		MDS-003[a]	MDS-004 (Dose Group as Randomised)[b]			MCL-002		MCL-001	NHL-002	NHL-003	NHL-007		NHL-008
		Len (10 mg) N = 148	Len (10 mg) N = 69	Len (5 mg) N = 69	Placebo[c] N = 67	Len N = 167	Control N = 83	Len N = 134	Len N = 49	Len N = 217	PBO+ Rit N = 148	Len+ Rit N = 146	Len+ Rit N = 177
		n (%)											
Other haematologic malignancies	Death	0	0	0	0	0	0	0	0	0	0	0	0
	Resolved/recovered with/without sequelae	0	0	0	0	0	0	0	0	0	0	0	0
	Not recovered/not resolved	1 (0.7)	0	0	0						0	0	1 (0.6)
	Ongoing at death	0	0	0	0	0	0	1 (0.7)	0	0	0	0	0
	Unknown/missing	0	0	0	0	0	0	0	0	0	0	0	0
Solid Tumours	Death	2 (1.4)	0	1 (1.4)	1 (1.5)	0	1 (1.2)	0	0	1 (0.5)	0	0	0
	Resolved/recovered with/without sequelae	2 (1.4)	2 (2.9)	0	0	NA	NA	NA	NA	NA	0	0	0
	Recovered/resolved	NA	NA	NA	NA	2 (1.2)	1 (1.2)	1 (0.7)	0	0	3 (2.0)	1 (0.7)	0
	Recovered with sequelae	0	1 (1.4)	0	0	1 (0.6)	0	1 (0.7)	0	0	0	0	0
	Not recovered/not resolved	0	1 (1.4)	1 (1.4)	1 (1.5)	1 (0.6)	1 (1.2)	3 (2.2)	2 (4.1)	0	0	1 (0.7)	1 (0.6)
	Unknown/missing	3 (2.0)	0	2 (2.9)	0	0	0	0	0	2 (0.9)	0	0	0

Table 45: Outcomes of Second Primary Malignancies: MDS and Lymphoma Studies (Continued)

SPM		MDS				Lymphoma							
		MDS-003[a]	MDS-004 (Dose Group as Randomised)[b]			MCL-002		MCL-001	NHL-002	NHL-003	NHL-007		NHL-008
		Len (10 mg) N = 148	Len (10 mg) N = 69	Len (5 mg) N = 69	Placebo[c] N = 67	Len N = 167	Control N = 83	Len N = 134	Len N = 49	Len N = 217	PBO+ Rit N = 148	Len+ Rit N = 146	Len+ Rit N = 177
		n (%)											
NON-INVASIVE													
NMSC	Death	0	0	0	0	0	0	0	0	0	0	0	0
	Resolved/recovered with/without sequelae	0	0	0	0	NA	NA	NA	NA	NA	0	0	8 (4.5)
	Recovered/resolved	NA	NA	NA	NA	4 (2.4)	1 (1.2)	6 (4.5)	0	3 (1.4)	2 (1.4)	2 (1.4)	0
	Not recovered/not resolved	0	0	0	0	1 (0.6)	0	1 (0.7)	0	0	0	1 (0.7)	0
	Unknown/missing	6 (4.1)	1 (1.4)	1 (1.4)	0	0	0	0	0	3 (1.4)	0	0	0

N = number of patients; NA = not applicable.
[a] Median time on treatment was 52.5 weeks.
[b] For Study MDS-004, the analysis of SPM includes data from the open label phase as well as the double blind phase.
[c] Patients could cross over to lenalidomide 5 mg after 16 weeks of placebo treatment.
[d] Survival status is provided for 147 patients because 1 patient in MDS-003 had AML at baseline and is therefore not included in the analysis.
Note: there were no AEs of B-cell malignancy in Study MDS-004.
Data cutoff: MCL-001: 21 Mar 2014; MCL-002: 07 Mar 2014; NHL-002: 23 Jun 2008; NHL-003: 25 Mar 2013; MDS-003 27 Aug 2008; MDS-004: 26 Nov 2012; NHL-007: 22 Jun 2018; NHL-008: 01 May 2017.
Patients may be counted more than once across SPM subcategories.

Table 46: Severity and Nature of Risk of Second Primary Malignancies: NDMM RVd

SPM		**SWOG S0777**	
		Arm B (RVd) N = 262	**Arm A (Rd) N = 256**
		n (%)	
INVASIVE			
Haematologic Malignancies			
- AML[a]	All SPM	0	0
	Grade 3 or 4	0	0
	SPM leading to discontinuation	NC	NC
	SPM leading to dose interruption	NC	NC
	SPM leading to dose reduction	NC	NC
- B-cell Malignancies	All SPM	0	2 (0.8)
	Grade 3 or 4	0	2 (0.8)
	SPM leading to discontinuation	NC	NC
	SPM leading to dose interruption	NC	NC
	SPM leading to dose reduction	NC	NC
- MDS	All SPM	2 (0.8)	1 (0.4)
	Grade 3 or 4	1 (0.4)	1 (0.4)
	SPM leading to discontinuation	NC	NC
	SPM leading to dose interruption	NC	NC
	SPM leading to dose reduction	NC	NC
Solid Tumours	All SPM	8 (3.1)	10 (3.9)
	Grade 3 or 4	5 (1.9)	6 (2.3)
	SPM leading to discontinuation	NC	NC
	SPM leading to dose interruption	NC	NC
	SPM leading to dose reduction	NC	NC

Table 46: Severity and Nature of Risk of Second Primary Malignancies: NDMM RVd (Continued)

SPM		**SWOG S0777**	
		Arm B (RVd) N = 262	**Arm A (Rd) N = 256**
		n (%)	
NON-INVASIVE			
NMSC	All SPM	11 (4.2)	7 (2.7)
	Grade 3 or 4	6 (2.3)	2 (0.8)
	SPM leading to discontinuation	NC	NC
	SPM leading to dose interruption	NC	NC
	SPM leading to dose reduction	NC	NC

n = number of patients; NC = not collected.
[a] Includes patients with the event of 'MDS to AML'.
Data cutoff: 01 Dec 2016.
Patients may be counted more than once across SPM subcategories.

Table 47: Severity and Nature of Risk of Second Primary Malignancies: NDMM Studies

SPM		TE NDMM						TNE NDMM					
		IFM 2005-02		CALGB 100104		GIMEMA		MM-020			MM-015		
		Len N = 306	Placebo N = 302	Len N = 224	Placebo N = 221	Len N = 56	Control N = 79	Rd N = 532	Rd18 N = 540	MPT N = 541	MPR+R N = 150	MPR+p N = 152	MPp+p N = 153
		n (%)											
INVASIVE													
Haematologic Malignancies													
- AML[a]	All SPM	6 (2.0)	3 (1.0)	7 (3.1)	0	0	0	1 (0.2)	1 (0.2)	6 (1.1)	5 (3.3)	5 (3.3)	1 (0.7)
	Grade 3 or 4	4 (1.3)	2 (0.7)	0	0	0	0	1 (0.2)	0	5 (0.9)	4 (2.7)	3 (2.0)	1 (0.7)
	SPM leading to discontinuation	2 (0.7)	2 (0.7)	NC	NC	NC	NC	1 (0.2)	0	0	4 (2.7)	0	0
	SPM leading to dose interruption	0	0	NC	NC	NC	NC	0	0	0	0	0	0
	SPM leading to dose reduction	NC	NC	NC	NC	NC	NC	0	0	0	0	0	0
- MDS	All SPM	4 (1.3)	3 (1.0)	4 (1.8)	4 (1.8)	0	0	1 (0.2)	1 (0.2)	6 (1.1)	3 (2.0)	2 (1.3)	1 (0.7)
	Grade 3 or 4	2 (0.7)	2 (0.7)	2 (0.9)	1 (0.5)	0	0	1 (0.2)	0	5 (0.9)	3 (2.0)	1 (0.7)	0
	SPM leading to discontinuation	0	0	NC	NC	0	0	1 (0.2)	0	0	1 (0.7)	1 (0.7)	0
	SPM leading to dose interruption	0	0	NC	NC	0	0	0	0	0	0	0	0
	SPM leading to dose reduction	0	0	NC	NC	0	0	0	0	0	0	0	0

Table 47: Severity and Nature of Risk of Second Primary Malignancies: NDMM Studies (Continued)

SPM		TE NDMM						TNE NDMM					
		IFM 2005-02		CALGB 100104		GIMEMA		MM-020			MM-015		
		Len N = 306	Placebo N = 302	Len N = 224	Placebo N = 221	Len N = 56	Control N = 79	Rd N = 532	Rd18 N = 540	MPT N = 541	MPR+R N = 150	MPR+p N = 152	MPp+p N = 153
- B-cell Malignancies	All SPM	11 (3.6)	2 (0.7)	4 (1.8)	3 (1.4)	0	0	0	0	0	0	0	0
	Grade 3 or 4	9 (2.9)	1 (0.3)	0	0	0	0	0	0	0	0	0	0
	SPM leading to discontinuation	1 (0.3)	0	NC	NC	NC	NC	0	0	0	0	0	0
	SPM leading to dose interruption	0	0	NC	NC	NC	NC	0	0	0	0	0	0
	SPM leading to dose reduction	NC	NC	NC	NC	NC	NC	0	0	0	0	0	0
Other haematologic malignancies	All SPM	1 (0.3)	1 (0.3)	0	1 (0.5)	0	0	0	0	0	1 (0.7)	0	0
	Grade 3 or 4	1 (0.3)	1 (0.3)	0	0	0	0	0	0	0	1 (0.7)	0	0
	SPM leading to discontinuation	0	0	NC	NC	0	0	0	0	0	1 (0.7)	0	0
	SPM leading to dose interruption	0	0	NC	NC	0	0	0	0	0	0	0	0
	SPM leading to dose reduction	0	0	NC	NC	0	0	0	0	0	0	0	0
Solid Tumours	All SPM	21 (6.9)	13 (4.3)	17 (7.6)	10 (4.5)	5 (8.9)	2 (2.5)	15 (2.8)	29 (5.4)	15 (2.8)	5 (3.3)	11 (7.2)	4 (2.6)
	Grade 3 or 4	17 (5.6)	10 (3.3)	0	1 (0.5)	NC	NC	12 (2.3)	20 (3.7)	4 (0.7)	4 (2.7)	6 (3.9)	2 (1.3)
	SPM leading to discontinuation	3 (1.0)	1 (0.3)	NC	NC	NC	NC	5 (0.9)	3 (0.6)	0	2 (1.3)	3 (2.0)	1 (0.7)
	SPM leading to dose interruption	1 (0.3)	0	NC	NC	NC	NC	2 (0.4)	4 (0.7)	0	0	0	0
	SPM leading to dose reduction	0	0	NC	NC	NC	NC	0	0	0	0	0	0

Table 47: Severity and Nature of Risk of Second Primary Malignancies: NDMM Studies (Continued)

SPM		TE NDMM						TNE NDMM					
		IFM 2005-02		CALGB 100104		GIMEMA		MM-020			MM-015		
		Len N = 306	Placebo N = 302	Len N = 224	Placebo N = 221	Len N = 56	Control N = 79	Rd N = 532	Rd18 N = 540	MPT N = 541	MPR+R N = 150	MPR+p N = 152	MPp+p N = 153
NON-INVASIVE													
NMSC	All SPM	10 (3.3)	7 (2.3)	12 (5.4)	9 (4.1)	1 (1.8)	1 (1.3)	22 (4.1)	17 (3.1)	21 (3.9)	4 (2.7)	6 (3.9)	8 (5.2)
	Grade 3 or 4	8 (2.6)	5 (1.7)	1 (0.4)	2 (0.9)	NC	NC	10 (1.9)	12 (2.2)	3 (0.6)	2 (1.3)	4 (2.6)	5 (3.3)
	SPM leading to discontinuation	0	0	NC	NC	NC	NC	1 (0.2)	1 (0.2)	0	1 (0.7)	0	0
	SPM leading to dose interruption	0	1 (0.3)	NC	NC	NC	NC	1 (0.2)	0	0	0	0	2 (1.3)
	SPM leading to dose reduction	0	0	NC	NC	NC	NC	0	0	0	0	0	0

n = number of patients; NC = not collected per study design.
[a] Patients with the event of 'MDS to AML' were included in this category.
Data cutoff: IFM 2005-02: 01 Mar 2015; CALGB 100104: 01 Mar 2015; GIMEMA: 01 Mar 2015; MM-020: 24 May 2013; MM-015: 30 Apr 2013.
Actions taken due to AEs (eg, treatment discontinued, dose reduced, dose interrupted) in Studies CALGB 100104 and GIMEMA, and AE grade in Study GIMEMA, were not collected on the CRF.
Patients may be counted more than once across SPM subcategories.

Table 48: Severity and Nature of Risk of Second Primary Malignancies: RRMM

SPM		MM-009 and MM-010[a]	
		Len/Dex N = 352	Len/Dex N = 352
		n (%)	
INVASIVE			
Haematologic Malignancies			
- MDS	All SPM	2 (0.6)	0
	Grade 3 or 4	2 (0.6)	0
	SPM leading to discontinuation	0	0
	SPM leading to dose interruption	0	0
	SPM leading to dose reduction	0	0
- Other haematologic malignancies	All SPM	0	0
	Grade 3 or 4	0	0
	SPM leading to discontinuation	0	0
	SPM leading to dose interruption	0	0
	SPM leading to dose reduction	0	0
Solid Tumours	All SPM	6 (1.7)	2 (0.6)
	Grade 3 or 4	6 (1.7)	1 (0.3)
	SPM leading to discontinuation	3 (0.8)	0
	SPM leading to dose interruption	1 (0.3)	0
	SPM leading to dose reduction	0	0
NON-INVASIVE			
NMSC	All SPM	11 (3.1)	2 (0.6)
	Grade 3 or 4	4 (1.1)	1 (0.3)
	SPM leading to discontinuation	0	0
	SPM leading to dose interruption	3 (0.8)	0
	SPM leading to dose reduction	0	0

n = number of patients

[a] Incidence between arms was not adjusted for actual time on treatment (mean treatment duration 44 weeks [Len/Dex] versus 23 weeks [Placebo/Dex])

Data cutoff: MM-009: 23 Jul 2008; MM-010: 02 Mar 2008

Table 49: Severity and Nature of Risk of Second Primary Malignancies: MDS and Lymphoma Studies

SPM		MDS				Lymphoma							
		MDS-003[a]	MDS-004 (Dose Group as Randomised)[b]			MCL-002		MCL-001	NHL-002	NHL-003	NHL-007		NHL-008
		Len (10 mg) N = 148	Len (10 mg) N = 69	Len (5 mg) N = 69	Placebo[d] N = 67	Len N = 167	Control N = 83	Len N = 134	Len N = 49	Len N = 217	PBO+ Rit N = 148	Len+ Rit N = 146	Len+ Rit N = 177
		n (%)											
INVASIVE													
Haematologic Malignancies													
- AML	All SPM	-[c]	-[c]	-[c]	-[c]	0	0	1 (0.7)	0	1 (0.5)	1 (0.7)	1 (0.7)	0
	Grade 3 or 4	-[c]	-[c]	-[c]	-[c]	0	0	1 (0.7)	0	1 (0.5)	1 (0.7)	1 (0.7)	0
	SPM leading to discontinuation	-[c]	-[c]	-[c]	-[c]	0	0	0	0	1 (0.5)	NC	NC	0
	SPM leading to dose interruption	-[c]	-[c]	-[c]	-[c]	0	0	0	0	0	NC	NC	0
	SPM leading to dose reduction	-[c]	-[c]	-[c]	-[c]	0	0	0	0	0	NC	NC	0
- MDS	All SPM	NA	NA	NA	NA	1 (0.6)	0	1 (0.7)	0	1 (0.5)	0	0	0
	Grade 3 or 4	NA	NA	NA	NA	1 (0.6)	0	0	0	1 (0.5)	0	0	0
	SPM leading to discontinuation	NA	NA	NA	NA	0	0	0	0	0	0	0	0
	SPM leading to dose interruption	NA	NA	NA	NA	0	0	0	0	0	0	0	0
	SPM leading to dose reduction	NA	NA	NA	NA	0	0	0	0	0	0	0	0
- B-cell Malignancies	All SPM	1 (0.7)	0	0	0	1 (0.6)	1 (1.2)	0	0	0	0	0	0
	Grade 3 or 4	1 (0.7)	0	0	0	1 (0.6)	1 (1.2)	0	0	0	0	0	0

Table 49: Severity and Nature of Risk of Second Primary Malignancies: MDS and Lymphoma Studies (Continued)

SPM		MDS				Lymphoma							
		MDS-003[a]	MDS-004 (Dose Group as Randomised)[b]			MCL-002		MCL-001	NHL-002	NHL-003	NHL-007		NHL-008
		Len (10 mg) N = 148	Len (10 mg) N = 69	Len (5 mg) N = 69	Placebo[d] N = 67	Len N = 167	Control N = 83	Len N = 134	Len N = 49	Len N = 217	PBO+ Rit N = 148	Len+ Rit N = 146	Len+ Rit N = 177
		n (%)											
- B-cell Malignancies (Continued)	SPM leading to discontinuation	0	0	0	0	1 (0.6)	0	0	0	0	0	0	0
	SPM leading to dose interruption	0	0	0	0	0	0	0	0	0	0	0	0
	SPM leading to dose reduction	0	0	0	0	0	0	0	0	0	0	0	0
- Other haematologic malignancies	All SPM	1 (0.7)	0	0	0	0	0	0	0	0	0	0	1 (0.6)
	Grade 3 or 4	1 (0.7)	0	0	0	0	0	0	0	0	0	0	1 (0.6)
	SPM leading to discontinuation	0	0	0	0	0	0	0	0	0	0	0	0
	SPM leading to dose interruption	0	0	0	0	0	0	0	0	0	0	0	0
	SPM leading to dose reduction	0	0	0	0	0	0	0	0	0	0	0	0
Solid Tumours	All SPM	7 (4.7)	4 (5.8)	4 (5.8)	2 (3.0)	4 (2.4)	3 (3.6)	5 (3.7)	2 (4.1)	4 (1.8)	3 (2.0)	2 (1.4)	1 (0.6)
	Grade 3 or 4	5 (3.4)	3 (4.3)	1 (1.4)	0	3 (1.8)	0	4 (3.0)	1 (2.0)	2 (0.9)	3 (2.0)	1 (0.7)	1 (0.6)
	SPM leading to discontinuation	0	0	0	0	1 (0.6)	0	1 (0.7)	0	2 (0.9)	NC	NC	1 (0.6)
	SPM leading to dose interruption	0	0	0	0	0	0	1 (0.7)	0	0	NC	NC	0
	SPM leading to dose reduction	0	0	0	0	0	0	0	0	0	NC	NC	0

Table 49: Severity and Nature of Risk of Second Primary Malignancies: MDS and Lymphoma Studies (Continued)

SPM		MDS				Lymphoma							
		MDS-003[a]	MDS-004 (Dose Group as Randomised)[b]			MCL-002		MCL-001	NHL-002	NHL-003	NHL-007		NHL-008
		Len (10 mg) N = 148	Len (10 mg) N = 69	Len (5 mg) N = 69	Placebo[d] N = 67	Len N = 167	Control N = 83	Len N = 134	Len N = 49	Len N = 217	PBO+ Rit N = 148	Len+ Rit N = 146	Len+ Rit N = 177
		n (%)											
NON-INVASIVE													
NMSC	All SPM	6 (4.1)	1 (1.4)	1 (1.4)	0	5 (3.0)	1 (1.2)	7 (5.2)	0	6 (2.8)	2 (1.4)	3 (2.1)	8 (4.5)
	Grade 3 or 4	1 (0.7)	0	0	0	3 (1.8)	1 (1.2)	5 (3.7)	0	5 (2.3)	0	0	3 (1.7)
	SPM leading to discontinuation	0	0	0	0						NC	NC	0
	SPM leading to dose interruption	0	0	0	0	0	0	1 (0.7)	0	0	NC	NC	1 (0.6)
	SPM leading to dose reduction	0	0	0	0	0	0	0	0	0	NC	NC	0

n = number of patients; NC = not calculable as action information is not available for most patients.
[a] Median time on treatment was 52.5 weeks.
[b] For Study MDS-004, the analysis of SPM includes data from the open label phase as well as the double blind phase.
[c] Severity of events is unknown for AML as most AML cases were captured during follow-up phase via phone contact.
[d] Patients could cross over to lenalidomide 5 mg after 16 weeks of placebo treatment.
Note: there were no AEs of B-cell malignancy in Study MDS-004.
Data cutoff: MCL-001: 21 Mar 2014; MCL-002: 07 Mar 2014; NHL-002: 23 Jun 2008; NHL-003: 25 Mar 2013; MDS-003 27 Aug 2008; MDS-004: 26 Nov 2012; NHL-007: 22 Jun 2018; NHL-008: 01 May 2017.
Patients may be counted more than once across SPM subcategories.

3.1.4. Important Identified Risk: Tumour Flare Reaction (MCL and FL Indications)

The important identified risk of TFR is specific to lenalidomide-treated patients with lymphomas. The risk described below in Table 50 reflects data from the studies in MCL and FL only. There were no reports of TFR in the MM or MDS pivotal studies.

Table 50: Important Identified Risk: Tumour Flare Reaction (MCL and FL Indications)

Tumour Flare Reaction (MCL and FL Indications)

Potential Mechanisms

Immune mediated responses have been postulated as an underlying mechanism that may be related to antitumour activity. In a case review of four patients using lenalidomide (Andritsos, 2008) the aetiology of tumour flare is hypothesised to be mediated through upregulation of B-cell activation markers including CD40, CD80, CD86, HLA-DR and CD95 expression in CLL cells. The effect of 10 or 20 mg lenalidomide on upregulation of CD80 molecules was studied in vitro (Aue, 2009) in CLL with attention to TFR, also referred to as cytokine release syndrome. Strong CD80 upregulation and T-cell activation predicted more severe side effects, manifesting in 83% of patients as cytokine release syndrome within 8 to 72 hours after the first dose of lenalidomide, and neither the severity of the cytokine release syndrome nor the degree of T-cell activation correlated with clinical response. Tumour flare reaction may correlate with response to treatment (Chanan-Khan, 2006), although this has not been reproduced (Ferrajoli, 2008) across all clinical trials describing the phenomenon.

Evidence Source(s) and Strength of Evidence:

Based on clinical trial data, lenalidomide may increase the risk of TFR in patients with CLL and other lymphomas.

Characterisation of the Risk

Frequency with 95% CI

FL Studies:

Tumour Flare Reaction	NHL-007		NHL-008	Pooled NHL-007 and NHL-008
	PBO+Rit	Len+Rit	Len+Rit	Len+Rit
Total number of patients	148	146	177	323
Patients with ≥ 1 SAE	0	1	1	2
Patients with ≥ 1 AE	1	19	7	26
Incidence (% of patients) with ≥ 1 AE (95% CI)	0.7 (0.0 to 3.7)	13.0 (8.0 to 19.6)	4.0 (1.6 to 8.0)	-

Overall, in pooled Studies NHL-007 and NHL-008, TFR AEs were reported for 26 lenalidomide plus rituximab-treated patients.

In Study NHL-007, the proportion of FL patients experiencing at least one TFR event was higher among lenalidomide plus rituximab-treated patients than patients treated with rituximab plus placebo (risk ratio = 19.3 [95% CI: 2.6-143.9]).

In Study NHL-008, TFR AEs were reported for 4.0% of lenalidomide plus rituximab-treated patients.

Table 50: Important Identified Risk: Tumour Flare Reaction (MCL and FL Indications) (Continued)

Tumour Flare Reaction (MCL and FL Indications)

MCL Studies:

Tumour Flare Reaction	MCL-002		All MCL Lenalidomide Patients (MCL-002, MCL-001, NHL-002, NHL-003)
	Len	Control	
Total number of patients	167	83	373
Patients with ≥ 1 SAE	1	0	1
Patients with ≥ 1 AE	16	0	30
Incidence (% of patients) with ≥ 1 AE (95% CI)	9.6 (5.6 to 15.1)	0	8.0 (5.5 to 11.3)

In Study MCL-002, TFR AEs were reported in the lenalidomide treatment group (9.6%), whereas no events were reported in the control group.

Seriousness/Outcomes

FL Studies:

SAE outcomes reported in the FL studies are summarised below.

Outcome	NHL-007		NHL-008	Pooled NHL-007 and NHL-008
	PBO+Rit	Len+Rit	Len+Rit	Len+Rit
Total number of patients	148	146	177	323
Patients with ≥ 1 SAE	0	1 (0.7)	1 (0.6)	2 (0.6)
Resolved	0	1 (0.7)	1 (0.6)	2 (0.6)

In Study NHL-007, TFR SAEs were reported for 1/146 (0.7%) lenalidomide plus rituximab-treated patient and 0/148 rituximab plus placebo-treated patients. No TFR SAEs had an outcome of death.

In Study NHL-008, TFR SAEs were reported for 1/177 (0.6%) lenalidomide plus rituximab-treated patients. No TFR SAEs had an outcome of death.

MCL Studies:

The outcomes of the TFR SAEs are summarised below.

Outcome	MCL-002		All MCL Lenalidomide Patients (MCL-002, MCL-001, NHL-002, NHL-003)
	Len	Control	
Total number of patients	167	83	373
Patients with ≥ 1 SAE	1 (0.6)	0	1 (0.3)
Ongoing at death	1 (0.6)	0	1 (0.3)

In Study MCL-002, 1 (0.6%) lenalidomide-treatment patient experienced a TFR SAE (PT tumour flare) that was ongoing at the time of the patient's death.

Table 50: Important Identified Risk: Tumour Flare Reaction (MCL and FL Indications) (Continued)

Tumour Flare Reaction (MCL and FL Indications)

Severity and Nature of Risk

FL Studies:

Details of AEs pertaining to TFR that were reported in FL studies are summarised below.

Tumour Flare Reaction	NHL-007		NHL-008	Pooled NHL-007 and NHL-008
	PBO+Rit	Len+Rit	Len+Rit	Len+Rit
Total number of patients	148	146	177	323
All AEs	1	19	7	26
Grade 3 or 4	0	1 (0.7)	0	1 (0.3)
AEs leading to discontinuation	0	0	0	0
AEs leading to dose interruption	0	2 (1.4)	1 (0.6)	3 (0.9)
AEs leading to dose reduction	0	0	0	0

In Study NHL-007, 1.4% of lenalidomide plus rituximab-treated patients experienced TFR AEs leading to dose interruption, and 0.7% of lenalidomide plus rituximab-treated patients experienced Grade 3 or 4 AEs of TFR. No lenalidomide plus rituximab-treated patients experienced TFR AEs leading to dose discontinuation or dose reduction. In the rituximab plus placebo arm, no patients had Grade 3 or 4 AEs of TFR, or TFR AEs leading to dose interruption, dose reduction and study treatment discontinuation.

In Study NHL-008, no Grade 3 or 4 AEs of TFR, or AEs leading to dose reduction and study treatment discontinuation were reported. TFR AEs leading to dose interruption were reported for 0.6% of lenalidomide plus rituximab-treated patients.

MCL Studies:

Tumour Flare Reaction	MCL-002		All MCL Lenalidomide Patients (MCL-002, MCL-001, NHL-002, NHL-003) (N = 373)
	Len (N = 167)	Control (N = 83)	
All AEs	16 (9.6)	0	30 (8.0)
Grade 3 or 4	3 (1.8)	0	3 (0.8)
AEs leading to discontinuation	1 (0.6)	0	1 (0.3)
AEs leading to dose interruption	1 (0.6)	0	1 (0.3)
AEs leading to dose reduction	1 (0.6)	0	1 (0.3)

In Study MCL-002, Grade 3 or 4 TFR AEs were reported in 3 (1.8%) patients in the lenalidomide group and no patients in the control group. Tumour flare reaction AEs led to study treatment being permanently withdrawn, dose interruption and dose reduction in 1 (0.6%) lenalidomide-treated patient each. No patients in the control group had TFR AEs.

Risk Groups and Risk Factors

Tumour flare reaction has been associated with greater tumour burden in CLL (Ferrajoli, 2008). In Study MCL-002, in the final multivariate model, high MIPI score at diagnosis (p=0.084) and bulky disease at baseline (p=0.020) appeared to be strong and independent risk factors for TFR.

Table 50: Important Identified Risk: Tumour Flare Reaction (MCL and FL Indications) (Continued)

Tumour Flare Reaction (MCL and FL Indications)
Preventability When using steroids in the first days in CLL, there was a decrease in severity, but not in TFR incidence (Chanan-Khan, 2006; Chen, 2011). The frequency of TFR also appears to be lower when lenalidomide is used in combination with rituximab (James, 2011) and higher sequential treatment with ofatumumab (Costa, 2012). A recommendation regarding careful monitoring and evaluation for TFR is included in the SmPC (SmPC, Section 4.4).
Impact on the Risk-benefit Balance of the Product Clinical manifestations of TFR can include sudden onset of painful, tender swelling of disease-involved lymph nodes, spleen, and/or liver along with a low-grade fever. Also, rash and a rise in the peripheral blood white cell count can occur (Chanan–Khan, 2008). Generally, interruption or modification of lenalidomide dosing is not required in MCL, and use of non-steroidal, analgesic and anti-inflammatory drugs has been shown to be effective in cases when TFR does develop (Goy, 2013).
Public Health Impact Tumour flare reaction is a side effect of cancer treatment that may mimic disease progression. Within the realm of haematologic malignancies, TFR is specific to lenalidomide treatment of CLL and B-cell lymphomas. Among patients with CLL, Chanan-Khan (Chanan-Khan, 2006) reported 58% of 45 patients experienced TFR and Ferrajoli (Ferrajoli, 2008) reported 30% of 44 patients were affected following lenalidomide starting doses of 25 mg/day and 10 mg/day, respectively. The frequency of TFR among MCL patients in a small Phase II study of lenalidomide was reported by Eve (2010) to be 12% (3/25 patients). Among 134 MCL patients treated with lenalidomide at 25 mg, 13 (10%) experienced Grade 1 or 2 TFR (Goy, 2013). In this study, lenalidomide 25 mg (10 mg for CLcr 30 to 60 mL/min) was self-administered orally on Days 1 through 21 of each 28-day cycle until PD, intolerance, or voluntary withdrawal. Tumour flare reaction has been reported in Hodgkin's disease (Corazzelli, 2010), but not in association with MM or myelodysplasia (Eve, 2010). Most TFRs develop very early in the course of therapy and may mimic progression of disease (including increased absolute lymphocyte count); however, they subside over time and resolve within 2 weeks. Tumour flare reaction is a common ADR of lenalidomide treatment (SmPC, Section 4.8). Tumour flare reaction is an important, transient and manageable adverse effect that may mimic disease progression and clinicians therefore need to be aware of this specific complication. Tumour flare reaction, however, can be quite confidently distinguished from progressing MCL based on its timing and clinical grounds (including signs of inflammatory reaction and the lack of nights sweats and weight loss), so that lenalidomide treatment is not discontinued unnecessarily.
Data Source: Study NHL-007 and Study NHL-008 (13 Aug 2018); Study MCL-001 (20 Mar 2013); Study MCL-002 (07 Mar 2014); Study NHL-002 (23 Jun 2008); Study NHL-003 (27 Apr 2011). **MedDRA Terms** *MCL (MCL-001, MCL-002, NHL-002 and NHL-003)* The MedDRA v16.1 PT of tumour flare reaction. *FL (NHL-007 and NHL-008)* The MedDRA v21.0 PT of tumour flare reaction.

3.1.5. Important Potential Risk: Cardiac Failure

Information concerning the risk of cardiac failure is summarised in Table 51.

Table 51: Important Potential Risk: Cardiac Failure

Cardiac Failure

Potential Mechanisms

A mechanism by which lenalidomide could cause cardiac failure has not been identified.

Evidence Source(s) and Strength of Evidence:

Based on clinical trial data, a higher incidence of cardiac failure has been observed; the reason for this is not clear.

Characterisation of the Risk

Frequency with 95% CI

FL Studies:

Cardiac Failure	NHL-007		NHL-008	Pooled NHL-007 and NHL-008
	PBO+Rit	Len+Rit	Len+Rit	Len+Rit
Total number of patients	148	146	177	323
Patients with ≥ 1 SAE	0	0	0	0
Patients with ≥ 1 AE	2	0	1	1
Incidence (% of patients) with ≥ 1 AE (95% CI)	1.4 (0.2 to 4.8)	0	0.6 (0.0 to 3.1)	-

Overall, in pooled Studies NHL-007 and NHL-008, cardiac failure AEs were reported for 1 (0.3%) lenalidomide plus rituximab-treated patient.

In Study NHL-007, no FL patients treated with lenalidomide plus rituximab-treated patients experienced cardiac failure events.

In Study NHL-008, cardiac failure events were reported for 1(0.6%) lenalidomide plus rituximab-treated patient.

NDMM RVd Study:

Cardiac Failure	SWOG S0777	
	Arm B (RVd)	Arm A (Rd)
Total number of patients	262	256
Patients with ≥ 1 SAE	2	3
Patients with ≥ 1 AE	6	3
Incidence (% of patients) with ≥ 1 AE (95% CI)	2.3 (0.8 to 4.9)	1.2 (0.2 to 3.4)

In Study SWOG S0777, the proportion of patients experiencing at least one cardiac failure event was greater among patients treated with RVd than patients treated with Rd (risk ratio = 1.95 [95% CI: 0.49-7.73]).

TE NDMM Studies:

Cardiac Failure	CALGB 100104 Maintenance		IFM 2005-02 Maintenance	
	Len	Placebo	Len	Placebo
Total number of patients	224	221	293	280
Patients with ≥ 1 SAE	0	0	0	1
Patients with ≥ 1 AE	0	1	0	2
Incidence (% of patients) with ≥ 1 AE (95% CI)[a]	0	0.5 (0.0 to 2.5)	0	0.7 (0.1 to 2.6)

[a] Incidence was not adjusted for time on treatment.

Table 51: Important Potential Risk: Cardiac Failure (Continued)

Cardiac Failure

In Study CALGB 100104, cardiac failure AEs were reported in 1 (0.5%) patient treated with placebo and no lenalidomide-treated patients. In Study IFM 2005-02, cardiac failure AEs were reported in 2 (0.7%) patients treated with placebo; no lenalidomide-treated patients experienced cardiac failure AEs.

TNE NDMM Studies:

Cardiac Failure	MM-020			MM-015		
	Rd	Rd18	MPT	MPR+R	MPR+p	MPp+p
Total number of patients	532	540	541	150	152	153
Patients with ≥ 1 SAE	26	21	17	6	2	2
Patients with ≥ 1 AE	47	28	27	7	4	4
Incidence (% of patients) with ≥ 1 AE (95% CI)[a]	8.8 (6.6 to 11.6)	5.2 (3.5 to 7.4)	5.0 (3.3 to 7.2)	4.7 (1.9 to 9.4)	2.6 (0.7 to 6.6)	2.6 (0.7 to 6.6)

[a] Incidence was not adjusted for time on treatment.

In Study MM-020, the proportion of patients experiencing at least one cardiac failure event was greater among lenalidomide-treated patients than patients treated with control (risk ratio = 1.40 [95% CI: 0.91-2.15]; p = 0.122). Note that treatment duration was longer in Arm Rd compared with Arms Rd18 and MPT (see Section 1.2.2 in Part II Module SIII). In Study MM-015, the proportion of patients experiencing at least one cardiac failure event was greater among lenalidomide-treated patients than patients treated with control (risk ratio = 1.39 [95% CI: 0.45-4.30]; p = 0.564).

RRMM Studies:

Cardiac Failure	MM-009 and MM-010	
	Len/Dex	PBO/Dex
Total number of patients	353	350
Patients with ≥ 1 SAE	6	4
Patients with ≥ 1 AE	12	8
Incidence (% of patients) with ≥ 1 AE (95% CI)[a]	3.4 (1.8 to 5.9)	2.3 (1.0 to 4.5)

[a] Incidence between arms was not adjusted for actual time on treatment (mean treatment duration 44 weeks [Len/Dex] versus 23 weeks [PBO/Dex]).

The risk ratio versus placebo is 1.49 (95% CI: 0.62–3.59 p = 0.39).

Del 5q MDS Studies:

Cardiac Failure	MDS-003[a] Len (10 mg)	MDS-004[b]		
		Len (10 mg)	Len (5 mg)	PBO[c]
Total number of patients	148	69	69	67
Patients with ≥ 1 SAE	8	1	2	0
Patients with ≥ 1 AE	11	2	3	1
Incidence (% of patients) with ≥ 1 AE (95% CI)	7.4 (3.8 to 12.9)	2.9 (0.4 to 10.1)	4.3 (0.9 to 12.2)	1.5 (0.0 to 8.0)

[a] Median time on treatment was 52.5 weeks.
[b] Median time on treatment was 50.3 weeks in the 10 mg group, 18.0 weeks in the 5 mg group and 16.0 weeks in the PBO group.
[c] Data in PBO group is from the first 16 weeks of the double-blind phase.

Table 51: Important Potential Risk: Cardiac Failure (Continued)

Cardiac Failure

In Study MDS-004, no appreciable difference in risk of cardiac failure was seen across all treatment groups (1.5% to 4.3%).

MCL Studies:

Cardiac Failure	MCL-002		All MCL Lenalidomide Patients (MCL-002, MCL-001, NHL-002, NHL-003)
	Len	Control	
Total number of patients	167	83	373
Patients with ≥ 1 SAE	4	2	5
Patients with ≥ 1 AE	9	2	14
Incidence (% of patients) with ≥ 1 AE (95% CI)	5.4 (2.5 to 10.0)	2.4 (0.3 to 8.4)	3.8 (2.1 to 6.2)

In Study MCL-002, the proportion of patients experiencing at least one cardiac failure event was greater among lenalidomide-treated patients than patients treated with control (risk ratio = 2.24 [95% CI: 0.49-10.12]; p = 0.296).

Seriousness/Outcomes

FL Studies:

In FL patients in Studies NHL-007 and NHL-008, no cardiac failure SAE was reported.

NDMM RVd Study:

The outcomes of the cardiac failure SAEs are summarised below.

Outcome	SWOG S0777	
	Arm B (RVd)	Arm A (Rd)
Patients with ≥ 1 SAE	2 (0.8)	3 (1.2)
Death	0	0
Ongoing at death	0	1 (0.4)
Recovered/resolved	1 (0.4)	0
Recovered/resolved with sequelae	1 (0.4)	0
Recovering/resolving	0	1 (0.4)
Unknown	0	1 (0.4)

In Study SWOG S0777, cardiac failure SAEs were reported for 2/262 (0.8%) patients treated with RVd (PTs: cardiac failure) and 3/256 (1.2%) patients treated with Rd (PTs: cardiac failure and cardiac failure congestive). No cardiac failure SAEs had an outcome of death.

Table 51: Important Potential Risk: Cardiac Failure (Continued)

Cardiac Failure

TE NDMM Studies:

No cardiac failure SAEs were reported in Study CALGB 100104. One (0.4%) patient treated with placebo in Study IFM 2005-02 experienced a cardiac failure SAE, with an outcome of recovering/resolving.

TNE NDMM Studies:

The outcomes of the cardiac failure SAEs are summarised below.

Outcome	MM-020			MM-015		
	Rd N = 532	Rd18 N = 540	MPT N = 541	MPR+R N = 150	MPR+p N = 152	MPp+p N = 153
Patients with ≥ 1 SAE	26 (4.9)	21 (3.9)	17 (3.1)	6 (4.0)	2 (1.3)	2 (1.3)
Death	5 (0.9)	3 (0.6)	2 (0.4)	2 (1.3)	0	0
Ongoing at death	2 (0.4)	0	1 (0.2)	0	1 (0.7)	0
Recovered/resolved	16 (3.0)	12 (2.2)	11 (2.0)	3 (2.0)	1 (0.7)	0
Recovered with sequelae	0	1 (0.2)	2 (0.4)	1 (0.7)	0	0
Not recovered/not resolved	1 (0.2)	3 (0.6)	0	0	0	0
Missing	2 (0.4)	2 (0.4)	1 (0.2)	0	0	2 (1.3)

In Study MM-020, cardiac failure SAEs were experienced by a comparable proportion of patients in the Rd18 and MPT arms of the study (3.9% and 3.1%, respectively) and a slightly higher proportion in the Rd arm of the study (4.9%). PTs reported for more than 2 patients overall were acute pulmonary oedema, cardiac failure, cardiac failure congestive, cardiogenic shock and pulmonary oedema. An outcome of death was reported for SAEs of cardiac failure in 5 (0.9%), 3 (0.6%) and 2 (0.4%) patients in Arms Rd, Rd18 and MPT, respectively.

In Study MM-015, cardiac failure SAEs were experienced by 6/150 (4.0%), 2/152 (1.3%) and 2/153 (1.3%) patients in the MPR+R, MPR+p and MPp+p arms, respectively. PTs reported for more than 2 patients overall were cardiac failure and cardiogenic shock. A total of 2 (1.3%) patients in the MPR+R arm had cardiac failure SAEs with outcomes of death.

RRMM Studies:

The outcomes of the cardiac failure SAEs reported in the RRMM studies are summarised below.

Outcome	Number (%) of Patients[a]	
	MM-009 and MM-010	
	Len/Dex N = 353	PBO/Dex N = 350
Patients with ≥ 1 SAE	6 (1.7)	4 (1.1)
Death	1 (0.3)	1 (0.3)
Resolved/recovered with/without sequelae (MM-009 and MM-010)	4 (1.1)	0
Not recovered/not resolved/ongoing	0	0
Unknown/missing (MM-009 and MM-010)	1 (0.3)	4 (1.1)

[a] Patients can be counted more than once.

The SAEs reported for lenalidomide/dexamethasone-treated patients were cardiac failure congestive (5 patients) and pulmonary oedema NOS (one patient). Five of these SAEs were of Grade 3 or 4 intensity and 2 were considered related to treatment (Grade 3 CHF and Grade 2 congestive cardiac failure). In 3 of the 6 patients, the dose of lenalidomide/dexamethasone was interrupted (2 SAEs of cardiac failure congestive and 1 SAE of pulmonary oedema NOS). One patient died of CHF, which was not considered related to lenalidomide/dexamethasone by the investigator. The 6 SAEs reported for 4 placebo/dexamethasone-treated patients were pulmonary oedema NOS (4 patients), and cardiac failure acute and cardiac failure NOS (one patient each).

Table 51: Important Potential Risk: Cardiac Failure (Continued)

Cardiac Failure

Del 5q MDS Studies:

The outcomes of the cardiac failure SAEs reported in Studies MDS-003 and MDS-004 are summarised below.

Outcome	Number (%) of Patients[a]			
	MDS-003[b] Len (10 mg) N = 148	MDS-004[c]		
		Len (10 mg) N = 69	Len (5 mg) N = 69	PBO[d] N = 67
Patients with ≥ 1 SAE	8 (5.4)	1 (1.4)	2 (2.9)	0
Death	3 (2.0)	0	0	0
Not recovered/not resolved	1 (0.7)	0	0	0
Resolved/recovered with/without sequelae	3 (2.0)	0	2 (2.9)	0
Unknown/missing	1 (0.7)	1 (1.4)	0	0

[a] Patients may be counted more than once.
[b] Median time on treatment was 52.5 weeks.
[c] Median time on treatment was 50.3 weeks in the 10 mg group, 18.0 weeks in the 5 mg group and 16.0 weeks in the PBO group.
[d] Data in PBO group is from the first 16 weeks of the double-blind phase.

In Study MDS-004, cardiac failure SAEs were experienced by 1/69 (1.4%) and 2/69 (2.9%) patients in the lenalidomide 10 mg and 5 mg groups, respectively, (all PTs were cardiac failure) compared with no patients in the placebo group. The SAEs were of Grade 3 intensity in the lenalidomide 5 mg group and of Grade 5 intensity in the lenalidomide 10 mg group. One patient each in the lenalidomide 10 mg and 5 mg groups experienced SAEs of cardiac failure considered related to treatment.

In Study MDS-003, 3 patients experienced cardiac failure SAEs that resulted in death (PTs: cardiac failure [2] and cardiac failure congestive [1]). The SAEs were considered not related to study medication.

MCL Studies:

The outcomes of the cardiac failure SAEs are summarised below.

Outcome	MCL-002		All MCL Lenalidomide Patients (MCL-002, MCL-001, NHL-002, NHL-003)
	Len	Control	
Total number of patients	167	83	373
Patients with ≥ 1 SAE	4 (2.4)	2 (2.4)	5 (1.3)
Death	1 (0.6)	2 (2.4)	1 (0.3)
Recovered with sequelae	1 (0.6)	0	1 (0.3)
Recovered/resolved	1 (0.6)	0	2 (0.5)
Unknown	1 (0.6)	0	1 (0.3)

In Study MCL-002, cardiac failure SAEs were experienced by 4/167 (2.4%) lenalidomide-treated patients and 2/83 (2.4%) patients in the control group. The SAEs (PTs) experienced by lenalidomide-treated patients were: cardiac failure (2 [1.2%] patients), cardiac failure congestive and left ventricular failure (1 [0.6%] patient each). The SAEs (PTs) experienced by patients in the control group were cardiac failure and cardiac failure acute (1 [1.2%] patient each). One patient in the lenalidomide group and two patients in the control group experienced a cardiac failure SAE that had an outcome of death.

In the combined MCL Studies MCL-002, MCL-001, NHL-002 and NHL-003, cardiac failure SAEs were experienced by 5/373 (1.3%) lenalidomide-treated patients. These SAEs (PTs) were cardiac failure, cardiac failure congestive (2 [0.5%] patients each) and left ventricular failure (1 [0.3%] patient). One patient experienced a cardiac failure SAE that had an outcome of death.

Table 51: Important Potential Risk: Cardiac Failure (Continued)

Cardiac Failure

Severity and Nature of Risk

FL Studies:

Details of AEs pertaining to cardiac failure that were reported in FL studies are summarised below.

Cardiac Failure	NHL-007		NHL-008	Pooled NHL-007 and NHL-008
	PBO+Rit	Len+Rit	Len+Rit	Len+Rit
Total number of patients	148	146	177	323
All AEs	2	0	1	1
Grade 3 or 4	1 (0.7)	0	0	0
AEs leading to discontinuation	1 (0.7)	0	0	0
AEs leading to dose interruption	0	0	0	0
AEs leading to dose reduction	0	0	0	0

In Study NHL-007, less than 1% of patients in the rituximab plus placebo arm and no patients in the lenalidomide plus rituximab arm experienced Grade 3 or 4 AEs of cardiac failure. No patients in the lenalidomide plus rituximab arm experienced cardiac failure AEs leading to dose reduction, dose interruption and study treatment discontinuation.

In Study NHL-008, no Grade 3 or 4 AEs of cardiac failure were reported. No cardiac failure AEs led to dose reduction, dose interruption or study treatment discontinuation.

NDMM RVd Study:

Cardiac failure AEs reported in Study SWOG S0777 are summarised below.

Cardiac Failure	SWOG S0777	
	Arm B (RVd)	Arm A (Rd)
Patients with ≥ 1 AE	6 (2.3)	3 (1.2)
Grade 3 or 4	4 (1.5)	3 (1.2)
AEs leading to dose withdrawn permanently	1 (0.4)	0
AEs leading to dose interruption	NC	NC
AEs leading to dose reduction	NC	NC

NC = not collected.

In Study SWOG S0777, the frequencies of Grade 3 or 4 cardiac failure AEs were < 2% in the RVd and Rd arms. In the RVd arm, a cardiac failure AE leading to study treatment withdrawal was reported in 1 (0.4%) patient (PT: cardiac failure congestive). No cardiac failure AEs led to study treatment withdrawal in the Rd arm.

Table 51: Important Potential Risk: Cardiac Failure (Continued)

Cardiac Failure

TE NDMM Studies:

Cardiac failure AEs reported in the TE NDMM studies are summarised below.

Cardiac Failure	CALGB 100104 Maintenance		IFM 2005-02 Maintenance	
	Len	Placebo	Len	Placebo
Patients with ≥ 1 AE	0	1 (0.5)	0	2 (0.7)
Grade 3 or 4	0	0	0	1 (0.4)
AEs leading to dose withdrawn permanently[a]	0	0	0	1 (0.4)
AEs leading to dose interruption[a]	NC	NC	0	0
AEs leading to dose reduction[a]	NC	NC	0	0

NC = not collected per study design.

[a] In Study CALGB 100104, actions taken due to AEs (eg, treatment discontinued, dose reduced, dose interrupted) were not collected on the CRF. AEs leading to treatment discontinuation were derived retrospectively from the Off Treatment Notice form.

There were no Grade 3 or 4 cardiac failure AEs or cardiac failure AEs leading to permanent withdrawal of study treatment reported in Study CALGB 100104. In Study IFM 2005-02, no lenalidomide-treated patients experienced cardiac failure AEs. Grade 3 or 4 cardiac failure AEs and cardiac failure AEs leading to permanent withdrawal of study treatment were each reported in 1 (0.4%) patient treated with placebo; no placebo-treated patients had their dose interrupted or reduced due to AEs of cardiac failure.

TNE NDMM Studies:

Cardiac failure AEs reported in the TNE NDMM studies are summarised below.

Cardiac Failure	MM-020			MM-015		
	Rd N = 532	Rd18 N = 540	MPT N = 541	MPR+R N = 150	MPR+p N = 152	MPp+p N = 153
Patients with ≥ 1 AE	47 (8.8)	28 (5.2)	27 (5.0)	7 (4.7)	4 (2.6)	4 (2.6)
Grade 3 or 4	27 (5.1)	16 (3.0)	17 (3.1)	3 (2.0)	2 (1.3)	0
AEs leading to dose withdrawn permanently	8 (1.5)	7 (1.3)	2 (0.4)	2 (1.3)	0	1 (0.7)
AEs leading to dose interruption	10 (1.9)	7 (1.3)	4 (0.7)	1 (0.7)	1 (0.7)	0
AEs leading to dose reduction	1 (0.2)	2 (0.4)	1 (0.2)	0	0	0

In Study MM-020, Grade 3 or 4 cardiac failure AEs were reported for a greater proportion of patients in Arm Rd (5.1%) than Arm Rd18 and Arm MPT (3.0% and 3.1%, respectively). Cardiac failure AEs led to withdrawal of study treatment permanently or dose interruption in ≤ 1.9% of patients in all treatment arms. In Study MM-015, Grade 3 or 4 cardiac failure AEs were reported for 2.0% and 1.3% of patients in the MPR+R and MPR+p arms, respectively, and no patients in the MPp+p arm. Cardiac failure AEs led to dose interruption in single patients in the MPR+R and MPR+p arms, and to withdrawal of lenalidomide permanently in 1.3% patients in the MPR+R arm and 0.7 patients in the MPp+p arm.

Table 51: Important Potential Risk: Cardiac Failure (Continued)

Cardiac Failure

RRMM Studies:

Cardiac Failure	Number (%) of Patients	
	MM-009 and MM-010	
	Len/Dex N = 353	PBO/Dex N = 350
All AEs	12 (3.4)	8 (2.3)
Grade 3 or 4	6 (1.7)	6 (1.7)
AEs leading to discontinuation	1 (0.3)[a]	3 (0.9)[b]
AEs leading to dose interruption	3 (0.8)[c]	1 (0.3)[d]
AEs leading to dose reduction	0	0

[a] Includes PT of cardiac failure congestive (1)
[b] Includes PTs of pulmonary oedema NOS (3) and cardiac failure acute (1)
[c] Includes PTs of cardiac failure congestive (2) and pulmonary oedema NOS (2)
[d] Includes PT of pulmonary oedema NOS (1)

Overall, only 6/353 (1.7%) lenalidomide/dexamethasone-treated patients experienced a Grade 3 or 4 cardiac failure AE, with cardiac failure congestive and pulmonary oedema NOS accounting for the majority of these AEs (5 and 4 patients, respectively). The same proportion of placebo /dexamethasone-treated patients (6; 1.7%) experienced a Grade 3 or 4 cardiac failure AE.

Del 5q MDS Studies:

Details of cardiac failure AEs reported for patients in Studies MDS-003 and MDS-004 are summarised below.

Cardiac Failure	Number (%) of Patients			
	MDS-003[a] Len (10 mg) N = 148	MDS-004[b]		
		Len (10 mg) N = 69	Len (5 mg) N = 69	PBO[c] N = 67
All AEs	11 (7.4)	2 (2.9)	3 (4.3)	1 (1.5)
Grade 3 or 4	9 (6.1)	1 (1.4)	2 (2.9)	0
AEs leading to discontinuation	1 (0.7)	0	0	0
AEs leading to dose interruption	0	0	0	0
AEs leading to dose reduction	0	0	1 (1.4)[d]	0

[a] Median time on treatment was 52.5 weeks.
[b] Median time on treatment was 50.3 weeks in the 10 mg group, 18.0 weeks in the 5 mg group and 16.0 weeks in the PBO group.
[c] Data in PBO group is from the first 16 weeks of the double-blind phase.
[d] Includes PT of cardiac failure (1).

In Study MDS-004, few patients experienced a Grade 3 or 4 cardiac failure AE or a cardiac failure AE leading to dose reduction. No patients reported a cardiac failure AE resulting in dose interruption or discontinuation.

Table 51: Important Potential Risk: Cardiac Failure (Continued)

Cardiac Failure

MCL Studies:

Cardiac failure AEs reported in the studies in MCL are summarised below.

Cardiac Failure	MCL-002		All MCL Lenalidomide Patients (MCL-002, MCL-001, NHL-002, NHL-003) (N = 373)
	Len (N = 167)	Control (N = 83)	
All AEs	9 (5.4)	2 (2.4)	14 (3.8)
Grade 3 or 4	5 (3.0)	0	6 (1.6)
AEs leading to dose interruption	1 (0.6)	0	2 (0.5)

In Study MCL-002, Grade 3 or 4 cardiac failure AEs were reported in a greater proportion of patients in the lenalidomide group than the control group (3.0% versus 0%). The proportion of patients with cardiac failure AEs leading to dose interruption was greater in the lenalidomide group than the control group (0.6% versus 0%). No cardiac failure AEs led to discontinuation or dose reduction.

Risk Groups and Risk Factors

No particular risk groups or risk factors have been identified for lenalidomide. In MM and MDS no differences in frequency, severity, serious outcomes and apparent risk level of cardiac failure AEs have been observed.

Cardiac symptoms in patients with MDS are often due to anaemia and may be due to iron overload and side effects of therapy (Mateen, 2006). In a study of 840 MDS patients, Della Porta (2007) reported that heart failure (28% versus 18%, $p = 0.001$) and cardiac death (69% versus 55%, $p = 0.03$) were significantly more frequent in transfusion-dependent patients. In a Cox analysis with time-dependent covariates, transfusion-dependent patients showed an increased risk of non-leukemic death (HR = 2.12; $p \leq 0.001$), heart failure (HR = 1.34; $p = 0.03$), and cardiac death (HR = 2.99; $p = 0.01$). The development of secondary iron overload significantly affected the risk of non-leukemic death and OS (HR = 1.25 and 1.16, respectively; $p < 0.001$), and this effect was maintained after adjusting for transfusion burden. Iron overload specifically increased the risk of developing heart failure (HR = 1.17, $p < 0.001$). General risk factors for CHF include increasing age, previous heart disease, diabetes, hypertension, amyloidosis, and previous anthracycline based chemotherapy treatment (Hershman, 2008).

Preventability

Careful monitoring of patients with known medical history that may be contributory to a cardiac failure event should be carried out. Additionally, if serious infection occurs in patients, they should be monitored carefully for cardiac failure events.

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.

Public Health Impact

Data concerning the incidence of cardiac failure in patients with MM and MDS are limited. However, high-output cardiac failure is one of the known cardiovascular issues associated with MM and is frequently seen in patients with extensive bone lesions (Inanir, 1998). Cardiac failure is a common cardiovascular event in the elderly. Based upon the prospective Rotterdam Study of 7983 participants ≥ 55 years of age, the point prevalence of CHF on 01 Jan 1999 was 7.0%. Prevalence was higher in males aged 55+ (8.0%) than in women similarly aged (6.0%). Prevalence increased rapidly with age, rising from 0.9% in patients aged 55 to 64, to 4.0% in patients aged 65 to 74, 9.7% in those aged 75 to 84, to 17.4% in those aged 85 years or older. Lifetime risk for CHF was 33% for men and 29% for women at the age of 55 (Bleumink, 2004). Based upon the most recent US statistics on CHF (Go, 2014), the overall prevalence of CHF is 2.1%, with 825,000 new cases annually. Prevalence is greater in males (2.5%) than females (1.8%), and rises dramatically with age. Among persons less than 60, the prevalence of CHF is less than 2.0%.

Table 51: Important Potential Risk: Cardiac Failure (Continued)

Cardiac Failure
These prevalence proportions rise to 7.8% among males 60 to 79, and 8.6% among males aged 80+. Corresponding figures for females are 4.5% and 11.5%, respectively. The prevalence of cardiac failure or ejection fraction ≤ 50% as a comorbid disorder was determined to be 19% among 840 consecutively diagnosed MDS patients seen at the Fondazione IRCCS Policlinico San Matteo, Pavia, Italy, between 1992 and 2007, based upon detailed review of patients' medical charts and laboratory values at diagnoses and during the course of disease (Della Porta, 2011). In a study cohort of 23,855 MDS patients identified in the SEER-Medicare database, the overall baseline prevalence of CHF was 30.6%, based upon ICD-9-CM diagnoses in the 12 months prior to MDS diagnoses (Zeidan, 2013). An association between cardiac failure and lenalidomide combined with dexamethasone or lenalidomide alone cannot be established.
Data Source: Studies NHL-007 and NHL-008 (13 Aug 2018); Study SWOG S0777 (01 Dec 2016); Study CALGB 100104 (01 Mar 2015); Study IFM 2005-02 (01 Mar 2015); Study MM-020 (24 May 2013); Study MM-015 (30 Apr 2013); Integrated Summary of Safety (Dec 2005) for Studies MM-009 and MM-010; Study MDS-003 CSR; Study MDS-004 CSR; Study MCL-001 (20 Mar 2013); Study MCL-002 (07 Mar 2014); Study NHL-002 (23 Jun 2008); Study NHL-003 (27 Apr 2011). **MedDRA Terms** *FL (NHL-007 and NHL-008)* PTs listed within the MedDRA v21.0 SMQ narrow scope of Cardiac failure are collectively referred to as cardiac failure. *NDMM RVd Study (SWOG S0777)* PTs listed within the MedDRA v15.1 SMQ narrow scope of Cardiac failure are collectively referred to as cardiac failure. *TE NDMM (CALGB 100104 and IFM 2005-02)* PTs listed within the MedDRA v15.1 SMQ narrow scope of Cardiac failure are collectively referred to as cardiac failure. *TNE NDMM (MM-020 and MM-015)* PTs listed within the MedDRA v15.1 SMQ narrow scope of Cardiac failure are collectively referred to as cardiac failure. *RRMM (MM-009 and MM-010)* The MedDRA v11.0 SMQ of Cardiac failure (narrow scope), and the MedDRA v5.1 PTs of cardiac failure NOS and pulmonary oedema NOS are collectively referred to as cardiac failure. *Del 5q MDS (MDS-003 and MDS-004)* PTs listed within the MedDRA v13.0 SMQ narrow scope of Cardiac failure are collectively referred to as cardiac failure. *MCL (MCL-001, MCL-002, NHL-002 and NHL-003)* PTs listed within the MedDRA v16.1 SMQ narrow scope of cardiac failure are collectively referred to as cardiac failure.

3.1.6. Important Potential Risk: Cardiac Arrhythmias

Information concerning the risk of cardiac arrhythmias is summarised in Table 52.

Table 52: Important Potential Risk: Cardiac Arrhythmias

Cardiac Arrhythmias

Potential Mechanisms

No mechanisms by which lenalidomide may cause cardiac arrhythmias have been identified.

Evidence Source(s) and Strength of Evidence:

Based on clinical trial data, a higher incidence of cardiac arrhythmia was observed in the lenalidomide arm.

Frequency with 95% CI

FL Studies:

Cardiac Arrhythmias	NHL-007		NHL-008	Pooled NHL-007 and NHL-008
	PBO+Rit	Len+Rit	Len+Rit	Len+Rit
Total number of patients	148	146	177	323
Patients with ≥ 1 SAE	3	4	1	5
Patients with ≥ 1 AE	13	17	12	29
Incidence (% of patients) with ≥ 1 AE (95% CI)	8.8 (4.8 to 14.6)	11.6 (6.9 to 18.0)	6.8 (3.6 to 11.5)	-

Overall, in pooled Studies NHL-007 and NHL-008, cardiac arrhythmia AEs were reported for 29 lenalidomide plus rituximab-treated patients.

In Study NHL-007, the proportion of patients experiencing at least one cardiac arrhythmia event was slightly higher in the lenalidomide plus rituximab arm than the rituximab plus placebo arm (risk ratio = 1.3 [95% CI: 0.6-2.7]).

In Study NHL-008, cardiac arrhythmia events were reported for 6.8% lenalidomide plus rituximab-treated patients.

NDMM RVd Study:

Cardiac Arrhythmias	SWOG S0777	
	Arm B (RVd)	Arm A (Rd)
Total number of patients	262	256
Patients with ≥ 1 SAE	16	4
Patients with ≥ 1 AE	43	21
Incidence (% of patients) with ≥ 1 AE (95% CI)	16.4 (12.1 to 21.5)	8.2 (5.1 to 12.3)

In Study SWOG S0777, the proportion of patients experiencing at least one cardiac arrhythmia event was greater among patients treated with RVd than patients treated with Rd (risk ratio = 2.00 [95% CI: 1.22-3.27]).

Table 52: Important Potential Risk: Cardiac Arrhythmias (Continued)

Cardiac Arrhythmias

Characterisation of the Risk

TE NDMM Studies:

Cardiac Arrhythmias	CALGB 100104 Maintenance		IFM 2005-02 Maintenance	
	Len	Placebo	Len	Placebo
Total number of patients	224	221	293	280
Patients with ≥ 1 SAE	2	2	3	1
Patients with ≥ 1 AE	12	8	11	16
Incidence (% of patients) with ≥ 1 AE (95% CI)[a]	5.4 (2.8 to 9.2)	3.6 (1.6 to 7.0)	3.8 (1.9 to 6.6)	5.7 (3.3 to 9.1)

[a] Incidence was not adjusted for time on treatment.

In Study CALGB 100104, the proportion of patients experiencing at least one cardiac arrhythmia event was greater among lenalidomide-treated patients than patients treated with placebo (risk ratio = 1.48 [95% CI: 0.62-3.55]; p = 0.380). In Study IFM 2005-02, the proportion of patients experiencing at least one cardiac arrhythmia event was smaller among lenalidomide-treated patients than patients treated with placebo (risk ratio = 0.66 [95% CI: 0.31-1.39]; p = 0.272).

TNE NDMM Studies:

Cardiac Arrhythmias	MM-020			MM-015		
	Rd	Rd18	MPT	MPR+R	MPR+p	MPp+p
Total number of patients	532	540	541	150	152	153
Patients with ≥ 1 SAE	45	35	32	10	6	8
Patients with ≥ 1 AE	133	94	123	33	30	25
Incidence (% of patients) with ≥ 1 AE (95% CI)[a]	25.0 (21.4 to 28.9)	17.4 (14.3 to 20.9)	22.7 (19.3 to 26.5)	22.0 (15.7 to 29.5)	19.7 (13.7 to 27.0)	16.3 (10.9 to 23.2)

[a] Incidence was not adjusted for time on treatment.

In Study MM-020, the proportion of patients experiencing at least one cardiac arrhythmia event was similar among lenalidomide-treated patients and patients treated with control (risk ratio = 0.93 [95% CI: 0.77-1.13]; p = 0.472). In Study MM-015, the proportion of patients experiencing at least one cardiac arrhythmias event was slightly higher among lenalidomide-treated patients than patients treated with control (risk ratio = 1.28 [95% CI: 0.84-1.94]; p = 0.255).

The most frequent cardiac arrhythmia events in Study MM-020 were atrial fibrillation, reported for 37, 25 and 25 patients each in Arms Rd, Rd18 and MPT, followed by syncope (22, 17 and 27 patients in these respective arms) and bradycardia (20, 11 and 25 patients in these respective arms). In Study MM-015, the most frequent cardiac arrhythmia events were atrial fibrillation, reported for 8, 5 and 9 patients each in the MPR+R, MPR+p and MPp+p arms, followed by palpitations (6, 3 and 6 patients in these respective arms) and syncope (3, 5 and 2 patients in these respective arms).

Table 52: Important Potential Risk: Cardiac Arrhythmias (Continued)

Cardiac Arrhythmias

RRMM Studies:

Cardiac Arrhythmias	MM-009 and MM-010	
	Len/Dex	PBO/Dex
Total number of patients	353	350
Patients with ≥ 1 SAE	13	5
Patients with ≥ 1 AE	30	17
Incidence (% of patients) with ≥ 1 AE (95% CI)[a]	8.5 (5.8 to 11.9)	4.9 (2.9 to 7.7)

[a] Incidence between arms was not adjusted for actual time on treatment (mean treatment duration 44 weeks [Len/Dex] versus 23 weeks [PBO/Dex])

In the RRMM clinical studies, cardiac arrhythmias were noted in 8.5% (30/353) of lenalidomide/dexamethasone-treated patients and in 4.9% (17/350) of the placebo/dexamethasone-treated patients. The risk ratio for cardiac arrhythmia was 1.75 (95% CI: 0.98 – 3.11; p = 0.055).

Del 5q MDS Studies:

Cardiac Arrhythmias	MDS-003[a] Len (10 mg)	MDS-004[b]		
		Len (10 mg)	Len (5 mg)	PBO[c]
Total number of patients	148	69	69	67
Patients with ≥ 1 SAE	8	1	1	1
Patients with ≥ 1 AE	30	5	4	4
Incidence (% of patients) with ≥ 1 AE (95% CI)	20.3 (14.1 to 27.7)	7.2 (2.4 to 16.1)	5.8 (1.6 to 14.2)	6.0 (1.7 to 14.6)

[a] Median time on treatment was 52.5 weeks.
[b] Median time on treatment was 50.3 weeks in the 10 mg group, 18.0 weeks in the 5 mg group and 16.0 weeks in the PBO group.
[c] Data in PBO group is from the first 16 weeks of the double-blind phase.

In Study MDS-004, the risk of cardiac arrhythmias was comparable across the lenalidomide and placebo groups (5.8% to 7.2%). For the combined group (5 mg and 10 mg) versus placebo, the risk ratio is 1.09 (95% CI: 0.35-3.42).

The most frequent cardiac arrhythmia events were palpitations, reported for 3 patients each in the lenalidomide 5 mg and placebo groups, and by 1 patient in the lenalidomide 10 mg group, followed by atrial fibrillation (1, 2 and 1 patients in these respective groups). The other cardiac arrhythmia events (atrial flutter, tachycardia and tachyarrhythmia) were reported for single patients.

MCL Studies:

Cardiac Arrhythmias	MCL-002		All MCL Lenalidomide Patients (MCL-002, MCL-001, NHL-002, NHL-003)
	Len	Control	
Total number of patients	167	83	373
Patients with ≥ 1 SAE	7	1	12
Patients with ≥ 1 AE	16	4	35
Incidence (% of patients) with ≥ 1 AE (95% CI)	9.6 (5.6 to 15.1)	4.8 (1.3 to 11.9)	9.4 (6.6 to 12.8)

In Study MCL-002, the proportion of patients experiencing at least one cardiac arrhythmia event was greater among lenalidomide-treated patients than patients treated with control (risk ratio = 1.99 [95% CI: 0.69-5.76]; p = 0.205).

Table 52: Important Potential Risk: Cardiac Arrhythmias (Continued)

Cardiac Arrhythmias

Seriousness/Outcomes

FL Studies:

Serious AE outcomes reported in the FL studies are summarised below.

Outcome	NHL-007		NHL-008	Pooled NHL-007 and NHL-008
	PBO+Rit	Len+Rit	Len+Rit	Len+Rit
Total number of patients	148	146	177	323
Patients with ≥ 1 SAE	3 (2.0)	4 (2.7)	1 (0.6)	5 (1.5)
Death	0	1 (0.7)	1 (0.6)	2 (0.6)
Resolved	3 (2.0)	3 (2.1)	0	3 (0.9)

In Study NHL-007, cardiac arrhythmia SAEs were reported for 4/146 (2.7%) lenalidomide plus rituximab-treated patients (PTs reported were atrial fibrillation, supraventricular tachycardia and arrhythmia) and 3/148 (2.0%) rituximab plus placebo-treated patients (PTs reported were atrial fibrillation, syncope and atrial flutter). One (0.7%) cardiac arrhythmia SAE of arrhythmia had an outcome of death in the lenalidomide plus rituximab arm.

In Study NHL-008, cardiac arrhythmia SAEs were reported for 1/177 (0.6%) lenalidomide plus rituximab-treated patient (PT reported was cardio-respiratory arrest). This SAE of cardio-respiratory arrest had an outcome of death.

NDMM RVd Study:

The outcomes of the cardiac arrhythmia SAEs are summarised below.

Outcome	SWOG S0777	
	Arm B (RVd)	Arm A (Rd)
Patients with ≥ 1 SAE	16 (6.1)	4 (1.6)
Death	1 (0.4)	0
Recovered/resolved	6 (2.3)	1 (0.4)
Recovered/resolved with sequelae	0	0
Recovering/resolving	7 (2.7)	1 (0.4)
Not recovered/not resolved	2 (0.8)	1 (0.4)
Unknown	0	1 (0.4)

In Study SWOG S0777, cardiac arrhythmia SAEs were reported for 16/262 (6.1%) patients treated with RVd (PTs reported were atrial fibrillation, sudden death and syncope) and 4/256 (1.6%) patients treated with Rd (PTs reported were atrial fibrillation and syncope). One cardiac arrhythmia SAE in Study SWOG S0777 was fatal (PT: sudden death) and was reported in the RVd arm.

Table 52: Important Potential Risk: Cardiac Arrhythmias (Continued)

Cardiac Arrhythmias

TE NDMM Studies:

The outcomes of the cardiac arrhythmia SAEs are summarised below.

Outcome	CALGB 100104 Maintenance		IFM 2005-02 Maintenance	
	Len	Placebo	Len	Placebo
Patients with ≥ 1 SAE	2 (0.9)	2 (0.9)	3 (1.0)	1 (0.4)
Death	0	1 (0.5)	0	0
Resolved/recovered	1 (0.4)	0	1 (0.3)	0
Recovered with sequelae	1 (0.4)	0	0	0
Missing	0	0	2 (0.7)	1 (0.4)
Not recovered/not resolved	0	1 (0.5)	0	0

In Study CALGB 100104, cardiac arrhythmia SAEs were reported for 2/224 (0.9%) lenalidomide-treated patients (PTs were sick sinus syndrome and syncope). An outcome of death was reported for 1 (0.5%) placebo-treated patient in Study CALGB 100104 (PT: atrioventricular block).

In Study IFM 2005-02, cardiac arrhythmia SAEs were reported for 3/293 (1.0%) lenalidomide-treated patients (PTs were atrial fibrillation and sudden death).

TNE NDMM Studies:

The outcomes of the cardiac arrhythmia SAEs are summarised below.

Outcome	MM-020			MM-015		
	Rd N = 532	Rd18 N = 540	MPT N = 541	MPR+R N = 150	MPR+p N = 152	MPp+p N = 153
Patients with ≥ 1 SAE	45 (8.5)	35 (6.5)	32 (5.9)	10 (6.7)	6 (3.9)	8 (5.2)
Death	7 (1.3)	4 (0.7)	2 (0.4)	1 (0.7)	0	0
Ongoing at death	1 (0.2)	3 (0.6)	1 (0.2)	0	0	0
Not recovered/not resolved	0	0	0	0	0	0
Recovered/resolved	33 (6.2)	24 (4.4)	24 (4.4)	8 (5.3)	3 (2.0)	0
Recovered with sequelae	3 (0.6)	3 (0.6)	4 (0.7)	1 (0.7)	3 (2.0)	0
Missing	1 (0.2)	1 (0.2)	1 (0.2)	0	0	8 (5.2)

In Study MM-020, cardiac arrhythmia SAEs were experienced by a comparable proportion of patients in the Rd18 and MPT arms of the study (6.5% and 5.9%, respectively), and a slightly higher proportion in the Rd arm of the study (8.5%). In descending order of frequency, PTs reported for more than 2 patients overall were atrial fibrillation, syncope, cardiac arrest, sudden death, atrial flutter, bradycardia, supraventricular tachycardia, tachycardia, arrhythmia, loss of consciousness and sinus bradycardia. SAEs of cardiac arrhythmia had an outcome of death in 7 (1.3%), 4 (0.7%) and 2 (0.4%) patients in Arms Rd, Rd18 and MPT, respectively. These were PTs of sudden death (7 patients), cardiac arrest (5 patients) and cardio-respiratory arrest (1 patient).

In Study MM-015, cardiac arrhythmia SAEs were experienced by a slightly higher proportion of patients in the MPR+R arm (6.7%) than in the MPR+p and MPp+p arms (3.9% and 5.2%, respectively). In descending order of frequency, PTs reported for more than 2 patients overall were atrial fibrillation, syncope, bradycardia and palpitations. One (0.7%) patient in the MPR+R arm had an SAE of cardiac arrhythmia with an outcome of death.

Table 52: Important Potential Risk: Cardiac Arrhythmias (Continued)

Cardiac Arrhythmias

RRMM Studies:

The outcomes of the cardiac arrhythmia SAEs reported in the RRMM studies are summarised below.

Outcome	Number (%) of Patients[a]	
	MM-009 and MM-010	
	Len/Dex N = 353	PBO/Dex N = 350
Patients with ≥ 1 SAE	13 (3.7)	5 (1.4)
Death	1 (0.3)	3 (0.9)
Resolved/recovered with/without sequelae (MM-009 and MM-010)	6 (1.7)	2 (0.6)
Not recovered/not resolved/ongoing	0	0
Unknown/missing (MM-009 and MM-010)	6 (1.7)	0

[a] Patients may be counted more than once.

Thirteen out of 353 (3.7%) lenalidomide/dexamethasone-treated patients experienced 14 cardiac arrhythmia SAEs. These SAEs were atrial fibrillation (11 patients), and cardio-respiratory arrest and tachycardia NOS (one patient each). Thirteen of these 14 SAEs were of Grade 3 or 4 intensity. Eight of these 14 SAEs (all events of atrial fibrillation) were considered related to lenalidomide/dexamethasone by the investigator, and of these 8 related SAEs, 2 led to discontinuation of lenalidomide/dexamethasone treatment, and 2 led to interruption of lenalidomide/ dexamethasone treatment. One patient died as a result of cardio-respiratory arrest, which was not considered related to lenalidomide/dexamethasone by the investigator.

A total of 5 SAEs were reported in 5/350 (1.4%) patients treated with placebo/dexamethasone. These SAEs were atrial fibrillation (2 patients), and cardiac arrest, sinus tachycardia and cardio-respiratory arrest (one patient each).

Del 5q MDS Studies:

The outcomes of the cardiac arrhythmia SAEs reported in Studies MDS-003 and MDS-004 are summarised below.

Outcome	Number (%) of Patients[a]			
	MDS-003[b]	MDS-004[c]		
	Len (10 mg) N = 148	Len (10 mg) N = 69	Len (5 mg) N = 69	PBO[d] N = 67
Patients with ≥ 1 SAE	8 (5.4)	1 (1.4)	1 (1.4)	1 (1.5)
Death	2 (1.4)	0	0	0
Not recovered/not resolved	0	0	1 (1.4)	0
Resolved/recovered with/without sequelae	5 (3.4)	1 (1.4)	0	1 (1.5)
Unknown/missing	1 (0.7)	0	0	0

[a] Patients may be counted more than once.
[b] Median time on treatment was 52.5 weeks.
[c] Median time on treatment was 50.3 weeks in the 10 mg group, 18.0 weeks in the 5 mg group and 16.0 weeks in the PBO group.
[d] Data in PBO group is from the first 16 weeks of the double-blind phase.

In Study MDS-004, a cardiac arrhythmia SAE was experienced by 1 patient each in the lenalidomide 10 mg (PT: tachyarrhythmia), lenalidomide 5 mg (PT: atrial fibrillation) and placebo (PT: atrial flutter) groups. These 3 patients all experienced cardiac arrhythmia SAEs of Grade 2 or 3 intensity. The SAEs were considered not related to treatment.

In Study MDS-003, 2 patients experienced cardiac arrhythmia SAEs that resulted in death (PTs: atrial fibrillation and sudden death). The SAEs were considered not related to study medication.

Table 52: Important Potential Risk: Cardiac Arrhythmias (Continued)

Cardiac Arrhythmias

MCL Studies:

The outcomes of the cardiac arrhythmia SAEs are summarised below.

Outcome	MCL-002		All MCL Lenalidomide Patients (MCL-002, MCL-001, NHL-002, NHL-003)
	Len	Control	
Total number of patients	167	83	373
Patients with ≥ 1 SAE	7 (4.2)	1 (1.2)	12 (3.2)
Death	3 (1.8)	0	5 (1.3)
Recovered with sequelae	1 (0.6)	0	2 (0.5)
Recovered/resolved	2 (1.2)	1 (1.2)	4 (1.1)
Unknown	1 (0.6)	0	1 (0.3)

In Study MCL-002, cardiac arrhythmia SAEs were experienced by 7/167 (4.2%) lenalidomide-treated patients and 1/83 (1.2%) patient in the control group. The SAEs (PTs) experienced by lenalidomide-treated patients were cardiac arrest (2 [1.2%] patients), supraventricular tachycardia, atrial fibrillation, sudden death, atrioventricular block second degree and tachycardia (1 [0.6%] patient each). The SAE (PT) experienced by a single patient in the control group was atrial fibrillation. Three patients in the lenalidomide group experienced a cardiac arrhythmia SAE that had an outcome of death.

In the combined MCL Studies MCL-002, MCL-001, NHL-002 and NHL-003, cardiac arrhythmia SAEs were experienced by 12/373 (3.2%) lenalidomide-treated patients. These SAEs (PTs) were supraventricular tachycardia (3 [0.8%] patients); atrial fibrillation, cardiac arrest, sudden death (2 [0.5%] patients each); atrioventricular block second degree, bradycardia, cardio-respiratory arrest and tachycardia (1 [0.3%] patient each). Five patients experienced a cardiac arrhythmia SAE that had an outcome of death.

Severity and Nature of Risk

FL Studies

Details of AEs pertaining to cardiac arrhythmia that were reported in the FL studies are summarised below.

Cardiac Arrhythmias	NHL-007		NHL-008	Pooled NHL-007 and NHL-008
	PBO+Rit	Len+Rit	Len+Rit	Len+Rit
Total number of patients	148	146	177	323
All AEs	13 (8.8)	17 (11.6)	12 (6.8)	29 (9.0)
Grade 3 or 4	2 (1.4)	4 (2.7)	3 (1.7)	7 (2.2)
AEs leading to discontinuation	1 (0.7)	0	1 (0.6)	1 (0.3)
AEs leading to dose interruption	0	3 (2.1)	4 (2.3)	7 (2.2)
AEs leading to dose reduction	0	0	0	0

In Study NHL-007, a greater proportion of patients treated with lenalidomide plus rituximab than those treated with rituximab plus placebo experienced Grade 3 or 4 AEs of cardiac arrhythmia (2.7% versus 1.4%). Three (2.1%) patients treated with lenalidomide plus rituximab experienced cardiac arrhythmia AEs leading to dose interruption. No patients treated with lenalidomide plus rituximab experienced cardiac arrhythmia AEs leading to study treatment discontinuation or dose reduction.

In Study NHL-008, 1.7% lenalidomide plus rituximab-treated patients experienced a Grade 3 or 4 AE of cardiac arrhythmia. Cardiac arrhythmia AEs leading to dose interruption and study treatment discontinuation were experienced by 2.3% and 0.6% lenalidomide plus rituximab-treated patients, respectively. No patients treated with lenalidomide plus rituximab experienced cardiac arrhythmia AEs leading to dose reduction.

Table 52: Important Potential Risk: Cardiac Arrhythmias (Continued)

Cardiac Arrhythmias

NDMM RVd Study:

Cardiac arrhythmia AEs reported in Study SWOG S0777 are summarised below.

Cardiac Arrhythmias	SWOG S0777	
	Arm B (RVd)	Arm A (Rd)
Patients with ≥ 1 AE	43 (16.4)	21 (8.2)
Grade 3 or 4	27 (10.3)	9 (3.5)
AEs leading to dose withdrawn permanently	1 (0.4)	0
AEs leading to dose interruption	NC	NC
AEs leading to dose reduction	NC	NC

NC = not collected.

In Study SWOG S0777, the frequencies of Grade 3 or 4 cardiac arrhythmia AEs were 10.3% and 3.5% in the RVd and Rd arms, respectively. In the RVd arm only, a cardiac arrhythmia AE leading to study treatment withdrawal was reported in 1 (0.4%) patient (PT: syncope).

TE NDMM Studies:

Cardiac arrhythmia AEs reported in the TE NDMM studies are summarised below.

Cardiac Arrhythmias	CALGB 100104 Maintenance		IFM 2005-02 Maintenance	
	Len	Placebo	Len	Placebo
Patients with ≥ 1 AE	12 (5.4)	8 (3.6)	11 (3.8)	16 (5.7)
Grade 3 or 4	8 (3.6)	5 (2.3)	1 (0.3)	1 (0.4)
AEs leading to dose withdrawn permanently[a]	0	0	1 (0.3)	0
AEs leading to dose interruption[a]	NC	NC	0	0
AEs leading to dose reduction[a]	NC	NC	0	0

NC = not collected per study design.

[a] In Study CALGB 100104, actions taken due to AEs (eg, treatment discontinued, dose reduced, dose interrupted) were not collected on the CRF. AEs leading to treatment discontinuation were derived retrospectively from the Off Treatment Notice form.

In Study CALGB 100104, Grade 3 or 4 cardiac arrhythmia AEs were reported in 3.6% of lenalidomide-treated patients and 2.3% of placebo-treated patients. There were no cardiac arrhythmia AEs leading to permanent withdrawal of study treatment. In Study IFM 2005-02, Grade 3 or 4 cardiac arrhythmia AEs were reported in single lenalidomide-treated and placebo-treated patients. One patient treated with lenalidomide experienced at least one cardiac arrhythmia AE leading to withdrawal of study treatment permanently compared to no patients treated with placebo. No cardiac arrhythmia AEs leading to study treatment interruption or dose reduction were reported in Study IFM 2005-02.

Table 52: Important Potential Risk: Cardiac Arrhythmias (Continued)

Cardiac Arrhythmias

TNE NDMM Studies:

Cardiac arrhythmia AEs reported in the TNE NDMM studies are summarised below.

Cardiac Arrhythmias	MM-020			MM-015		
	Rd N = 532	Rd18 N = 540	MPT N = 541	MPR+R N = 150	MPR+p N = 152	MPp+p N = 153
Patients with ≥ 1 AE	133 (25.0)	94 (17.4)	123 (22.7)	33 (22.0)	30 (19.7)	25 (16.3)
Grade 3 or 4	41 (7.7)	30 (5.6)	43 (7.9)	9 (6.0)	8 (5.3)	5 (3.3)
AEs leading to dose withdrawn permanently	6 (1.1)	2 (0.4)	6 (1.1)	3 (2.0)	0	0
AEs leading to dose interruption	21 (3.9)	11 (2.0)	23 (4.3)	7 (4.7)	2 (1.3)	7 (4.6)
AEs leading to dose reduction	2 (0.4)	2 (0.4)	6 (1.1)	1 (0.7)	0	0

In Study MM-020, Grade 3 or 4 cardiac arrhythmia AEs were reported for relatively few patients, with no consistent pattern between treatment arms (Rd: 7.7%, Rd18: 5.6%, MPT: 7.9%). Cardiac arrhythmia AEs led to withdrawal of study treatment permanently, dose interruption or dose reduction in ≤ 4.3% of patients in all treatment arms.

In Study MM-015, Grade 3 or 4 cardiac arrhythmia AEs were reported for 6.0%, 5.3% and 3.3% of patients in the MPR+R, MPR+p and MPp+p arms, respectively. Cardiac arrhythmia AEs led to the withdrawal of lenalidomide permanently in 2.0% of patients in the MPR+R arm; dose interruption in 4.7%, 1.3% and 4.6% of patients in the MPR+R, MPR+p and MPp+p arms, respectively; and to dose reduction in 0.7% of patients in the MPR+R arm only.

RRMM Studies:

Details of AEs of cardiac arrhythmias that were reported in the RRMM studies are summarised below.

Cardiac Arrhythmias	Number (%) of Patients	
	RRMM	
	Len/Dex N = 353	PBO/Dex N = 350
All AEs	30 (8.5)	17 (4.9)
Grade 3 or 4	20 (5.7)	8 (2.3)
AEs leading to discontinuation	2 (0.6)[a]	1 (0.3)[b]
AEs leading to dose interruption	2 (0.6)[c]	2 (0.6)[d]
AEs leading to dose reduction	1 (0.3)[e]	0

[a] Includes PT of atrial fibrillation (2)
[b] Includes PT of cardiac arrest (1)
[c,d] Includes PTs of atrial fibrillation (c:1, d:1) and tachycardia NOS (1)
[e] Includes PT of sinus tachycardia (1)

Overall, only 20/353 (5.7%) lenalidomide/dexamethasone-treated patients experienced Grade 3 or 4 AEs of cardiac arrhythmias, with atrial fibrillation and tachycardia NOS accounting for the majority of these AEs (14 and 6 patients, respectively). A comparable proportion of placebo/dexamethasone-treated patients (8/350; 2.3%) experienced a Grade 3 or 4 cardiac arrhythmia AE.

Less than 1% of the patients in both arms were withdrawn from the trial or had to temporarily interrupt their treatment due to cardiac arrhythmias. The dose was reduced in just one patient in the lenalidomide/dexamethasone arm.

Table 52: Important Potential Risk: Cardiac Arrhythmias (Continued)

Cardiac Arrhythmias

Del 5q MDS Studies:

Details of cardiac arrhythmia AEs reported for patients in Studies MDS-003 and MDS-004 are summarised below.

Cardiac Arrhythmia	Number (%) of Patients			
	MDS-003[a] Len (10 mg) N = 148	MDS-004[b]		
		Len (10 mg) N = 69	Len (5 mg) N = 69	PBO[c] N = 67
All AEs	30 (20.3)	5 (7.2)	4 (5.8)	4 (6.0)
Grade 3 or 4	13 (8.8)	2 (2.9)	1 (1.4)	0
AEs leading to discontinuation	2 (1.4)	0	1 (1.4)[d]	1 (1.5)[e]
AEs leading to dose interruption	0	0	0	0
AEs leading to dose reduction	0	0	0	0

[a] Median time on treatment was 52.5 weeks.
[b] Median time on treatment was 50.3 weeks in the 10 mg group, 18.0 weeks in the 5 mg group and 16.0 weeks in the PBO group.
[c] Data in PBO group is from the first 16 weeks of the double-blind phase.
[d] Includes PT of atrial fibrillation (1).
[e] Includes PT of palpitations (1).

In Study MDS-004, few patients experienced a Grade 3 or 4 cardiac arrhythmia AE or a cardiac arrhythmia AE that resulted in dose discontinuation, interruption or reduction.

MCL Studies:

Cardiac arrhythmia AEs reported in the studies in MCL are summarised below.

Cardiac Arrhythmias	MCL-002		All MCL Lenalidomide Patients (MCL-002, MCL-001, NHL-002, NHL-003) (N = 373)
	Len (N = 167)	Control (N = 83)	
All AEs	16 (9.6)	4 (4.8)	35 (9.4)
Grade 3 or 4	4 (2.4)	2 (2.4)	7 (1.9)
AEs leading to discontinuation	0	1 (1.2)	1 (0.3)
AEs leading to dose interruption	4 (2.4)	1 (1.2)	5 (1.3)

In Study MCL-002, Grade 3 or 4 cardiac arrhythmia AEs were reported in the same proportion of patients in the lenalidomide and control groups (both 2.4%). The proportion of patients with cardiac arrhythmia AEs leading to discontinuation was lower in the lenalidomide group than the control group (0% versus 1.2%), whereas a greater proportion of patients in the lenalidomide group than the control group (2.4% versus 1.2%) experienced cardiac arrhythmia AEs leading to dose interruption.

Risk Groups and Risk Factors

Standard risk factors for atrial fibrillation include advancing age, European ancestry, body size (greater height and body mass index), electrocardiography features (left ventricular hypertrophy, left atrial enlargement), diabetes, systolic blood pressure and presence of cardiovascular disease (ie, CHD, heart failure, valvular heart disease). Other factors include clinical and subclinical hyperthyroidism, chronic kidney disease, and heavy alcohol consumption. Familial aggregation studies have identified a role for genetic factors, although such factors probably account for a small proportion of cases (Go, 2014). In a case-control study of 385 eligible cases of new-onset atrial fibrillation embedded within the Rotterdam study, the risk of new-onset atrial fibrillation was significantly higher for persons who received a corticosteroid prescription within 1 month before the atrial

Table 52: Important Potential Risk: Cardiac Arrhythmias (Continued)

Cardiac Arrhythmias
fibrillation index date (van der Hooft, 2006). Only high-dose corticosteroid use was associated with increased risk (OR = 6.07; 95% CI: 3.90-9.42). The association of atrial fibrillation was independent of indication for use. Risks were increased not only in patients with asthma or chronic obstructive pulmonary disease, but also in patients with rheumatic, allergic, or malignant haematologic diseases.
Preventability Patients with a known cardiac history should be carefully chosen for any chemotherapy and carefully monitored by their physician.
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 Data concerning the incidence of cardiac arrhythmias in patients with MM, MDS, MCL and FL are limited. As reported from the Rotterdam study, a prospective cohort study among patients aged 55+, the prevalence of atrial fibrillation at baseline among 6808 participants was 5.5% (Heeringa, 2006). Prevalence rose from 0.7% among those aged 55 to 59, to 17.8% among those aged 85 and above. The overall incidence rate was 9.9/1000 person-years. Prevalence and incidence were higher in men than women. Lifetime risks of atrial fibrillation at age 55 years were 23.8% in men and 22.2% in women. The prevalence of cardiac arrhythmias (defined as atrial fibrillation or flutter, sick sinus syndrome, or ventricular arrhythmias) was determined to be 7% among 840 consecutively diagnosed MDS patients seen at the Fondazione IRCCS Policlinico San Matteo, Pavia, Italy, between 1992 and 2007, based upon detailed review of patients' medical charts and laboratory values at diagnoses and during the course of disease (Della Porta, 2011). Patients who develop atrial fibrillation are at increased risk of serious cardiovascular complications, such as heart failure and ischaemic stroke (van der Hooft, 2006). However, an association between cardiac arrhythmias and lenalidomide in combination with dexamethasone or lenalidomide alone cannot be established. Most cardiac arrhythmias observed with lenalidomide treatment in the clinical setting were non-serious.
Data Source: Studies NHL-007 and NHL-008 (13 Aug 2018); Study SWOG S0777 (01 Dec 2016); Study CALGB 100104 (01 Mar 2015); Study IFM 2005-02 (01 Mar 2015); Study MM-020 (24 May 2013); Study MM-015 (30 Apr 2013); Integrated Summary of Safety (Dec 2005) for Studies MM-009 and MM-010; Study MDS-003 CSR; Study MDS-004 CSR; Study MCL-001 (20 Mar 2013); Study MCL-002 (07 Mar 2014); Study NHL-002 (23 Jun 2008); Study NHL-003 (27 Apr 2011). **MedDRA Terms** *FL (NHL-007 and NHL-008)* PTs listed within the MedDRA v21.0 narrow scope of sub-SMQ bradyarrhythmia terms, nonspecific, narrow scope of sub-SMQ conduction defects, narrow scope of sub-SMQ disorders of sinus node function, narrow scope of sub-SMQ cardiac arrhythmia terms, nonspecific, broad scope of sub-SMQ supraventricular tachyarrhythmias, narrow scope of sub-SMQ tachyarrhythmia terms, nonspecific, narrow scope of sub-SMQ ventricular tachyarrhythmias. *NDMM RVd Study (SWOG S0777)* PTs listed within the MedDRA v15.1 broad scope of all sub-SMQs under the SMQ cardiac arrhythmias (with the exception of the sub-SMQ of congenital and neonatal arrhythmias) are collectively referred to as cardiac arrhythmias.

Table 52: Important Potential Risk: Cardiac Arrhythmias (Continued)

Cardiac Arrhythmias
TE NDMM (CALGB 100104 and IFM 2005-02) PTs listed within the MedDRA v15.1 broad scope of all sub-SMQs under the SMQ cardiac arrhythmias (with the exception of the sub-SMQ of congenital and neonatal arrhythmias) are collectively referred to as cardiac arrhythmias. *TNE NDMM (MM-020 and MM-015)* PTs listed within the MedDRA v15.1 broad scope of all sub-SMQs under the SMQ cardiac arrhythmias (with the exception of the sub-SMQ of congenital and neonatal arrhythmias) are collectively referred to as cardiac arrhythmias. *RRMM (MM-009 and MM-010)* The MedDRA v11.0 SMQ for cardiac arrhythmias terms (including bradyarrhythmias and tachyarrhythmias), and the MedDRA v5.1 PTs of tachycardia NOS, bradycardia NOS, atrial fibrillation aggravated, supraventricular arrhythmia NOS and ventricular arrhythmia NOS are collectively referred to as cardiac arrhythmias. *Del 5q MDS (MDS-003 and MDS-004)* PTs listed within the MedDRA v13.0 SMQ broad scope of cardiac arrhythmias (with the exception of the sub-SMQ of congenital and neonatal arrhythmias) are collectively referred to as cardiac arrhythmias. *MCL (MCL-001, MCL-002, NHL-002 and NHL-003)* PTs listed within the MedDRA v16.1 SMQ broad scope of cardiac arrhythmias (except for the sub-SMQ of congenital and neonatal arrhythmias) are collectively referred to as cardiac arrhythmias.

3.1.7. Important Potential Risk: Ischaemic Heart Disease (Including Myocardial Infarction)

Information concerning the risk of ischaemic heart disease (including myocardial infarction) is summarised in Table 53. For the RRMM clinical studies the search criteria were based on the important potential risk of MI. However, for the FL, TE and TNE NDMM, del 5q MDS and MCL clinical studies, the search criteria were broadened to include ischaemic heart disease. Importantly, a number of patients experienced AEs pertaining to ischaemic heart disease in Studies SWOG S0777, CALGB 100104, IFM 2005-02, MM-020, MM-015, MDS-003, MDS-004 and MCL-002 using these broader search criteria (Table 53).

Table 53: Important Potential Risk: Ischaemic Heart Disease (Including Myocardial Infarction)

Ischaemic Heart Disease (Including Myocardial Infarction)
Potential Mechanisms A mechanism by which lenalidomide could cause MI has not been identified.
Evidence Source(s) and Strength of Evidence: In clinical trials, IHD has been reported in patients treated with lenalidomide. Myocardial infarction occurs relatively often in individuals of the older age groups that most often develop the target indications of MM, MDS, MCL and FL.

Table 53: Important Potential Risk: Ischaemic Heart Disease (Including Myocardial Infarction) (Continued)

Ischaemic Heart Disease (Including Myocardial Infarction)

Characterisation of the Risk

Frequency with 95% CI

FL Studies:

Ischaemic Heart Disease	NHL-007		NHL-008	Pooled NHL-007 and NHL-008
	PBO+Rit	Len+Rit	Len+Rit	Len+Rit
Total number of patients	148	146	177	323
Patients with ≥ 1 SAE	1	1	4	5
Patients with ≥ 1 AE	2	1	7	8
Incidence (% of patients) with ≥ 1 AE (95% CI)	1.4 (0.2 to 4.8)	0.7 (0 to 3.8)	4.0 (1.6 to 8.0)	-

Overall, in pooled Studies NHL-007 and NHL-008, IHD AEs were reported for 8 lenalidomide plus rituximab-treated patients.

In Study NHL-007, the proportion of patients experiencing at least one IHD event was low in both FL patients in the lenalidomide plus rituximab arm and rituximab plus placebo arm (risk ratio = 0.5 [95% CI: 0.0-5.6]).

In Study NHL-008, IHD events were reported for 4.0% of lenalidomide plus rituximab-treated patients.

NDMM RVd Study:

Ischaemic Heart Disease	SWOG S0777	
	Arm B (RVd)	Arm A (Rd)
Total number of patients	262	256
Patients with ≥ 1 SAE	1	2
Patients with ≥ 1 AE	1	3
Incidence (% of patients) with ≥ 1 AE (95% CI)	0.4 (0.0 to 2.1)	1.2 (0.2 to 3.4)

In Study SWOG S0777, the proportion of patients experiencing at least one ischaemic heart disease event was smaller among patients treated with RVd than patients treated with Rd (risk ratio = 0.33 [95% CI: 0.03-3.11]).

TE NDMM Studies:

Ischaemic Heart Disease	CALGB 100104 Maintenance		IFM 2005-02 Maintenance	
	Len	Placebo	Len	Placebo
Total number of patients	224	221	293	280
Patients with ≥ 1 SAE	1	2	0	2
Patients with ≥ 1 AE	1	2	2	2
Incidence (% of patients) with ≥ 1 AE (95% CI)[a]	0.4 (0.0 to 2.5)	0.9 (0.1 to 3.2)	0.7 (0.1 to 2.4)	0.7 (0.1 to 2.6)

[a] Incidence was not adjusted for time on treatment.

In Study CALGB 100104, the proportion of patients experiencing at least one IHD event was smaller among lenalidomide-treated patients than patients treated with placebo (risk ratio = 0.49 [95% CI: 0.05-5.40]; p = 0.563).
In Study IFM 2005-02, the proportion of patients experiencing at least one IHD event was the same among lenalidomide-treated patients and patients treated with placebo (risk ratio = 0.96 [95% CI: 0.14-6.74]; p = 0.964).

Table 53: Important Potential Risk: Ischaemic Heart Disease (Including Myocardial Infarction) (Continued)

Ischaemic Heart Disease (Including Myocardial Infarction)

TNE NDMM Studies:

Ischaemic Heart Disease	MM-020			MM-015		
	Rd	Rd18	MPT	MPR+R	MPR+p	MPp+p
Total number of patients	532	540	541	150	152	153
Patients with ≥ 1 SAE	30	6	10	5	3	3
Patients with ≥ 1 AE	43	17	17	14	7	10
Incidence (% of patients) with ≥ 1 AE (95% CI)[a]	8.1 (5.9 to 10.7)	3.1 (1.8 to 5.0)	3.1 (1.8 to 5.0)	9.3 (5.2 to 15.2)	4.6 (1.9 to 9.3)	6.5 (3.2 to 11.7)

[a] Incidence was not adjusted for time on treatment.

In Study MM-020, the proportion of patients experiencing at least one IHD event was greater among lenalidomide-treated patients than patients treated with control (risk ratio = 1.78 [95% CI: 1.05-3.02]; p = 0.032). In Study MM-015, the proportion of patients experiencing at least one IHD event was similar among lenalidomide-treated patients and patients treated with control (risk ratio = 1.06 [95% CI: 0.51-2.20]; p = 0.867).

RRMM Studies:

Myocardial Infarction	MM-009 and MM-010	
	Len/Dex	PBO/Dex
Total number of patients	353	350
Patients with ≥ 1 SAE	7	2
Patients with ≥ 1 AE	8	3
Incidence (% of patients) with ≥ 1 AE (95% CI)[a]	2.3 (0.7 to 3.8)	0.9 (0.0 to 1.8)

[a] Incidence between arms was not adjusted for actual time on treatment (mean treatment duration 44 weeks [Len/Dex] versus 23 weeks [PBO/Dex]).

In the RRMM clinical studies, the proportion of patients experiencing at least one MI meeting the criteria for an SAE was under 2% in both treatment arms. The proportion of patients affected was non-significantly higher (p = 0.11) among patients in the lenalidomide/dexamethasone arm (7/353; 1.98%) relative to the placebo/dexamethasone arm (2/350; 0.57%). The proportion of patients experiencing at least one MI event was greater in the lenalidomide/dexamethasone arm than in the placebo/dexamethasone arm (risk ratio 2.64 [95% CI: 0.71-9.88]).

Del 5q MDS Studies:

Ischaemic Heart Disease	MDS-003[a] Len (10 mg)	MDS-004[b]		
		Len (10 mg)	Len (5 mg)	PBO[c]
Total number of patients	148	69	69	67
Patients with ≥ 1 SAE	3	3	0	0
Patients with ≥ 1 AE	10	3	1	1
Incidence (% of patients) with ≥ 1 AE (95% CI)	6.8 (3.3 to 12.1)	4.3 (0.9 to 12.2)	1.4 (0.0 to 7.8)	1.5 (0.0 to 8.0)

[a] Median time on treatment was 52.5 weeks.
[b] Median time on treatment was 50.3 weeks in the 10 mg group, 18.0 weeks in the 5 mg group and 16.0 weeks in the PBO group.
[c] Data in PBO group is from the first 16 weeks of the double-blind phase.

Table 53: Important Potential Risk: Ischaemic Heart Disease (Including Myocardial Infarction) (Continued)

Ischaemic Heart Disease (Including Myocardial Infarction)

In Study MDS-004, the risk of IHD was slightly higher in the lenalidomide 10 mg group (4.3%) than the lenalidomide 5 mg and placebo groups (1.4% and 1.5%, respectively).

MCL Studies:

Ischaemic Heart Disease	MCL-002		All MCL Lenalidomide Patients (MCL-002, MCL-001, NHL-002, NHL-003)
	Len	Control	
Total number of patients	167	83	373
Patients with ≥ 1 SAE	3	0	5
Patients with ≥ 1 AE	7	0	12
Incidence (% of patients) with ≥ 1 AE (95% CI)	4.2 (1.7 to 8.4)	0	3.2 (1.7 to 5.6)

In Study MCL-002, at least one IHD event was reported in 4.2% of lenalidomide-treated patients, whereas no patient treated with control experienced an event of IHD.

Seriousness/Outcomes

FL Studies:

SAE outcomes reported in the FL studies are summarised below.

Outcome	NHL-007		NHL-008	Pooled NHL-007 and NHL-008
	PBO+Rit	Len+Rit	Len+Rit	Len+Rit
Total number of patients	148	146	177	323
Patients with ≥ 1 SAE	1 (0.7)	1 (0.7)	4 (2.3)	5 (1.5)
Recovered with sequelae	0	0	2 (1.1)	2 (0.6)
Resolved	1 (0.7)	1 (0.7)	2 (1.1)	3 (0.9)

In Study NHL-007, IHD SAEs were reported for 1/146 (0.7%) lenalidomide plus rituximab-treated patient (PT reported was angina pectoris) and 1/148 (0.7%) rituximab plus placebo-treated patients (PT reported was myocardial infarction). No IHD SAEs had an outcome of death.

In Study NHL-008, IHD SAEs were reported for 4/177 (2.3%) lenalidomide plus rituximab-treated patients (PTs reported were angina pectoris, acute coronary syndrome, acute myocardial infarction and troponin increased). No IHD SAEs had an outcome of death.

NDMM RVd Study:

The outcomes of the ischaemic heart disease SAEs are summarised below.

Outcome	SWOG S0777	
	Arm B (RVd)	Arm A (Rd)
Patients with ≥ 1 SAE	1 (0.4)	2 (0.8)
Death	0	0
Recovered/resolved	1 (0.4)	1 (0.4)
Recovering/resolving	0	1 (0.4)

In Study SWOG S0777, ischaemic heart disease SAEs were reported for 1/262 (0.4%) patient treated with RVd (PT: myocardial infarction) and 2/256 (0.8%) patients treated with Rd (PTs: angina pectoris and myocardial infarction). None of the ischaemic heart disease SAEs in Study SWOG S0777 had a fatal outcome.

Table 53: Important Potential Risk: Ischaemic Heart Disease (Including Myocardial Infarction) (Continued)

Ischaemic Heart Disease (Including Myocardial Infarction)

TE NDMM Studies:

The outcomes of the IHD SAEs are summarised below.

Outcome	CALGB 100104 Maintenance		IFM 2005-02 Maintenance	
	Len	Placebo	Len	Placebo
Patients with ≥ 1 SAE	1 (0.4)	2 (0.9)	0	2 (0.7)
Death	0	0	0	0
Resolved/recovered	0	1 (0.5)	0	0
Missing	0	0	0	2 (0.7)
Not recovered/not resolved	1 (0.4)	1 (0.5)	0	0

In Study CALGB 100104, IHD SAEs were reported for 1/224 (0.4%) lenalidomide-treated patient (PT: blood creatine phosphokinase increased). In Study IFM 2005-02, no IHD SAEs were reported for lenalidomide-treated patients.

No IHD SAEs had an outcome of death in the TE NDMM Studies CALGB 100104 and IFM 2005-02.

TNE NDMM Studies:

The outcomes of the IHD SAEs are summarised below.

Outcome	MM-020			MM-015		
	Rd N = 532	Rd18 N = 540	MPT N = 541	MPR+R N = 150	MPR+p N = 152	MPp+p N = 153
Patients with ≥ 1 SAE	30 (5.6)	6 (1.1)	10 (1.8)	5 (3.3)	3 (2.0)	3 (2.0)
Death	3 (0.6)	2 (0.4)	1 (0.2)	0	0	0
Ongoing at death	3 (0.6)	0	0	1 (0.7)	0	0
Resolved/recovered	19 (3.6)	4 (0.7)	8 (1.5)	3 (2.0)	2 (1.3)	0
Recovered with sequelae	4 (0.8)	0	1 (0.2)	1 (0.7)	1 (0.7)	0
Missing	1 (0.2)	0	0	0	0	3 (2.0)

In Study MM-020, IHD SAEs were experienced by a greater proportion of patients treated with lenalidomide or dexamethasone until disease progression (30/532 [5.6%] patients) than those treated with lenalidomide and dexamethasone for 18 cycles or in patients treated with MPT for 12 cycles (6/540 [1.1%] and 10/541 [1.8%]). PTs reported for more than 2 patients overall were acute coronary syndrome, AMI, angina pectoris, coronary artery disease, coronary artery stenosis and MI. An outcome of death was reported for SAEs of IHD in 3 (0.6%), 2 (0.4%) and 1 (0.2%) patients in Arms Rd, Rd18 and MPT, respectively.

In Study MM-015, IHD SAEs were experienced by similar proportions of patients in the MPR+R, MPR+p and MPp+p arms, respectively: 5/150 (3.3%), 3/152 (2.0%) and 3/153 (2.0%). The PTs were acute coronary syndrome, AMI, angina pectoris, coronary artery disease, coronary artery occlusion and myocardial ischaemia. No IHD SAEs had an outcome of death in Study MM-015.

Table 53: Important Potential Risk: Ischaemic Heart Disease (Including Myocardial Infarction) (Continued)

Ischaemic Heart Disease (Including Myocardial Infarction)

RRMM Studies:

The outcomes of the MI SAEs reported in the RRMM studies are summarised below.

Outcome	Number (%) of Patients[a]	
	MM-009 and MM-010	
	Len/Dex N = 353	PBO/Dex N = 350
Patients with ≥ 1 SAE	7 (2.0)	2 (0.6)
Death	4 (1.1)	0
Resolved/recovered with/without sequelae (MM-009 and MM-010)	3 (0.8)	2 (0.6)
Not recovered/not resolved/ongoing	0	0
Unknown/missing (MM-009 and MM-010)	0	0

[a] Patients can be counted more than once.

Seven out of 353 (0.2%) lenalidomide/dexamethasone-treated patients experienced 7 SAEs of MI. These SAEs were MI (5 patients), troponin I increased (one patient) and acute coronary syndrome (one patient). All of these SAEs were of Grade 3 or 4 intensity. Only one of the SAEs was considered related to lenalidomide and included a fatal report secondary to CVA. An outcome of death was reported for 4 patients and causes included MI (2) and CVA (1) and respiratory failure (1). In 3 of the 7 reports of SAEs lenalidomide/dexamethasone was withdrawn. Of these patients one recovered and 2 died. Dose was unchanged in 3 (1 SAE of acute coronary syndrome and 2 SAEs of acute MI); dose was interrupted in one patient who recovered (SAE of acute MI). A total of 3 SAEs (myocardial ischaemia and MI in one; MI in the other) were reported in 2 out of 350 (0.6%) placebo/dexamethasone-treated patients. In one patient who recovered the dose was interrupted and in the other patient the dose was unchanged and the patient recovered.

Del 5q MDS Studies:

The outcomes of the IHD SAEs reported in Studies MDS-003 and MDS-004 are summarised below.

Outcome	Number (%) of Patients[a]			
	MDS-003[b]	MDS-004[c]		
	Len (10 mg) N = 148	Len (10 mg) N = 69	Len (5 mg) N = 69	PBO[d] N = 67
Patients with ≥ 1 SAE	3 (2.0)	3 (4.3)	0	0
Death	1 (0.7)	0	0	0
Not recovered/not resolved	0	1 (1.4)	0	0
Resolved/recovered with/without sequelae	2 (1.4)	2 (2.9)	0	0
Unknown/missing	0	0	0	0

[a] Patients may be counted more than once.
[b] Median time on treatment was 52.5 weeks.
[c] Median time on treatment was 50.3 weeks in the 10 mg group, 18.0 weeks in the 5 mg group and 16.0 weeks in the PBO group.
[d] Data in PBO group is from the first 16 weeks of the double-blind phase.

In Study MDS-004, an IHD SAE was experienced by 3 patients in the lenalidomide 10 mg group (PTs: Acute MI [2 patients] and MI [1 patient]). All 3 patients experienced IHD SAEs of Grade 3 or 4 intensity and 1 patient experienced an IHD SAE considered related to treatment. No deaths were reported in Study MDS-004.

Table 53: Important Potential Risk: Ischaemic Heart Disease (Including Myocardial Infarction) (Continued)

Ischaemic Heart Disease (Including Myocardial Infarction)

In Study MDS-003, a single patient experienced an SAE of MI (PT) that resulted in death. The SAE was considered not related to study medication.

MCL Studies:

The outcomes of the IHD SAEs are summarised below.

Outcome	MCL-002		All MCL Lenalidomide Patients (MCL-002, MCL-001, NHL-002, NHL-003)
	Len	Control	
Total number of patients	167	83	373
Patients with ≥ 1 SAE	3 (1.8)	0	5 (1.3)
Death	1 (0.6)	0	1 (0.3)
Recovered with sequelae	0	0	1 (0.3)
Recovered/resolved	2 (1.2)	0	3 (0.8)

In Study MCL-002, IHD SAEs were experienced by 3/167 (1.8%) lenalidomide-treated patients. The SAEs (PTs) experienced by lenalidomide-treated patients were acute myocardial infarction, myocardial infarction and acute coronary syndrome (1 [0.6%] patient each). One patient in the lenalidomide group experienced an IHD SAE that had an outcome of death.

In the combined MCL Studies MCL-002, MCL-001, NHL-002 and NHL-003, IHD SAEs were experienced by 5/373 (1.3%) lenalidomide-treated patients. These SAEs (PTs) were acute myocardial infarction, myocardial infarction (2 [0.5%] patients each) and acute coronary syndrome (1 [0.3%] patient). One patient experienced an IHD SAE that resulted in death.

Severity and Nature of Risk

FL Studies:

Details of AEs pertaining to IHD that were reported in the FL studies are summarised below.

Ischaemic Heart Disease	NHL-007		NHL-008	Pooled NHL-007 and NHL-008
	PBO+Rit	Len+Rit	Len+Rit	Len+Rit
Total number of patients	148	146	177	323
All AEs	2 (1.4)	1 (0.7)	7 (4.0)	8 (2.5)
Grade 3 or 4	1 (0.7)	1 (0.7)	3 (1.7)	4 (1.2)
AEs leading to discontinuation	0	0	0	0
AEs leading to dose interruption	1 (0.7)	0	1 (0.6)	1 (0.3)
AEs leading to dose reduction	0	0	1 (0.6)	1 (0.3)

In Study NHL-007, < 1% of patients experienced Grade 3 or 4 IHD AEs. No patients treated with lenalidomide plus rituximab had study treatment discontinued, dose reduction or dose interruption due to an IHD AE.

In Study NHL-008, 1.7% lenalidomide plus rituximab-treated patients experienced a Grade 3 or 4 AE of IHD. IHD AEs leading to dose interruption or reduction were experienced by < 1% lenalidomide plus rituximab-treated patients. No patients had study treatment discontinued due to IHD AEs.

Table 53: Important Potential Risk: Ischaemic Heart Disease (Including Myocardial Infarction) (Continued)

Ischaemic Heart Disease (Including Myocardial Infarction)

NDMM RVd Study:

Ischaemic heart disease AEs reported in Study SWOG S0777 are summarised below.

Ischaemic Heart Disease	SWOG S0777	
	Arm B (RVd)	Arm A (Rd)
Patients with ≥ 1 AE	1 (0.4)	3 (1.2)
Grade 3 or 4	1 (0.4)	2 (0.8)
AEs leading to dose withdrawn permanently	1 (0.4)	0
AEs leading to dose interruption	NC	NC
AEs leading to dose reduction	NC	NC

NC = not collected.

In Study SWOG S0777, Grade 3 or 4 ischaemic heart disease AEs were reported in < 1% of patients in the RVd and Rd arms. Ischaemic heart disease AEs led to study treatment withdrawal of 1 (0.4%) patient in the RVd arm (PT: acute myocardial infarction); none lead to study treatment withdrawal in the Rd arm.

TE NDMM Studies:

Ischaemic heart disease AEs reported in the TE NDMM studies are summarised below.

Ischaemic Heart Disease	CALGB 100104 Maintenance		IFM 2005-02 Maintenance	
	Len	Placebo	Len	Placebo
Patients with ≥ 1 AE	1 (0.4)	2 (0.9)	2 (0.7)	2 (0.7)
Grade 3 or 4	1 (0.4)	2 (0.9)	0	1 (0.4)
AEs leading to dose withdrawn permanently[a]	0	0	0	0
AEs leading to dose interruption[a]	NC	NC	0	1 (0.4)
AEs leading to dose reduction[a]	NC	NC	0	0

NC = not collected per study design.

[a] In Study CALGB 100104, actions taken due to AEs (eg, treatment discontinued, dose reduced, dose interrupted) were not collected on the CRF. AEs leading to treatment discontinuation were derived retrospectively from the Off Treatment Notice form.

Grade 3 or 4 IHD AEs were reported in 1 (0.4%) patient treated with lenalidomide and 2 (0.9%) patients treated with placebo in Study CALGB 100104. There were no IHD AEs leading to permanent withdrawal of study treatment. In Study IFM 2005-02, no lenalidomide-treated patients experienced Grade 3 or 4 IHD AEs. Grade 3 or 4 IHD AEs were reported in 1 (0.4%) patient treated with placebo. One patient treated with placebo experienced at least one IHD AE leading to study treatment interruption. No patients in the study had their study treatment withdrawn permanently or their dose reduced due to IHD AEs.

Table 53: Important Potential Risk: Ischaemic Heart Disease (Including Myocardial Infarction) (Continued)

Ischaemic Heart Disease (Including Myocardial Infarction)

TNE NDMM Studies:

Ischaemic heart disease AEs reported in the TNE NDMM studies are summarised below.

Ischaemic Heart Disease	MM-020			MM-015		
	Rd N = 532	Rd18 N = 540	MPT N = 541	MPR+R N = 150	MPR+p N = 152	MPp+p N = 153
Patients with ≥ 1 AE	43 (8.1)	17 (3.1)	17 (3.1)	14 (9.3)	7 (4.6)	10 (6.5)
Grade 3 or 4	25 (4.7)	8 (1.5)	10 (1.8)	5 (3.3)	4 (2.6)	1 (0.7)
AEs leading to dose withdrawn permanently	2 (0.4)	0	1 (0.2)	0	1 (0.7)	0
AEs leading to dose interruption	13 (2.4)	3 (0.6)	7 (1.3)	4 (2.7)	3 (2.0)	3 (2.0)
AEs leading to dose reduction	0	0	0	0	0	0

In Study MM-020, the frequency of Grade 3 or 4 IHD AEs was comparable in patients treated with lenalidomide and dexamethasone for 18 cycles or in patients treated with MPT for 12 cycles (1.5% and 1.8%, respectively), and was higher in patients treated with lenalidomide and dexamethasone until disease progression (4.7%). Ischaemic heart disease AEs led to withdrawal of study treatment permanently or dose interruption in ≤ 2.4% of patients in all treatment arms, with no IHD AEs resulting in dose reduction in any treatment arms.

In Study MM-015, Grade 3 or 4 IHD AEs were reported for a similar proportion of patients in Arms MPR+R and MPR+p (3.3% and 2.6%, respectively) and a lower proportion of patients in Arm MPp+p (0.7%).

Ischaemic heart disease AEs led to the withdrawal of lenalidomide permanently in a single patient in Arm MPR+p, and dose interruption in 2.7%, 2.0% and 2.0% of patients in Arms MPR+R, MPR+p and MPp+p, respectively. No patients in any treatment arms had their dose reduced as a result of IHD AEs.

RRMM Studies:

Details of MI AEs that were reported in the RRMM studies, respectively, are summarised below.

Myocardial Infarction	Number (%) of Patients	
	RRMM	
	Len/Dex N = 353	PBO/Dex N = 350
All AEs	8 (2.3)	3 (0.9)
Grade 3 or 4	7 (2.0)	3 (0.9)
AEs leading to discontinuation	3 (0.8)[a]	0
AEs leading to dose interruption	1 (0.3)[b]	1 (0.3)[c]
AEs leading to dose reduction	3 (0.8)	1 (0.3)

[a] Includes PT of MI (3)
[b] Includes PT of MI (1)
[c] Includes PT of MI (1)

Overall, 7/353 (2.0%) lenalidomide/dexamethasone-treated patients experienced a Grade 3 or 4 MI AE, with the PT MI accounting for the majority of these AEs (5 patients). Two patients (3 SAEs) in the placebo/dexamethasone-treated patients experienced a Grade 3 or 4 MI AE.

Table 53: Important Potential Risk: Ischaemic Heart Disease (Including Myocardial Infarction) (Continued)

Ischaemic Heart Disease (Including Myocardial Infarction)

Del 5q MDS Studies:

Details of IHD AEs reported for patients in Studies MDS-003 and MDS-004 are summarised below.

Ischaemic Heart Disease	Number (%) of Patients			
	MDS-003[a] Len (10 mg) N = 148	MDS-004[b]		
		Len (10 mg) N = 69	Len (5 mg) N = 69	PBO[c] N = 67
All AEs	10 (6.8)	3 (4.3)	1 (1.4)	1 (1.5)
Grade 3 or 4	4 (2.7)	3 (4.3)	0	0
AEs leading to discontinuation	0	1 (1.4)[d]	0	0
AEs leading to dose interruption	0	1 (1.4)[e]	0	0
AEs leading to dose reduction	0	0	0	0

[a] Median time on treatment was 52.5 weeks.
[b] Median time on treatment was 50.3 weeks in the 10 mg group, 18.0 weeks in the 5 mg group and 16.0 weeks in the PBO group.
[c] Data in PBO group is from the first 16 weeks of the double-blind phase.
[d] Includes PT of MI (1)
[e] Includes PT of acute MI (1)

In Study MDS-004, 4.3% of patients in the lenalidomide 10 mg group experienced Grade 3 or 4 IHD. Ischaemic heart disease resulted in dose discontinuation and interruption for 1.4% of patients.

MCL Studies:

Ischaemic heart disease AEs reported in the studies in MCL are summarised below.

Ischaemic Heart Disease	MCL-002		All MCL Lenalidomide Patients (MCL-002, MCL-001, NHL-002, NHL-003) (N = 373)
	Len (N = 167)	Control (N = 83)	
All AEs	7 (4.2)	0	12 (3.2)
Grade 3 or 4	3 (1.8)	0	6 (1.6)
AEs leading to discontinuation	0	0	1 (0.3)
AEs leading to dose interruption	1 (0.6)	0	1 (0.3)

In Study MCL 002, Grade 3 or 4 IHD AEs were reported in 3 (1.8%) patients in the lenalidomide group. One (0.6%) patient experienced an AE that led to dose interruption.

Risk Groups and Risk Factors

Risk factors for 10-year coronary risk based upon the Framingham Heart Study include elevated blood pressure, elevated cholesterol, high-density lipoprotein-C, presence of diabetes and cigarette smoking (Go, 2014). These factors are in addition to the well-known relationships between coronary risk and age and gender.

In Europe, smoking remains a major public health issue and about 20% of death from CVD in men and about 3% of deaths from CVD in women are due to smoking. Levels of obesity are high across Europe in both adults and children, although rates vary substantially between countries. Participation in physical activity is low. Increases in population body mass index over the interval 1980 to 2008 were noted in almost all countries. The prevalence of diabetes in Europe is high and has increased rapidly over the last ten years, increasing by more than 50% in many countries (Nichols, 2012).

Table 53: Important Potential Risk: Ischaemic Heart Disease (Including Myocardial Infarction) (Continued)

Ischaemic Heart Disease (Including Myocardial Infarction)
Preventability MI has been reported in patients receiving lenalidomide, particularly in those with known risk factors and within the first 12 months when used in combination with dexamethasone. Patients with known risk factors – including prior thrombosis – should be closely monitored, and action should be taken to try to minimise all modifiable risk factors (eg, smoking, hypertension and hyperlipidaemia) (SmPC, Section 4.4).
Impact on the Risk-benefit Balance of the Product Ischaemic heart disease can be life-threatening or fatal depending on the severity and impacts activities of daily living.
Public Health Impact Information on the incidence/prevalence of MI in the EU is limited. Among 5148 participants in the Rotterdam prospective cohort study of persons at least age 55 with no evidence of prevalent infarction, 141 recognised MIs occurred and the incidence rate of this event was 5.0 per 1000 person-years (de Torbal, 2006). The incidence was higher in men (8.4) than in women (3.1). The incidence of unrecognised MI was 3.8 per 1000 person-years, with only small differences between men (4.2) and women (3.6). Rates generally increased with age for both recognised and unrecognised MI. In a population-based cohort of 3729 people older than 64 years identified in three geographical areas of Spain and free of previous MI, adjusted incidence rates of MI were higher in men (957 per 100,000 person-years) than in women (546 per 100,000; Gabriel, 2009). Thus, men showed a significantly ($p < 0.001$) higher cumulative incidence of MI at 10 years (7.2%) than women (3.8%). While cumulative incidence increased with age ($p < 0.05$), gender-differences tended to narrow. Using linked Hospital Episode Statistics and mortality information, the Oxford Record Linkage studied English individuals of any age, who were admitted to hospital for AMI or who died suddenly from AMI in 2010 (Smolina, 2012). They identified 82,252 AMI events. Age-standardised incidence of first AMI per 100,000 population was 130 (95% CI: 129–131) in men and 55.9 (95% CI: 55.3–56.6) in women. Incidence rates demonstrated a steep age gradient for both men and women, with about three-quarters of all AMIs occurring in individuals aged ≥ 65 years. About one in six AMIs are reinfarctions in both men and women, and this proportion increases with older age. Disease of the heart and circulatory system (cardiovascular disease) is the main cause of death in the EU, accounting for 1.9 million deaths each year. Forty percent of all deaths in the EU (43% of deaths in women and 36% of deaths in men) are from cardiovascular disease – slightly less than for Europe as a whole. Over a third of deaths from cardiovascular disease in the EU are from CHD. CHD by itself is the single most common cause of death in Europe and death rates from CHD are generally higher in Central and Eastern Europe than in Northern, Southern and Western Europe. CHD is also the single most common cause of death in the EU, accounting for over 681,000 deaths in the EU each year: 15% of deaths among men, and 13% of deaths among women (Nichols, 2012). The proportion of MDS patients with comorbid coronary artery disease or prevalent MI at baseline in the Pavia cohort was 8%. Coronary artery disease was defined as one or more vessel-coronary artery stenosis requiring medical treatment, stent or bypass graft (Della Porta, 2011). In the SEER-Medicare cohort of 23,855 patients with MDS, the proportion of patients with ischemic heart disease was 41.1% and those with prevalent MI was 3.3%. Baseline comorbidities were identified in the 12 months prior to the MDS diagnosis (Zeidan, 2013). MI is a leading cause of morbidity and mortality. Many of the risk factors associated with MI can be modified eg, through a change in lifestyle. An association between MI and lenalidomide combined with dexamethasone or lenalidomide alone is not established.

Table 53: Important Potential Risk: Ischaemic Heart Disease (Including Myocardial Infarction) (Continued)

Ischaemic Heart Disease (Including Myocardial Infarction)
Data Source: Studies NHL-007 and NHL-008 (13 Aug 2018); Study SWOG S0777 (01 Dec 2016); Study CALGB 100104 (01 Mar 2015); Study IFM 2005-02 (01 Mar 2015); Study MM-020 (24 May 2013); Study MM-015 (30 Apr 2013); Integrated Summary of Safety (Dec 2005) for Studies MM-009 and MM-010; Study MDS-003 CSR; Study MDS-004 CSR; Study MCL-001 (20 Mar 2013); Study MCL-002 (07 Mar 2014); Study NHL-002 (23 Jun 2008); Study NHL-003 (27 Apr 2011). **MedDRA Terms** *FL (NHL-007 and NHL-008)* PTs listed within the MedDRA v21.0 SMQs broad scope of sub-SMQ myocardial infarction and sub-SMQ other ischaemic heart disease. *NDMM RVd Study (SWOG S0777)* PTs listed within the MedDRA v15.1 SMQs broad scope of MI and other ischaemic heart disease are collectively referred to as ischaemic heart disease. *TE NDMM (CALGB 100104 and IFM 2005-02)* PTs listed within the MedDRA v15.1 SMQs broad scope of myocardial infarction and other ischaemic heart disease are collectively referred to as ischaemic heart disease. *TNE NDMM (MM-020 and MM-015)* PTs listed within the MedDRA v15.1 SMQs broad scope of myocardial infarction and other ischaemic heart disease are collectively referred to as ischaemic heart disease. *RRMM (MM-009 and MM-010)* PTs listed within the MedDRA v11.0 SMQ of myocardial infarction (narrow scope, excluding coronary artery embolism, coronary artery occlusion, and coronary artery thrombosis), and the PTs blood creatinine phosphokinase increased, blood creatinine phosphokinase MB increased, cardiac enzymes increased, ECG ST segment elevation, ECG ST-T segment elevation, troponin I increased, troponin increased and troponin T increased are collectively referred to as MI. *Del 5q MDS (MDS-003 and MDS-004)* PTs listed within the MedDRA v13.0 SMQs broad scope of myocardial infarction and other ischaemic heart disease are collectively referred to as ischaemic heart disease. *MCL (MCL-001, MCL-002, NHL-002 and NHL-003)* PTs listed within the MedDRA v16.1 SMQs broad scope of myocardial infarction and other ischaemic heart disease are collectively referred to as myocardial infarction/ischaemic heart disease.

3.1.8. Important Potential Risk: Off-label Use

Off-label use (ie, outside the indication of patients with transfusion-dependent anaemia due to low- or INT-1-risk MDS associated with an isolated del 5q cytogenetic abnormality when other therapeutic options are insufficient or inadequate) is an important potential risk in other MDS patients and will be monitored through MDS PASSes. Routine monitoring for off-label use includes the collection of detailed data relating to indication as part of the national controlled distribution system, where possible per national regulation.

An increased risk of mortality in patients with CLL, a current non-approved indication, was observed after unblinded review of data from Study CC-5013-CLL-008. The Data Monitoring Committee found an imbalance of safety between the two study arms, specifically an increased

number of deaths in the lenalidomide arm, and OS in favour of chlorambucil. Upon request, the MAH's Medical Information departments will provide available information and publications to physicians on the risk of the increase in mortality should a physician request information regarding use of lenalidomide in CLL.

Cumulative information on off-label use from the US postmarketing population and details of the available data on off-label use in the EU are provided in Section 2 of Part II Module SV.

3.2. Presentation of the Missing Information

Not applicable.

PART II – MODULE SVIII: SUMMARY OF THE SAFETY CONCERNS

1. SUMMARY – ONGOING SAFETY CONCERNS

Important identified and potential risks, together with missing information, are summarised in Table 54.

Table 54: Summary of Safety Concerns

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

PART III: PHARMACOVIGILANCE PLAN (INCLUDING POSTAUTHORISATION SAFETY STUDIES)

1. ROUTINE PHARMACOVIGILANCE ACTIVITIES

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

In addition to expedited reporting, Celgene 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.

1.1. Routine Pharmacovigilance Activities Beyond Adverse Reactions Reporting and Signal Detection

1.1.1. Specific Adverse Reaction Follow-up Questionnaires

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 is obtained.

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

1.1.2. Other Forms of Routine Pharmacovigilance Activities

1.1.2.1. 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 lenalidomide treatment. Lenalidomide is structurally related to thalidomide. Thalidomide is a known human teratogenic substance that causes severe life-threatening birth defects. If lenalidomide is taken during pregnancy, a teratogenic effect can be expected. The core PPP for lenalidomide reflects advice, guidance and direction obtained from the Member States.

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

In the EU Celgene uses the following methods 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 HCP Kit make reference to the requirement to report all suspected pregnancies to the local Celgene 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 risk of pregnancy. Similar advice is also provided with reference to female partners of male patients.

Database of Pregnancy Reports

All reports of pregnancies received by Celgene are entered into Celgene'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 are 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 EEA Qualified Person for Pharmacovigilance (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 Celgene, 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.

A status report of pregnancies in patients exposed to lenalidomide or female partners of male patients exposed to lenalidomide is provided in each PSUR. Each PSUR includes a comprehensive analysis of case reports including the reason for the occurrence of pregnancy.

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

Physicians are required to report pregnancies to Celgene. A specific Pregnancy Report Form is provided with each HCP Kit.

1.1.3. 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.

In addition, data regarding pregnancy exposure to lenalidomide is targeted for review and is 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. Occupational exposure in pregnant females (eg, a nurse opening the capsules, laboratory technician or carer) is also provided with the corresponding outcome in each PSUR.

PSURs are submitted in accordance with GVP in the EU. Periodicity of PSUR submissions is defined by the International Birth Date of 27 Dec 2005.

1.2. Additional Pharmacovigilance Activities

1.2.1. Pregnancy Prevention Programme Implementation

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

Physicians are required to report pregnancies to Celgene. A specific Pregnancy Report Form is provided with each HCP Kit (see Part III, Section 1.1.2.1).

Additional monitoring of the implementation of the Celgene PPP is carried out on a country basis in agreement with relevant NCA (Table 55).

The postmarketing surveillance study RRMM PASS (Table 58) was also performed in Member States where this was feasible. This study monitored compliance to the process indicators of the implemented PPP and reporting of exposure during pregnancy was also stimulated through this study.

Table 55: Pregnancy Prevention Programme Implementation

Study Short Name and Title	Rationale and Study Objectives	Study Design	Study Population	Milestones
Monitoring of Pregnancy Prevention Programme implementation.	Monitoring of implementation of PPP.	Additional monitoring implementation of Celgene PPP on a country specific basis in accordance with local legal framework and with agreement of the relevant NCA (ie, monitoring of patient card completion, monitoring by external agency and surveys)	Patients in the EU receiving lenalidomide.	Ongoing. In line with the PSUR.

1.2.2. Additional Studies

Connect® MM Registry

Celgene is currently sponsoring the Connect® MM registry, a US, multicentre, prospective, observational study that compiles data regarding treatment patterns and patient outcomes in patients with NDMM (both transplant eligible and non-eligible) (Table 56). The primary objectives of the registry are to describe practice patterns of common first-line and subsequent treatment regimens (including lenalidomide based) in patients with previously untreated MM, whether or not eligible for transplant, as well as diagnostic patterns and occurrence of SPM in a 'real world' population. All consecutive patients at more than 250 participating sites in community and academic settings in the US who have NDMM within 2 months of enrollment were eligible, with planned follow-up on a quarterly basis up to early discontinuation or study end, expected in 2024. This registry enrolled 3011 newly diagnosed MM patients in two cohorts. The first cohort (Cohort 1) consists of 1493 patients enrolled between Sep 2009 and Dec 2011. The extension cohort (Cohort 2) consists of 1518 patients enrolled between Dec 2012 and Apr 2016.

Table 56: Connect® MM Registry

Study Short Name and Title	Rationale and Study Objectives	Study Design	Study Population	Milestones
Connect® MM: The Multiple Myeloma Disease Registry	The primary objectives of the registry are to describe practice patterns of common first-line and subsequent treatment regimens (including lenalidomide based) in patients with previously untreated MM, whether or not eligible for transplant, as well as diagnostic patterns and occurrence of SPM in a 'real world' population.	A prospective, observational, longitudinal, multi-centre study.	Patients with NDMM (both transplant eligible and non-eligible).	Enrollment completed and follow up ongoing. As of DLP (26 Dec 2017), 3011 patients were enrolled and 1727 patients were discontinued from the study. Safety updates will be submitted with future PSURs.

Revlimid TNE NDMM Registry

The MAH proposes a PASS product registry with the primary objectives to compare the incidence of cardiovascular events between TNE NDMM patients treated with a first-line lenalidomide-containing regimen and those treated with a first-line non lenalidomide-containing regimen; and to identify, quantify, and characterise risk factors for cardiovascular events in this population of TNE NDMM patients (Table 57). The incidence of other treatment-emergent events will be examined to characterise the overall safety profile of lenalidomide among patients within the labelled indication. SPM follow-up will extend beyond active treatment.

The Revlimid TNE NDMM PASS is designed as a prospective non-interventional study to compare the incidence of cardiovascular events between TNE NDMM patients treated with a first-line lenalidomide-containing regimen and those treated with a first-line non-lenalidomide-containing regimen. The study will gather extensive risk factor information at baseline and throughout follow-up to aid in the interpretation of any observed differences in the

incidence of cardiovascular events between the two cohorts. Other safety endpoints of interest will be characterised through standard follow-up procedures.

This study will be implemented in a selected number of countries in the EU. Sites will be selected based on their expertise in treating patients with NDMM, access to lenalidomide through local reimbursement options, sufficient resources to conduct observational research, and on their ability to collect and report data for this study at the required quality standards. In particular, sites will be asked to confirm during the feasibility assessment that they are able to commit to liaise with other treating physicians (eg, cardiologists) to ensure sufficient follow-up with patients regarding any cardiovascular events; this may include, but is not limited to, tests, diagnoses, treatment, and outcome information. Site selection will attempt to cover multiple EU countries, urban and rural locations, as well as different types of medical centres (eg, public, private or university ownership).

It is anticipated that approximately 888 patients would be enrolled. The final study report could be available in 2025. Safety updates will be submitted with future PSURs.

Table 57: Revlimid TNE NDMM Registry

Study Short Name and Title	Rationale and Study Objectives	Study Design	Study Population	Milestones
Revlimid TNE NDMM Registry: A prospective non-interventional PASS of lenalidomide in previously untreated adult MM patients who are not eligible for transplant ("transplant noneligible" [TNE]) ("Revlimid® TNE NDMM PASS").	The primary objectives are to compare the incidence of cardiovascular events between TNE NDMM patients treated with a first-line lenalidomide-containing regimen and those treated with a first-line non lenalidomide-containing regimen; and to identify, quantify, and characterise risk factors for cardiovascular events in this population of TNE NDMM patients.	A prospective non-interventional PASS.	TNE NDMM patients.	Ongoing Final protocol dated 10 May 2016 was endorsed by PRAC on 02 Sep 2016. An interim study report is expected 30 Jun 2024. The final study report is expected 01 Dec 2025. Safety updates will be submitted with future PSURs.

RRMM PASS

The RRMM PASS to monitor safety in the 'real world' situation has been completed (Table 58).

Table 58: RRMM PASS

Study Short Name and Title	Rationale and Study Objectives	Study Design	Study Population	Milestones
RRMM PASS	To characterise and determine the incidence of adverse events of special interest; specifically neutropenia, thrombocytopenia, acute and opportunistic infections, bleeding events, venous thromboembolism, cardiac disorders (cardiac failure, arrhythmia, QT prolongation), neuropathy, rash, hypersensitivity, hypothyroidism and renal failure in patients treated with lenalidomide in a naturalistic setting and placing into context with the background incidence of these adverse events in a non-lenalidomide cohort of MM patients who newly receive second or later lines of treatment for MM.	A non-interventional observational PASS	Lenalidomide cohort: Patients who were commencing lenalidomide treatment. Background cohort: Patients with MM who had received at least one prior therapy and were commencing a new therapy but not lenalidomide.	Completed. Submission of protocol: 08 Aug 2007; CHMP Opinion: 18 Oct 2007. Submission of amendment 1: 08 Aug 2011; CHMP Opinion: 22 Oct 2011. CSR dated 19 Apr 2017. Submission of CSR: 05 May 2017; Positive CHMP Opinion: 12 Oct 2017.

MDS PASSes

The EC Decision for variation EMEA/H/C/717/II/056 (13 Jun 2013) in relation to the extension of indication for use of Revlimid in patients with transfusion-dependent anaemia due to low- or INT-1 risk MDS associated with an isolated del 5q cytogenetic abnormality when other therapeutic options are insufficient or inadequate, was granted with a Condition to the Marketing Authorisation. As described in Annex IID to the EC Decision, the MAH will conduct a non-interventional PASS of patients with MDS treated with lenalidomide to gather safety data on the use of lenalidomide in MDS patients and monitor off-label use. A synopsis for this study was adopted at the time of the Committee for Medicinal Products for Human Use (CHMP) Opinion for this variation (25 Apr 2013), and a full protocol was submitted for review by the PRAC on 24 May 2013. Following the latest PRAC request for two distinct MDS PASSes to be conducted, a prospective MDS disease registry (MDS-010, Table 59) and a retrospective Revlimid Drug Utilisation Study (MDS-012, Table 60), protocols were submitted by the MAH for review by the PRAC on 06 Nov 2013 and 31 Jan 2014, respectively. Both protocols were approved by PRAC on 10 Apr 2014. A protocol amendment for MDS-010 (Amendment 3, Version 5) with changes to the inclusion criterion was submitted on 29 Mar 2016 and was subsequently endorsed by PRAC on 07 Jul 2016 (this amendment was provided in Annex 6 of RMP Version 32.0). A subsequent protocol amendment (Amendment 4, Version 6) with changes to the primary population size and study timelines was submitted on 17 Sep 2018 and was endorsed by PRAC on 29 Nov 2018. Safety updates will be provided with future PSURs.

Table 59: MDS-010

Study Short Name and Title	Rationale and Study Objectives	Study Design	Study Population	Milestones
MDS-010: A prospective non-interventional postauthorisation safety study (PASS), designed as a disease registry of patients with transfusion dependent IPSS low or intermediate-1-risk myelodysplastic syndromes (MDS) and isolated del(5q).	The primary objective is to ascertain the progression to AML and survival among patients with transfusion-dependent IPSS low- or INT-1-risk MDS with del(5q) as an isolated cytogenetic abnormality who have been treated with lenalidomide.	A non-interventional, disease registry.	Patients with transfusion dependent IPSS low or INT-1-risk MDS and isolated del(5q). It is anticipated that approximately 664 patients would be enrolled.	Protocol submitted to PRAC on 06 Nov 2013 and approved on 10 Apr 2014. Protocol amendment (Amendment 3, Version 5) was submitted on 29 Mar 2016 and was subsequently approved by PRAC on 07 Jul 2016. Protocol amendment (Amendment 4, Version 6) was submitted on 17 Sep 2018 and was subsequently approved by PRAC on 29 Nov 2018. Safety updates will be submitted with future PSURs. The final study report for MDS-010 is expected Q1 2023.

Table 60: MDS-012

Study Short Name and Title	Rationale and Study Objectives	Study Design	Study Population	Milestones
MDS-012: A postauthorization, non-interventional, retrospective, drug-utilisation study to describe the pattern of use of lenalidomide in patients with myelodysplastic syndromes (MDS).	The primary objective is to describe the pattern of use of lenalidomide in the clinical routine practice of MDS patients.	A non-interventional, retrospective, drug-utilisation study.	Patients with MDS.	Protocol submitted to PRAC on 31 Jan 2014 and approved on 10 Apr 2014. Protocol Amendment 1, Version 3 was submitted on 20 Dec 2016. After several rounds of PRAC assessment, Amendment 1, Version 5 was submitted on 31 Oct 2017 and was subsequently approved by PRAC on 30 Nov 2017. Safety updates will be submitted with future PSURs. The final study report for MDS-012 is expected Q3 2023.

Connect® MDS/AML Disease Registry

Celgene is sponsoring Connect® MDS/AML Disease Registry, a US prospective, longitudinal, multi-centre observational cohort study of patients with newly diagnosed MDS, idiopathic cytopenia of undetermined significance (ICUS; > 18-years-old) or AML (≥ 55-years-old) to address important research questions in these specific diseases. The Connect® MDS/AML Disease Registry will collect data regarding diagnostic and treatment patterns and patient outcomes (Table 61). The objectives of the registry are: to describe patterns for diagnosis, prognosis, treatment, clinical monitoring and outcome measures in patients with MDS, ICUS and AML; to compare routine clinical practice patterns with existing management guidelines (eg,

National Comprehensive Cancer Network); to describe treatment patterns and outcomes in del(5q) patients with or without additional cytogenetic abnormalities, and in non-del(5q) patients; and to summarise patient-reported outcomes (eg, health related quality of life [HRQoL]) and economic outcomes, and their association with patient characteristics, treatment regimens, and clinical outcomes. Exploratory objectives are to evaluate molecular and/or cellular markers in the blood/bone marrow tissues and oral epithelial cells that may provide further prognostic classification of MDS and AML subtypes and/or may provide information on drug mechanism of action and on-therapy markers predictive of clinical outcomes and potentially impact clinical outcomes with therapy; to summarise the clinical status (eg, OS, PFS, response rate) of patients with or without mutations by treatment regimen, and to analyse the correlation between mutation detection/allele burden in bone marrow and peripheral blood samples. Data regarding SPM will also be collected. The planned follow-up in this longitudinal study will be for a maximum of 8 years. It is expected that patients will complete a set of concise HRQoL questionnaires on an approximate quarterly basis (AML patients will complete an additional set at 2 months following enrollment). Participating sites are required to report relevant data on a quarterly basis. The Connect® MDS/AML Disease Registry enrolled its first patient in Dec 2013. Data from Connect® MDS/AML Disease Registry will be included as part of future PSURs once available.

Table 61: Connect® MDS/AML Disease Registry

Study Short Name and Title	Rationale and Study Objectives	Study Design	Study Population	Milestones
Connect® MDS/AML Disease Registry	The objectives of the registry are: to describe patterns for diagnosis, prognosis, treatment, clinical monitoring and outcome measures in patients with MDS, ICUS and AML; to compare routine clinical practice patterns with existing management guidelines (eg, National Comprehensive Cancer Network); to describe treatment patterns and outcomes in del(5q) patients with or without additional cytogenetic abnormalities; and in non-del(5q) patients; and to summarise patient-reported outcomes (eg, HRQoL) and economic outcomes, and their association with patient characteristics, treatment regimens, and clinical outcomes. Exploratory objectives are: to evaluate molecular and/or cellular markers in the blood/bone marrow tissues and oral epithelial cells that may provide further prognostic classification of MDS and AML subtypes and/or may provide information on drug mechanism of action and on-therapy markers predictive of clinical outcomes and potentially impact clinical outcomes with therapy; to summarise the clinical status (eg, OS, PFS, response rate) of patients with or without mutations by treatment regimen, and to analyse the correlation between mutation detection/allele burden in bone marrow and peripheral blood samples. Data regarding SPM are also being collected.	US prospective, longitudinal, multicentre observational cohort study.	Patients with newly diagnosed MDS, ICUS (> 18-years-old) and AML (≥ 55-years-old)	Ongoing Enrolment started Dec 2013. Safety updates will be submitted with future PSURs.

RRMCL PASS

This RRMCL PASS (Table 62) was designed to gather additional safety information as a multinational, non-interventional study following the request for further assessment of safety issues via postmarketing surveillance.

The proposed European, retrospective study has two cohorts:

For Cohort 1, MCL patients in the Nordic countries (inter alia Denmark and Sweden) will be identified through electronic medical records, enabling identification of RRMCL patients.

Exposure to lenalidomide will be identified through prescription registers or medical chart review.

For Cohort 2, sites will be identified in other European countries (inter alia Germany) where patients have been treated with lenalidomide for RRMCL. Identification of sites will be completed through partnership with the European MCL Registry, and in addition, sites will be identified by Celgene.

For both cohorts, only sites where lenalidomide treatment for RRMCL is reimbursed will be selected for the study.

All data will be collected retrospectively from identified patients following the first dose of lenalidomide treatment for up to 6 months, including those patients who died within this data collection period.

Table 62: RRMCL PASS

Study Short Name and Title	Rationale and Study Objectives	Study Design	Study Population	Milestones
RRMCL PASS	The study is designed as a retrospective non-interventional study of patients with RRMCL with the objective to quantify and characterise the event of TFR by tumour burden and the proportion of early deaths by tumour burden in patients treated with lenalidomide in a 'real world' setting.	Multinational safety surveillance study, designed as a postauthorisation non-interventional study.	Patients with RRMCL.	Version 3 of the protocol was submitted on 14 Aug 2017, approved by PRAC on 26 Oct 2017 and endorsed by CHMP on 09 Nov 2017. The final study report could be available in Q4 2027. Safety updates will be submitted with future PSURs.

1.2.3. Second Primary Malignancies Monitoring in Ongoing Studies

Invasive SPM will be considered important medical events. Celgene will perform long-term follow-up in ongoing clinical studies to monitor SPM for Celgene-sponsored studies. For Study MCL-002: the follow-up phase is to continue until 70% of patients in the study have died, or the median follow-up for responding patients is > 2 years, or the median duration of response has been reached, or 4 years from the date the last patient was randomised is reached, whichever comes latest.

For Study MM-020, SPM was to be documented for 5 years following randomisation of the last patient. For Study MM-015, patients were contacted in the follow-up phase (for at least 5 years) to determine if the patient had been diagnosed with SPM.

2. SUMMARY TABLE OF THE ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

Links to the protocols are provided in Annex 3.

2.1. Ongoing and Planned Additional Pharmacovigilance Activities

Ongoing and planned additional pharmacovigilance activities are presented in Table 63.

Table 63: Category 1 to 3: Ongoing and Planned Studies/Activities in the Postauthorisation Pharmacovigilance Development Plan

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

Table 63: Category 1 to 3: Ongoing and Planned Studies/Activities in the Postauthorisation Pharmacovigilance Development Plan (Continued)

Study/Activity Type, Title and Category (1 to 3)	Objectives	Safety Concerns Addressed	Status (planned, started)	Date for Submission of Interim or Final Reports (planned or actual)
Connect® MM Registry. *Category 3*	The primary objectives of the registry are to describe practice patterns of common first-line and subsequent treatment regimens (including lenalidomide based) in patients with previously untreated MM, whether or not eligible for transplant, as well as diagnostic patterns and occurrence of SPM in a 'real world' population.	SPM (AML and B-cell malignancies, NMSC and other SPM), cardiac events (cardiac failure, cardiac arrhythmias, IHD [including MI]), Serious Infection due to Neutropenia.	Ongoing	Safety updates will be submitted with future PSURs.
Connect® MDS/AML Disease Registry *Non-interventional: observational Category 3*	The objectives of the registry are: to describe patterns for diagnosis, prognosis, treatment, clinical monitoring and outcome measures in patients with MDS, ICUS and AML; to compare routine clinical practice patterns with existing management guidelines (eg, National Comprehensive Cancer Network); to describe treatment patterns and outcomes in del(5q) patients with or without additional cytogenetic abnormalities; and in non-del(5q) patients; and to summarise patient-reported outcomes (eg, HRQoL) and economic outcomes, and their association with patient characteristics, treatment regimens, and clinical outcomes. Exploratory objectives are: to evaluate molecular and/or cellular markers in the blood/bone marrow tissues and oral epithelial cells that may provide further prognostic classification of MDS and AML subtypes and/or may provide information on drug mechanism of action and on-therapy markers predictive of clinical outcomes and potentially impact clinical outcomes with therapy; to summarise the clinical status (eg, OS, PFS, response rate) of patients with or without mutations by treatment regimen, and to	SPM	Ongoing	Safety updates will be submitted with future PSURs.

Table 63: Category 1 to 3: Ongoing and Planned Studies/Activities in the Postauthorisation Pharmacovigilance Development Plan (Continued)

Study/Activity Type, Title and Category (1 to 3)	Objectives	Safety Concerns Addressed	Status (planned, started)	Date for Submission of Interim or Final Reports (planned or actual)
Connect® MDS/AML Disease Registry *Non-interventional: observational Category 3* (Continued)	analyse the correlation between mutation detection/allele burden in bone marrow and peripheral blood samples. Data regarding SPM are also being collected.			
RRMCL PASS *Category 3*	The study is designed as a retrospective non-interventional study of patients with RRMCL with the objective to quantify and characterise the event of TFR by tumour burden and the proportion of early deaths by tumour burden in patients treated with lenalidomide in a 'real world' setting.	TFR/high tumour burden and early deaths	Ongoing	Version 3 of the protocol was submitted on 14 Aug 2017, approved by PRAC on 26 Oct 2017 and endorsed by CHMP on 09 Nov 2017. The final study report could be available in Q4 2027. Safety updates will be submitted with future PSURs.

PART IV: PLANS FOR POSTAUTHORISATION EFFICACY STUDIES

1. PLANNED AND ONGOING POSTAUTHORISATION EFFICACY STUDIES THAT ARE CONDITIONS OF THE MARKETING AUTHORISATION OR THAT ARE SPECIFIC OBLIGATIONS

Study/ Status	Summary of Objectives	Efficacy Uncertainties Addressed	Milestones	Due Dates
Efficacy studies which are conditions of the marketing authorisation				
Not applicable.				
Efficacy studies which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
CC-5013-MCL-004: Multicentre, observational study to evaluate the effectiveness of lenalidomide in patients with MCL who have relapsed or progressed after treatment with ibrutinib or are refractory or intolerant to ibrutinib.	To investigate the clinical activity of lenalidomide in RRMCL patients who previously failed treatment with ibrutinib	Efficacy of lenalidomide in patients with MCL who have relapsed or progressed after treatment with ibrutinib or are refractory or intolerant to ibrutinib	Study closed. CSR dated 06 Mar 2017	

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

1. RISK MINIMISATION PLAN

The following sets out the basis of the Risk Minimisation Programme, where applicable for the safety concerns discussed in this document.

The same core requirements of the Risk Minimisation Programme apply across all indications for lenalidomide in the EU, since the Risk Minimisation Programme is product and not indication specific. Furthermore, the core requirements of the Risk Minimisation Programme apply across all Member States, however, the local implementation differs between Member States taking into account the local differences in healthcare system, legal framework and culture. Therefore, consultations have taken place with NCAs to determine the appropriate method of implementation of the Risk Minimisation Programme in each Member State.

Consultations also took place with haematology physicians, pharmacists and oncology nurses throughout Europe in order to determine the method of delivery of the Risk Minimisation Programme appropriate to each Member State. Thus, the local implementation of the Risk Minimisation Programme has taken into account the differing healthcare systems throughout the EU Member States.

For lenalidomide, the PPP is a key element of the Risk Minimisation Programme. However, it must also be noted that other activities aimed at minimising the risk of other adverse reactions, such as serious infection due to neutropenia and bleeding due to thrombocytopenia are also included in the Risk Minimisation Programme.

1.1. Routine Risk Minimisation Measures

Summaries of the routine risk minimisation measures for each safety concern included in Part II SVIII are provided in Table 64.

Table 64: Description of Routine Risk Minimisation Measures by Safety Concern

Safety Concern	Routine Risk Minimisation Activities
Teratogenicity	**Routine risk communication** **SmPC** **Section 4.6 Fertility, pregnancy and lactation.** **Section 4.8 Undesirable effects.** **Section 5.3 Preclinical safety data.** These sections highlight the potential teratogenic effects of lenalidomide. **PL** This document warns of the potential teratogenic effects of lenalidomide and the need to avoid pregnancy. **Routine risk minimisation activities recommending specific clinical measures to address the risk:** **SmPC** **Section 4.3 Contraindications** Lenalidomide is contraindicated in pregnant women and in FCBP unless all the conditions of the Celgene PPP are met.

Table 64: Description of Routine Risk Minimisation Measures by Safety Concern (Continued)

Safety Concern	Routine Risk Minimisation Activities
Teratogenicity (Continued)	**Section 4.4 Special warnings and precautions for use** This section highlights the potential teratogenic effects of lenalidomide. Stringent controls are required to ensure exposure of an unborn child to lenalidomide does not occur. These include: – Criteria for women of non-childbearing potential – Counselling – Contraception – Pregnancy testing – Precautions for men – Additional precautions – Reference to educational materials, prescribing and dispensing restrictions. **Other routine risk minimisation measures beyond the Product Information:** Pack size: The pack is based on a maximum 4-week supply of capsules to ensure that FCBP are required to obtain a new monthly prescription with a medically supervised pregnancy test. Legal status: Lenalidomide is subject to restricted medical prescription.
Serious Infection due to Neutropenia	**Routine risk communication** **SmPC** **Section 4.8 Undesirable effects** Listed as ADRs. **PL** This document warns that lenalidomide may cause neutropenia and infections, and that if a patient has, or has had a HBV infection, lenalidomide may cause the virus to become active again. Viral infections, including herpes zoster (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:** **SmPC** **Section 4.2 Posology and method of administration** Dose reduction advice for neutropenia. **Section 4.4 Special warnings and precautions for use** Warning of neutropenia, and infection with or without neutropenia, and advice for monitoring patients, including blood testing for neutropenia. Advice that patients should report febrile episodes promptly. Advice that HBV status should be established before initiating treatment with lenalidomide and advice to exercise caution when lenalidomide is used in patients previously infected with HBV. In addition, advice that the patients should be closely monitored for signs and symptoms of active HBV infection throughout therapy.

Table 64: Description of Routine Risk Minimisation Measures by Safety Concern (Continued)

Safety Concern	Routine Risk Minimisation Activities
Serious Infection due to Neutropenia (Continued)	**PL** Advice to the doctor to check if the patient has ever had hepatitis B infection prior to lenalidomide treatment. **Other routine risk minimisation measures beyond the Product Information:** Legal status: Lenalidomide is subject to restricted medical prescription.
SPM	**Routine risk communication** **SmPC** **Section 4.8 Undesirable effects** Listed as ADRs. **PL** Informs patients on: – risk of SPM – need for the doctor to carefully evaluate benefit and risk, and – when lenalidomide is contraindicated. **Routine risk minimisation activities recommending specific clinical measures to address the risk:** **SmPC** **Section 4.4 Special warnings and precautions for use** This section highlights the risk of SPM, and advises standard cancer screening before and during lenalidomide use, with instigation of treatment as necessary. **Other routine risk minimisation measures beyond the Product Information:** Legal status: Lenalidomide is subject to restricted medical prescription.
Tumour Flare Reaction (MCL and FL Indications)	**Routine risk communication** **SmPC** **Section 4.8 Undesirable effects** Listed as an ADR. **PL** This document details the risks associated with lenalidomide use, their symptoms, and any actions to be taken by the patient. **Routine risk minimisation activities recommending specific clinical measures to address the risk:** **SmPC** **Section 4.2 Posology and method of administration** This section includes dose interruption advice for TFR. **Section 4.4 Special warnings and precautions for use** This section highlights the risk of TFR in lenalidomide-treated patients with CLL and other lymphomas, and warns that tumour flare may mimic disease progression.

Table 64: Description of Routine Risk Minimisation Measures by Safety Concern (Continued)

Safety Concern	Routine Risk Minimisation Activities
Tumour Flare Reaction (MCL and FL Indications) (Continued)	**Other routine risk minimisation measures beyond the Product Information:** Legal status: Lenalidomide is subject to restricted medical prescription.
Cardiac Failure and Cardiac Arrhythmias	**Routine risk communication** **SmPC** **Section 4.8 Undesirable effects** Listed as ADRs. **PL** This document details the risks associated with lenalidomide use, their symptoms, and any actions to be taken by the patient. Symptoms of cardiac failure and cardiac arrhythmia are listed as side effects. **Routine risk minimisation activities recommending specific clinical measures to address the risk:** None. **Other routine risk minimisation measures beyond the Product Information:** Legal status: Lenalidomide is subject to restricted medical prescription.
Ischaemic Heart Disease (Including MI)	**Routine risk communication** **SmPC** **Section 4.8 Undesirable effects** Listed as ADRs. **PL** This document details the risks associated with lenalidomide use, their symptoms, and any actions to be taken by the patient. Symptoms of MI are listed as side effects. **Routine risk minimisation activities recommending specific clinical measures to address the risk:** **SmPC** **Section 4.4 Special warnings and precautions for use** This section highlights the possible occurrence of MI, and advises monitoring of patients with known risk factors. **Other routine risk minimisation measures beyond the Product Information:** Legal status: Lenalidomide is subject to restricted medical prescription.
Off-label Use	**Routine risk communication** **SmPC** **Section 4.4 Special warnings and precautions for use** This section describes the collecting of detailed data relating to the indication in order to monitor closely the off-label use within the national territory.

Table 64: Description of Routine Risk Minimisation Measures by Safety Concern (Continued)

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

1.2. Additional Risk Minimisation Measures

Additional risk minimisation measures are presented in Table 65 to Table 68.

Table 65: Additional Risk Minimisation: Pregnancy Prevention Programme

Pregnancy Prevention Programme
Objectives: The objectives of the Celgene PPP are: – Ensuring that exposure of an unborn child to lenalidomide does not occur. – Ensuring early alert to the physician of any pregnancies. – Educating patients and HCPs on the safe use of lenalidomide. – Pregnancy testing and contraception requirements. – A system to ensure that all appropriate measures have been performed prior to the drug being dispensed. – Follow-up on the effectiveness of the PPP.
Rationale for the Additional Risk Minimisation Activity: The Celgene PPP is designed to minimise the risk of teratogenicity and provide education on the risk and the necessary steps to prevent foetal exposure.
Target Audience and Planned Distribution Path: Proposed actions The key elements of the Celgene PPP are set out below and further details are provided as Annexes in previous RMPs. – Educational Programme – Therapy management – Prescribing controls – Dispensing controls – Assessment.

Table 65: Additional Risk Minimisation: Pregnancy Prevention Programme (Continued)

Pregnancy Prevention Programme
Plans to Evaluate the Effectiveness of the Interventions and Criteria for Success: Proposed review period The Celgene 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. – 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 as per pregnancy report form. – Outcome of pregnancy. – Modifications and corrective action will be taken accordingly. Criteria for Success: Outcome indicator: pregnancy exposures.

Table 66: Additional Patient Educational Materials

Additional Patient Educational Materials
Objectives: Provision of information to patients for the risk of: • Teratogenicity • SPM.
Rationale for the Additional Risk Minimisation Activity: Patients to understand the occurrence of the risks specified above and the appropriate management of these risks.
Target Audience and Planned Distribution Path: The target audience is patients who are prescribed lenalidomide and the planned distribution path is the provision of patient brochure by healthcare professionals.
Plans to Evaluate the Effectiveness of the Interventions and Criteria for Success: Expedited reporting (E+R) as per EU guidance, GVP PSUR as per EU guidance, GVP (E+R) [E = Evaluation; R = Reporting] Methods of assessment – AE reports to be reviewed on an ongoing basis. AEs to be summarised at the time of the PSUR. – Assessment through PASSes. – Modifications and corrective action will be taken accordingly. Criteria for Success: Outcome Indicator: Frequency and severity of events. No significant increase in frequency of reports in the postmarketing setting as presented in the SmPC.

Table 66: Additional Patient Educational Materials (Continued)

Additional Patient Educational Materials
Planned Dates for Assessment: Next PSUR update with next data lock point (DLP) covered.

Table 67: Direct HCP Communication Prior to Launch ('Dear HCP' Letter)

Direct HCP Communication Prior to Launch ('Dear HCP' Letter)
Objectives: Provision of information to HCPs for the risks of: • Teratogenicity • SPM.
Rationale for the Additional Risk Minimisation Activity: HCPs to understand the occurrence of the risks specified above and the appropriate management of these risks.
Target Audience and Planned Distribution Path: The target audience is HCPs who intend to prescribe lenalidomide.
Plans to Evaluate the Effectiveness of the Interventions and Criteria for Success: Expedited reporting (E+R) as per EU guidance, GVP PSUR as per EU guidance, GVP (E+R) [E = Evaluation; R = Reporting]
Methods of assessment – AE reports to be reviewed on an ongoing basis. AEs to be summarised at the time of the PSUR. – Assessment through PASSes. – Modifications and corrective action will be taken accordingly. Criteria for Success: Outcome Indicator: Frequency and severity of events. 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 DLP covered.

Table 68: Additional HCP Educational Materials

Additional HCP Educational Materials
Objectives: Lenalidomide HCP educational materials to be provided to prescribing physicians and pharmacists for the risks of: • Teratogenicity • SPM • TFR.
Rationale for the Additional Risk Minimisation Activity: HCPs to understand the occurrence of the risks specified above and the appropriate management of these risks.
Target Audience and Planned Distribution Path: The target audience is HCPs who intend to prescribe lenalidomide.

Table 68: Additional HCP Educational Materials (Continued)

Additional HCP Educational Materials
Plans to Evaluate the Effectiveness of the Interventions and Criteria for Success: Expedited reporting (E+R) as per EU guidance, GVP PSUR as per EU guidance, GVP (E+R) [E = Evaluation; R = Reporting] Methods of assessment – AE reports to be reviewed on an ongoing basis. AEs to be summarised at the time of the PSUR. – Assessment through PASSes. – Modifications and corrective action will be taken accordingly. Criteria for Success: Outcome Indicator: Frequency and severity of events. 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 DLP covered.

1.3. Summary of Risk Minimisation Measures

A summary of the EU-RMP is outlined in Table 69.

Table 69: Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Important Identified Risks		
Teratogenicity	**Routine risk minimisation activities**: Section 4.3 of SmPC: contraindicated in pregnant women and in FCBP unless all the conditions of the Celgene PPP are met. Section 4.4 of SmPC: warnings and precautions for use – Criteria for women of non-childbearing potential – Counselling – Contraception – Pregnancy testing – Precautions for men – Additional precautions – Reference to educational materials, prescribing and dispensing restrictions. Section 4.6 of SmPC: fertility, pregnancy and lactation. Sections 4.8 and 5.3 of SmPC: the potential teratogenic effects of lenalidomide are highlighted.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** o Expedited reporting of all pregnancies as a serious event. o Optimise data collection and reporting of pregnancies by use of specific pregnancy reporting forms for collection of the pregnancy exposure and follow-up in HCP Kits. o Follow-up of all pregnancies until one year after delivery. o Root cause analysis of failed Celgene PPP as part of standard follow-up. o Review of PSURs (periodic and cumulative). **Additional pharmacovigilance activities:** o MDS PASSes.

Table 69: Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern (Continued)

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Teratogenicity (Continued)	Pack size: The pack is based on a maximum 4-week supply of capsules to ensure that FCBP are required to obtain a new monthly prescription with a medically supervised pregnancy test. Legal status: Lenalidomide is subject to restricted medical prescription. **Additional risk minimisation measures** – Celgene PPP – Educational Programme o Direct HCP communication prior to launch o Direct HCP communication with findings from CC-501-TOX-004 o HCP kit to include booklet o Treatment algorithm, pregnancy reporting form, patient card, patient guide and checklists. – Therapy management o Criteria for determining FCBP, Contraceptive measures and pregnancy testing for FCBP o Advice in SmPC, Dear HCP letter and educational materials – System to ensure appropriate measures have been completed. – Patient card to document childbearing status, counselling and pregnancy testing.	o Additional monitoring of implementation of Celgene PPP on a country specific basis in accordance with local legal framework and with agreement of the relevant NCA (ie, monitoring of patient card completion, monitoring by external agency and surveys).
Serious Infection due to Neutropenia	**Routine risk minimisation activities**: – Section 4.2 of SmPC: dose reduction advice for neutropenia. – Section 4.4 of SmPC: warning of neutropenia, and infection with or without neutropenia, and advice for monitoring patients, including blood testing for neutropenia. Advice that patients should report febrile episodes promptly. Advice regarding establishing HBV status before treatment, use in patients previously infected with HBV and monitoring for signs and symptoms of active HBV infection throughout therapy. – Listed as ADRs in Section 4.8 of SmPC.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Event specific questionnaire for the collection of the AE and follow-up. **Additional pharmacovigilance activities:** o Connect® MM Registry o MDS PASSes.

Table 69: Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern (Continued)

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Serious Infection due to Neutropenia (Continued)	– Advice to patients in PL, including that the doctor is advised to check if the patient has ever had hepatitis B infection prior to starting lenalidomide treatment. **Additional risk minimisation measures:** None.	
SPM	**Routine risk minimisation activities**: – Section 4.4 of SmPC warning of SPM and advice for cancer screening. – Listed as ADRs in Section 4.8 of SmPC. – Advice to patients provided in PL. **Additional risk minimisation measures:** – Dear HCP letter. – HCP Kit: HCP Guide.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Event specific questionnaire for the collection of the AE and follow-up. **Additional pharmacovigilance activities:** o Connect® MM Registry o MDS PASSes o Connect® MDS/AML Disease Registry. o Long-term follow-up (at least 5 years from the date of the randomisation of the last patient in the study) for SPM in all Celgene-sponsored clinical trials; 3 years for MDS PASSes. o Solicited reporting of SPM in all Celgene-sponsored clinical trials (status of trials will be updated with each PSUR and DSUR cycle).
Tumour Flare Reaction (MCL and FL Indications)	**Routine risk minimisation activities**: – Section 4.2 of SmPC: dose interruption advice for TFR. – Section 4.4 of SmPC warning. – Listed as an ADR in Section 4.8 of SmPC. **Additional risk minimisation measures:** – HCP Kit: HCP Guide.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Event specific questionnaire for the collection of the AE and follow-up. **Additional pharmacovigilance activities:** o RRMCL PASS.
Important Potential Risks		
Cardiac Failure and Cardiac Arrhythmias	**Routine risk minimisation activities**: – Listed as ADRs in Section 4.8 of SmPC. – Listed in PL. **Additional risk minimisation measures:** None.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Event specific questionnaire for the collection of the AE and follow-up. **Additional pharmacovigilance activities:** o Connect® MM Registry

Table 69: Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern (Continued)

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Cardiac Failure and Cardiac Arrhythmias (Continued)		o Revlimid TNE NDMM Registry o MDS PASSes.
Ischaemic Heart Disease (including myocardial infarction)	**Routine risk minimisation activities**: The association between ischaemic heart disease and lenalidomide is unknown. Close monitoring will continue. – Myocardial infarction is included in Sections 4.4 and 4.8 of the SmPC. **Additional risk minimisation measures:** None.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Event specific questionnaire for the collection of the AE and follow-up. **Additional pharmacovigilance activities:** o Connect® MM Registry. o Revlimid TNE NDMM Registry. o MDS PASSes.
Off-label Use	**Routine risk minimisation activities**: – Collection of off-label use data detailed in Section 4.4 of SmPC. **Additional risk minimisation measures:** None.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Collection of detailed data relating to indication as part of the national controlled distribution system, where possible per national regulation. **Additional pharmacovigilance activities:** o MDS PASSes.

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

1. SUMMARY OF RISK MANAGEMENT PLAN FOR REVLIMID (LENALIDOMIDE)

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

REVLIMID's Summary of Product Characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how REVLIMID should be used.

This summary of the RMP for REVLIMID 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 REVLIMID's RMP.

1.1. The Medicine and what it is Used for

REVLIMID is authorised in combination with rituximab for the treatment of adult patients with previously treated follicular lymphoma (FL); as monotherapy for the maintenance treatment of adult patients with newly diagnosed multiple myeloma (NDMM) who have undergone autologous stem cell transplantation (ASCT); in combination with dexamethasone for the treatment of MM in adult patients who have received at least one prior therapy; in combination with dexamethasone, or bortezomib and dexamethasone, or melphalan and prednisone for the treatment of adult patients with previously untreated MM who are not eligible for transplant; as monotherapy for the treatment of adult patients with transfusion-dependent anaemia due to low- or intermediate 1 (INT-1) risk myelodysplastic syndrome (MDS) associated with an isolated deletion 5q (del 5q) cytogenetic abnormality when other therapeutic options are insufficient or inadequate; and as monotherapy for the treatment of adult patients with relapsed or refractory mantle cell lymphoma (RRMCL) (see SmPC for the full indication). REVLIMID contains lenalidomide as the active substance and it is given by oral route of administration.

Further information about the evaluation of REVLIMID's benefits can be found in REVLIMID's EPAR, including in its plain-language summary, available on the European Medicines Agency (EMA) website, under the medicine's webpage http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000717/human_med_001034.jsp&mid=WC0b01ac058001d124.

1.2. Risks Associated with the Medicine and Activities to Minimise or Further Characterise the Risks

Important risks of REVLIMID, together with measures to minimise such risks and the proposed studies for learning more about REVLIMID'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 (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute routine risk minimisation measures.

In the case of REVLIMID, 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.

If important information that may affect the safe use of REVLIMID is not yet available, it is listed under 'missing information' below.

1.3. List of Important Risks and Missing Information

Important risks of REVLIMID 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 REVLIMID. 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 (e.g. on the long-term use of the medicine).

Important identified and potential risks are summarised in Table 1.

Table 1: List of Important Risks and Missing Information

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

1.4. Summary of Important Risks

The important risks are summarised in Table 2 to Table 7.

Table 2: Important Identified Risk: Teratogenicity

Important Identified Risk: Teratogenicity	
Evidence for linking the risk to the medicine	Lenalidomide is structurally related to thalidomide, which is known to cause serious birth defects and death of the foetus. In nonclinical studies, lenalidomide induced malformations similar to those described with thalidomide. Therefore, a teratogenic effect of lenalidomide is expected and lenalidomide is contraindicated during pregnancy.
Risk factors and risk groups	The 'at risk' group comprises FCBP or female partners of male patients treated with lenalidomide and there are no risk factors.
Risk minimisation measures	**Routine risk minimisation activities**: Section 4.3 of SmPC: contraindicated in pregnant women and in FCBP unless all the conditions of the Celgene PPP are met. Section 4.4 of SmPC: warnings and precautions for use – Criteria for women of non-childbearing potential – Counselling – Contraception – Pregnancy testing – Precautions for men – Additional precautions – Reference to educational materials, prescribing and dispensing restrictions. Section 4.6 of SmPC: fertility, pregnancy and lactation. Sections 4.8 and 5.3 of SmPC: the potential teratogenic effects of lenalidomide are highlighted. Pack size: The pack is based on a maximum 4-week supply of capsules to ensure that FCBP are required to obtain a new monthly prescription with a medically supervised pregnancy test. Legal status: Lenalidomide is subject to restricted medical prescription. **Additional risk minimisation measures** – Celgene PPP – Educational Programme o Direct HCP communication prior to launch o Direct HCP communication with findings from CC-501-TOX-004 o HCP kit to include booklet o Treatment algorithm, pregnancy reporting form, patient card, patient guide and checklists. – Therapy management o Criteria for determining FCBP, Contraceptive measures and pregnancy testing for FCBP o Advice in SmPC, Dear HCP letter and educational materials – System to ensure appropriate measures have been completed. – Patient card to document childbearing status, counselling and pregnancy testing.

Table 2: Important Identified Risk: Teratogenicity (Continued)

Important Identified Risk: Teratogenicity	
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** – MDS PASSes. – Additional monitoring of implementation of Celgene PPP on a country specific basis in accordance with local legal framework and with agreement of the relevant NCA (ie, monitoring of patient card completion, monitoring by external agency and surveys).

Table 3: Important Identified Risk: Serious Infection due to Neutropenia

Important Identified Risk: Serious Infection due to Neutropenia	
Evidence for linking the risk to the medicine	In clinical trials, neutropenia has been reported as a consequence of lenalidomide treatment; ≥ Grade 3 and ≥ Grade 4 infections have occurred in the context of neutropenia (any grade).
Risk factors and risk groups	Haematologic malignancies by themselves or by virtue of their therapeutic strategies, chemotherapy, radiation or haematopoietic stem cell transplant put patients at risk of infections (Khayr 2012). The introduction of stem cell transplantation and novel anti-myeloma agents has improved the outcome of patients with MM. These advances have transformed MM into a chronic condition, with multiple relapses and salvage therapies, all of which results in cumulative immunosuppression and higher risk of infection. For example, application of stem cell transplantation has broadened the spectrum of infection to include those caused by Clostridium difficile, cytomegalovirus, and opportunistic moulds. Risk factors include myeloma-related innate immunodeficiency, which involves various arms of the immune system and includes B-cell dysfunction (manifested as hypogammaglobulinemia). Polyclonal hypogammaglobulinemia has been classically associated with infection by encapsulated bacteria, such as Streptococcus pneumoniae and Haemophilus influenzae. Myeloma and treatment-associated organ dysfunctions and comorbidities also increase the risk of infection. These dysfunctions and comorbidities include (1) renal failure (cast nephropathy, hypercalcemia, deposition disease, and others), respiratory compromise, caused by collapse of thoracic vertebra and opiate therapy (which may depress the central nervous system) given to patients with painful fractures (3) severe alimentary mucosal damage (caused by chemotherapy, radiation therapy, or graft-versus-host disease) (4) hyperglycemia induced by dexamethasone (5) transfusional iron overload and (6) the multisystem involvement by myeloma-associated deposition diseases (AL-amyloidosis and light chain deposit disease). Indeed, levels of CD4+ T cells, particularly naive and activated subsets, decrease significantly with increasing cycles of chemotherapy, a decrease strongly associated with opportunistic infections. Finally, myeloma typically affects an older population, with a median age of 62 to 73 years. These patients frequently experience an age-related decline in physiologic reserve of various organs and from other age-related conditions, including frailty, geriatric syndromes, cognitive dysfunction, and social isolation, all of which may increase the risk of infection (Nucci 2009). Lenalidomide treatment in combination with dexamethasone in MM patients with at least one prior therapy is associated with a higher incidence of Grade 4 neutropenia compared to placebo-dexamethasone treated patients (SmPC,

Table 3: Important Identified Risk: Serious Infection due to Neutropenia (Continued)

Important Identified Risk: Serious Infection due to Neutropenia	
Risk factors and risk groups (Continued)	Section 4.4). The combination of lenalidomide with melphalan and prednisone in clinical trials of NDMM patients is associated with a higher incidence of Grade 4 neutropenia than MPp+p treated patients (SmPC, Section 4.4). The proportion of patients who experienced Grade 3 or 4 myelosuppression in one study of lenalidomide-treated patients with MM was significantly higher for patients who had prior high-dose chemotherapy and stem cell transplantation, compared with those that did not (Richardson, 2006b). Impairment of antibody response, neutropenia, treatment with glucocorticoids, and reduction of normal Ig all increase the likelihood of infection. While a much greater proportion of lenalidomide/dexamethasone patients experienced neutropenia relative to placebo/dexamethasone patients, this increased risk did not translate into an infection risk of the same magnitude in either the total study population or in the study population restricted to Grade 3 or 4 toxicities. Lenalidomide treatment in MDS patients is associated with a higher incidence of Grade 3 or 4 neutropenia compared with patients on placebo (SmPC, Section 4.4). In patients with MDS, those experiencing neutropenia while receiving lenalidomide may be at increased risk for infections.
Risk minimisation measures	**Routine risk minimisation activities**: – Section 4.2 of SmPC: dose reduction advice for neutropenia. – Section 4.4 of SmPC: warning of neutropenia, and infection with or without neutropenia, and advice for monitoring patients, including blood testing for neutropenia. Advice that patients should report febrile episodes promptly. Advice regarding establishing HBV status before treatment, use in patients previously infected with HBV and monitoring for signs and symptoms of active HBV infection throughout therapy. – Listed as ADRs in Section 4.8 of SmPC. – Advice to patients in PL, including that the doctor is advised to check if the patient has ever had hepatitis B infection prior to starting lenalidomide treatment. **Additional risk minimisation measures:** – None.
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** – Connect® MM Registry – MDS PASSes.

Table 4: Important Identified Risk: SPM

Important Identified Risk: SPM	
Evidence for linking the risk to the medicine	In clinical trials, AML and B-cell malignancies have been reported in patients treated with lenalidomide. Based on clinical trial data, lenalidomide may increase the risk of NMSC. Patients with MM also have an increased risk of NMSC. Patients treated with lenalidomide may be at increased risk of developing new cancers. The reason for this is not clear, but further investigations are being undertaken.

Table 4: Important Identified Risk: SPM (Continued)

Important Identified Risk: SPM	
Risk factors and risk groups	Details are provided in Table 37.
Risk minimisation measures	**Routine risk minimisation activities**: – Section 4.4 of SmPC warning of SPM and advice for cancer screening. – Listed as ADRs in Section 4.8 of SmPC. – Advice to patients provided in PL. **Additional risk minimisation measures:** – Dear HCP letter. – HCP Kit: HCP Guide.
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** – Connect® MM Registry. – MDS PASSes. – Connect® MDS/AML Disease Registry. – Long-term follow-up (at least 5 years from the date of the randomisation of the last patient in the study) for SPM in all Celgene-sponsored clinical trials; 3 years for MDS PASSes. – Solicited reporting of SPM in all Celgene-sponsored clinical trials (status of clinical trials will be updated with each PSUR and DSUR cycle).

Table 5: Important Identified Risk: Tumour Flare Reaction (MCL and FL Indications)

Important Identified Risk: Tumour Flare Reaction (MCL and FL Indications)	
Evidence for linking the risk to the medicine	Based on clinical trial data, lenalidomide may increase the risk of TFR in patients with CLL and other lymphomas.
Risk factors and risk groups	Tumour flare reaction has been associated with greater tumour burden in CLL (Ferrajoli, 2008). In Study MCL-002, in the final multivariate model, high MIPI score at diagnosis ($p = 0.084$) and bulky disease at baseline ($p = 0.020$) appeared to be strong and independent risk factors for TFR.
Risk minimisation measures	**Routine risk minimisation activities**: – Section 4.2 of SmPC: dose interruption advice for TFR. – Section 4.4 of SmPC warning. – Listed as an ADR in Section 4.8 of SmPC. **Additional risk minimisation measures:** – HCP Kit: HCP Guide.
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** – RRMCL PASS.

Table 6: Important Potential Risk: Cardiac Failure and Cardiac Arrhythmias

Important Potential Risk: Cardiac Failure and Cardiac Arrhythmias	
Evidence for linking the risk to the medicine	Based on clinical trial data, a higher incidence of cardiac failure has been observed; the reason for this is not clear. Based on clinical trial data, a higher incidence of cardiac arrhythmia was observed in the lenalidomide arm.
Risk factors and risk groups	No particular risk groups or risk factors have been identified for lenalidomide. In MM and MDS no differences in frequency, severity, serious outcomes and apparent risk level of cardiac failure AEs have been observed. Cardiac symptoms in patients with MDS are often due to anaemia and may be due to iron overload and side effects of therapy (Mateen, 2006). In a study of 840 MDS patients, Della Porta (2007) reported that heart failure (28% versus 18%, p = 0.001) and cardiac death (69% versus 55%, p = 0.03) were significantly more frequent in transfusion-dependent patients. In a Cox analysis with time-dependent covariates, transfusion-dependent patients showed an increased risk of non-leukemic death (HR = 2.12; p ≤ 0.001), heart failure (HR = 1.34; p = 0.03), and cardiac death (HR = 2.99; p = 0.01). The development of secondary iron overload significantly affected the risk of non-leukemic death and OS (HR = 1.25 and 1.16, respectively; p < 0.001), and this effect was maintained after adjusting for transfusion burden. Iron overload specifically increased the risk of developing heart failure (HR = 1.17, p < 0.001). General risk factors for CHF include increasing age, previous heart disease, diabetes, hypertension, amyloidosis, and previous anthracycline based chemotherapy treatment (Hershman, 2008). Standard risk factors for atrial fibrillation include advancing age, European ancestry, body size (greater height and body mass index), electrocardiography features (left ventricular hypertrophy, left atrial enlargement), diabetes, systolic blood pressure and presence of cardiovascular disease (ie, CHD, heart failure, valvular heart disease). Other factors include clinical and subclinical hyperthyroidism, chronic kidney disease, and heavy alcohol consumption. Familial aggregation studies have identified a role for genetic factors, although such factors probably account for a small proportion of cases (Go, 2014). In a case-control study of 385 eligible cases of new-onset atrial fibrillation embedded within the Rotterdam study, the risk of new-onset atrial fibrillation was significantly higher for persons who received a corticosteroid prescription within 1 month before the atrial fibrillation index date (van der Hooft, 2006). Only high-dose corticosteroid use was associated with increased risk (OR = 6.07; 95% CI: 3.90-9.42). The association of atrial fibrillation was independent of indication for use. Risks were increased not only in patients with asthma or chronic obstructive pulmonary disease, but also in patients with rheumatic, allergic, or malignant haematologic diseases.
Risk minimisation measures	**Routine risk minimisation activities**: – Listed as ADRs in Section 4.8 of SmPC. – Listed in PL. **Additional risk minimisation measures:** None.

Table 6: Important Potential Risk: Cardiac Failure and Cardiac Arrhythmias (Continued)

Important Potential Risk: Cardiac Failure and Cardiac Arrhythmias	
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** – Connect® MM Registry. – Revlimid TNE NDMM Registry. – MDS PASSes.

Table 7: Important Potential Risk: Ischaemic Heart Disease (Including Myocardial Infarction)

Important Potential Risk: Ischaemic Heart Disease (Including Myocardial Infarction)	
Evidence for linking the risk to the medicine	In clinical trials, ischaemic heart disease has been reported in patients treated with lenalidomide. Myocardial infarction occurs relatively often in individuals of the older age groups that most often develop the target indications of MM, MDS, MCL and FL.
Risk factors and risk groups	Risk factors for 10-year coronary risk based upon the Framingham Heart Study include elevated blood pressure, elevated cholesterol, high-density lipoprotein-C, presence of diabetes and cigarette smoking (Go, 2014). These factors are in addition to the well-known relationships between coronary risk and age and gender. In Europe, smoking remains a major public health issue and about 20% of death from CVD in men and about 3% of deaths from CVD in women are due to smoking. Levels of obesity are high across Europe in both adults and children, although rates vary substantially between countries. Participation in physical activity is low. Increases in population body mass index over the interval 1980 to 2008 were noted in almost all countries. The prevalence of diabetes in Europe is high and has increased rapidly over the last ten years, increasing by more than 50% in many countries (Nichols, 2012).
Risk minimisation measures	**Routine risk minimisation activities**: The association between ischaemic heart disease and lenalidomide is unknown. Close monitoring will continue. – Myocardial infarction is included in Sections 4.4 and 4.8 of the SmPC. **Additional risk minimisation measures:** None.
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** – Connect® MM Registry. – Revlimid TNE NDMM Registry. – MDS PASSes.

Table 8: Important Potential Risk: Off-label Use

Important Potential Risk: Off-label Use	
Evidence for linking the risk to the medicine	There is potential for the use of lenalidomide in indications other than the approved indications.
Risk factors and risk groups	Not applicable
Risk minimisation measures	**Routine risk minimisation activities**: – Collection of off-label use data detailed in Section 4.4 of SmPC. **Additional risk minimisation measures:** None.
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** – MDS PASSes.

1.5. Postauthorisation Development Plan

1.5.1. Studies which are Conditions of the Marketing Authorisation

The following studies are conditions of the marketing authorisation:

Monitoring of Pregnancy Prevention Programme Implementation

Purpose of the study: Monitoring implementation of the Pregnancy Prevention Programme.

Revlimid TNE NDMM Registry

Purpose of the study: The primary objectives are to compare the incidence of cardiovascular events between TNE NDMM patients treated with a first-line lenalidomide-containing regimen and those treated with a first-line non lenalidomide-containing regimen; and to identify, quantify, and characterise risk factors for cardiovascular events in this population of TNE NDMM patients.

MDS PASS (MDS-010):

Purpose of the study: The primary objective is to ascertain the progression to AML and survival among patients with transfusion-dependent IPSS low- or INT-1-risk MDS with del(5q) as an isolated cytogenetic abnormality who have been treated with lenalidomide.

MDS PASS (MDS-012):

Purpose of the study: The primary objective is to describe the pattern of use of lenalidomide in the clinical routine practice of MDS patients.

1.5.2. Other Studies in Postauthorisation Development Plan

Connect® MM: The Multiple Myeloma Disease Registry

Purpose of the study: The primary objectives of the registry are to describe practice patterns of common first-line and subsequent treatment regimens (including lenalidomide-based) in patients with previously untreated MM, whether or not eligible for transplant, as well as diagnostic patterns and occurrence of SPM in a 'real world' population.

Connect® MDS/AML Disease Registry

Purpose of the study: The primary objectives of the registry are to describe patterns for diagnosis, prognosis, treatment, clinical monitoring and outcome measures in patients with MDS, ICUS and AML; to compare routine clinical practice patterns with existing management guidelines (eg, National Comprehensive Cancer Network); to describe treatment patterns and outcomes in del(5q) patients with or without additional cytogenetic abnormalities; and in non-del(5q) patients; and to summarise patient-reported outcomes (eg, health related Quality of Life [HRQoL]) and economic outcomes, and their association with patient characteristics, treatment regimens, and clinical outcomes. Exploratory objectives are to evaluate molecular and/or cellular markers in the blood/bone marrow tissues and oral epithelial cells that may provide further prognostic classification of MDS and AML subtypes and/or may provide information on drug mechanism of action and on-therapy markers predictive of clinical outcomes and potentially impact clinical outcomes with therapy; to summarise the clinical status (eg, overall survival [OS], progression-free survival [PFS], response rate) of patients with or without mutations by treatment regimen, and to analyse the correlation between mutation detection/allele burden in bone marrow and peripheral blood samples. Data regarding SPM are also being collected.

RRMCL PASS

Purpose of the study: To quantify and characterise the event of tumour flare reaction (TFR) by tumour burden and the proportion of early deaths by tumour burden in patients treated with lenalidomide in a ‘real world’ setting.

PART VII: ANNEXES

1. ANNEXES TO THE RISK MANAGEMENT PLAN

Annex Number	Document Title
1	EudraVigilance Interface
2	Tabulated Summary of Planned, Ongoing, and Completed Pharmacovigilance Study Programme
3	Protocols for Proposed, Ongoing and Completed Studies in the Pharmacovigilance Plan
4	Specific Adverse Drug Reaction Follow-up Forms
5	Protocols for Proposed and Ongoing Studies in RMP Part IV
6	Details of Proposed Additional Risk Minimisation Activities (if Applicable)
7	Other Supporting Data (Including Referenced Material)
8	Summary of Changes to the Risk Management Plan Over Time

ANNEX 1: EUDRAVIGILANCE INTERFACE

Not applicable. This is available in electronic format only.

ANNEX 2: TABULATED SUMMARY OF PLANNED, ONGOING, AND COMPLETED PHARMACOVIGILANCE STUDY PROGRAMME

Table 1: Annex II: Planned and Ongoing Studies

Study/Activity Type, Title and Category (1 to 3)	**Summary of Objectives**	**Safety Concerns Addressed**	**Protocol Link Milestones**
MDS PASSes *Non-interventional: observational Category 1*	To gather safety data on the use of lenalidomide in MDS patients and monitor off-label use (prospective disease registry in transfusion-dependent low- and INT-1-risk MDS with an isolated del 5q [MDS-010] and a retrospective drug utilisation study of Revlimid in MDS [MDS-012]).	AML and survival. Safety profile in a 'real world' setting.	Sequence 0117 Sequence 0168 Sequence 0215 Sequence 0121 Sequence 0197 Ongoing Safety updates will be submitted with future PSURs. The final study report for MDS-010 is expected Q1 2023. The final study report for MDS-012 is expected Q3 2023.
Revlimid TNE NDMM Registry *Non-interventional: Category 1*	The primary objectives are to compare the incidence of cardiovascular events between TNE NDMM patients treated with a first-line lenalidomide-containing regimen and those treated with a first-line non lenalidomide-containing regimen; and to identify, quantify, and characterise risk factors for cardiovascular events in this population of TNE NDMM patients.	Cardiac events (cardiac failure, cardiac arrhythmias, IHD [including MI]).	Sequence 0176 Ongoing Final protocol dated 10 May 2016 was endorsed by PRAC on 02 Sep 2016. An interim study report is expected 30 Jun 2024. The final study report is expected 01 Dec 2025. Safety updates will be submitted with future PSURs.
Monitoring of Pregnancy Prevention Programme implementation *Category 3*	Monitoring of implementation of PPP.	Monitoring pregnancy prevention.	Ongoing Safety updates will be submitted with future PSURs.
Connect® MM Registry. *Category 3*	The primary objectives of the registry are to describe practice patterns of common first-line and subsequent treatment regimens (including lenalidomide based) in patients with previously untreated MM, whether or not eligible for transplant, as well as diagnostic patterns and occurrence of SPM in a 'real world' population.	SPM (AML and B-cell malignancies, NMSC and other SPM), cardiac events (cardiac failure, cardiac arrhythmias, IHD [including MI]), renal failure, Serious Infection due to Neutropenia.	Sequence 0187 Ongoing Safety updates will be submitted with future PSURs.

Table 1: Annex II: Planned and Ongoing Studies (Continued)

Study/Activity Type, Title and Category (1 to 3)	**Summary of Objectives**	**Safety Concerns Addressed**	**Protocol Link Milestones**
Connect® MDS/AML Disease Registry *Non-interventional: observational Category 3*	The objectives of the registry are: to describe patterns for diagnosis, prognosis, treatment, clinical monitoring and outcome measures in patients with MDS, ICUS and AML; to compare routine clinical practice patterns with existing management guidelines (eg, National Comprehensive Cancer Network); to describe treatment patterns and outcomes in del(5q) patients with or without additional cytogenetic abnormalities, and in non-del(5q) patients; and to summarise patient-reported outcomes (eg, HRQoL) and economic outcomes, and their association with patient characteristics, treatment regimens and clinical outcomes. Exploratory objectives are: to evaluate molecular and/or cellular markers in the blood/bone marrow tissues and oral epithelial cells that may provide further prognostic classification of MDS and AML subtypes and/or may provide information on drug mechanism of action and on-therapy markers predictive of clinical outcomes and potentially impact clinical outcomes with therapy; to summarise the clinical status (eg, OS, PFS, response rate) of patients with or without mutations by treatment regimen, and to analyse the correlation between mutation detection/allele burden in bone marrow and peripheral blood samples. Data regarding SPM are also being collected.	SPM	Sequence 0187 Ongoing Safety updates will be submitted with future PSURs.

Table 1: Annex II: Planned and Ongoing Studies (Continued)

Study/Activity Type, Title and Category (1 to 3)	**Summary of Objectives**	**Safety Concerns Addressed**	**Protocol Link Milestones**
RRMCL PASS *Category 3*	The study is designed as a retrospective non-interventional study of patients with RRMCL with the objective to quantify and characterise the event of TFR by tumour burden and the proportion of early deaths by tumour burden in patients treated with lenalidomide in a 'real world' setting.	TFR/high tumour burden and early deaths	Sequence 0194 Version 3 of the protocol was submitted on 14 Aug 2017, approved by PRAC on 26 Oct 2017 and endorsed by CHMP on 09 Nov 2017. Final report expected Q4 2027. Safety updates will be submitted with future PSURs.

Table 2: Annex II: Completed Studies

Study/Activity Type, Title and Category (1 to 3)	**Summary of Objectives**	**Safety Concerns Addressed**	**Date of Final Study Report Submission Link to Report**
RRMM PASS *Category 3*	To characterise and determine the incidence of adverse events of special interest; specifically neutropenia, thrombocytopenia, acute and opportunistic infections, bleeding events, venous thromboembolism, cardiac disorders (cardiac failure, arrhythmia, QT prolongation), neuropathy, rash, hypersensitivity, hypothyroidism and renal failure in patients treated with lenalidomide in a naturalistic setting and placing into context with the background incidence of these adverse events in a non-lenalidomide cohort of MM patients who newly receive second or later lines of treatment for MM.	Celgene PPP. Safety profile in a 'real world' setting.	CSR dated 19 Apr 2017. Sequence 0191
Pooled analysis of data from clinical trials of Revlimid. *Category 3*	To determine the incidence of VTEs and ATEs in patients with MM, with consideration of the thromboprophylactic agents used.	Thromboembolic events	Final Report submitted 31 Mar 2014 to the FDA. The label was formally approved on 12 Sep 2014. Submitted 04 Mar 2015 to the EMA with PSUR 11 (cut-off date 26 Dec 2014). Sequence 0140

Table 2: Annex II: Completed Studies (Continued)

Study/Activity Type, Title and Category (1 to 3)	**Summary of Objectives**	**Safety Concerns Addressed**	**Date of Final Study Report Submission Link to Report**
CC-5013-TOX-004 *Category 3*	A dose range finding study, performed to identify the responsiveness of the test system (cynomolgus monkeys) to thalidomide (positive control group; dosed at 15 mg/kg/day) and the effects of administration of oral lenalidomide dosages of 0 (Vehicle), 0.5, 1, 2 or 4 mg/kg/day to the maternal animals on their pregnancies and conceptuses.	Embryofoetal development	Final report submitted to the EMA on 17 Apr 2009. Sequence 0000
CC-5013-PK-007 *Category 3*	Thorough QTc study in healthy volunteers	QTc prolongation	FDA: Submitted Sep 2011 EMA: Submitted 22 Dec 2011. Sequence 0069
CC-5013 PK-006 *Category 3*	A pharmacokinetic study to evaluate the transfer of lenalidomide in semen after exposure to a single 25 mg dose of [14C] lenalidomide.	Transfer of lenalidomide in semen	CSR submitted to the CHMP on 19 Dec 2007. Sequence 0024
CC-5013-PK-008 *Category 3*	A further pharmacokinetic study to evaluate the transfer of lenalidomide in semen in healthy volunteers after 4 doses of lenalidomide (25 mg QD) at 2, 24, 72 and 168 hours post Day 4 dose after achievement of steady state.	Transfer of lenalidomide in semen	Submitted to the EMA on 06 Apr 2009. Sequence 0000
CC-5013-PK-001	– To evaluate the effect of renal insufficiency and haemodialysis on the pharmacokinetics of lenalidomide. – To evaluate the safety in this patient population treated with a single, oral 25 mg dose of lenalidomide – To determine the extent of plasma protein-binding	Influence of renal impairment on the pharmacokinetics of lenalidomide	31 Dec 2010. Sequence 0042

ANNEX 3: PROTOCOLS FOR PROPOSED, ONGOING AND COMPLETED STUDIES IN THE PHARMACOVIGILANCE PLAN

Table 1: Approved Protocols

Study/Activity	Procedure Number where the Protocol was Approved	Full Protocols or Links/References to eCTD Documents
MDS PASSes		
CC-5013-MDS-010, Amendment 2.0 (Version 3.0)	EMEA/H/C/717/ANX/0041.3 PRAC outcome: 10 Apr 2014	Sequence 0117
CC-5013-MDS-010, Amendment 3.0 (Version 5.0)	EMEA/H/C/PSP/0044.1 PRAC outcome: 07 Jul 2016	Sequence 0168
CC-5013-MDS-010, Amendment 4.0 (Version 6.0)	EMEA/H/C/PSA/S/0034 PRAC outcome: 29 Nov 2018	Sequence 0215
CC-5013-MDS-012 (Version 2.0)	EMEA/H/C/717/ANX/0041.4 PRAC outcome: 10 Apr 2014	Sequence 0121
CC-5013-MDS-012, Amendment 1 (Version 5.0)	EMEA/H/C/PSA/S/0016.2 PRAC outcome: 30 Nov 2017	Sequence 0197
Revlimid TNE NDMM Registry		
CC-5013-MM-034 (Final)	EMEA-H-C-PSP-0020.3 PRAC outcome: 02 Sep 2016	Sequence 0176
RRMM PASS		
Original	EMEA/H/C/000717/FUM026 CHMP Opinion: 18 Oct 2007	Sequence 0000
Amendment 1	EMEA-H-C-000717-A-20-048 CHMP Opinion: 22 Sep 2011	Sequence 0057
RRMCL PASS		
CC-5013-MCL-005 (Version 3.0)	EMEA/H/C/000717/MEA/046.2 PRAC outcome: 26 Oct 2017	Sequence 0194

Table 2: Final Protocols Not Reviewed or Not Approved

Study/Activity	Full Protocols or Links/References to eCTD Documents
Connect® MM Registry (V5.0, 29 Feb 2016)	Sequence 0187
Connect® MDS/AML Disease Registry (V3.0, 30 Sep 2015)	Sequence 0187

ANNEX 4: SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

Important Identified or Potential Risk	**Follow-up Form Title**
Teratogenicity	Event-Specific Questionnaire for HCP – Pregnancy Background (Patient or Partner of Patient) Event-Specific Questionnaire for Patient or Male Patient of Pregnant Partner – Pregnancy Background Event-Specific Questionnaire for HCP – Pregnancy Follow-up (Patient or Partner of Patient) Event-Specific Questionnaire for HCP – Pregnancy Outcome (Patient or Partner of Patient) Event-Specific Questionnaire for Patient or Male Patient of Pregnant Partner – Pregnancy Outcome Event-Specific Questionnaire for Primary Care Physician or Pediatrician – Infant Follow-up
Serious Infection due to Neutropenia	Neutropenia
Acute Myeloid Leukaemia and B-cell malignancies	Acute Myeloid Leukaemia AML or MDS in Non-MDS Indication
Non-melanoma skin cancer	Second Primary Malignancies
Tumour Flare Reaction	Tumour Flare Reaction
Cardiac failure	Cardiac failure
Cardiac arrhythmias	Cardiac arrhythmia and ECG Changes
Ischaemic heart disease (including myocardial infarction)	Myocardial infarction
Other Second Primary Malignancies	Second Primary Malignancies

Event-Specific Questionnaire for HCP – Pregnancy Background
(Patient or Partner of Patient)
Telephone: _____
Fax: _____
Email: Drugsafety@celgene.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 ☐ AFRICAN-AMERICAN ☐ ASIAN ☐ OTHER, SPECIFY:	
Partner of Patient Information ☐ Not applicable			
DATE OF BIRTH:	ETHNICITY: ☐ WHITE ☐ AFRICAN-AMERICAN ☐ ASIAN ☐ OTHER, SPECIFY:		
Patient Treatment Information:			
LOT NO.:	EXPIRY DATE:	DOSE:	FREQUENCY:
ROUTE:	START DATE:	STOP DATE:	
INDICATION FOR USE:			
CYTOGENETIC ABNORMALITIES: ☐ NO ☐ YES If Yes, specify: _____			

Current Pregnancy					
Date of Last Menstrual Period:		Estimated Delivery Date:			
PREGNANCY TEST	REFERENCE RANGE	DATE			
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 deliveries:	No. of pre-term births:
No. of fetal deaths:	No. of living children:	No. of abortions: Elective _____ Spontaneous _____

Type of delivery: ☐ Vaginal ☐ C-section ☐ Other: specify

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

If Yes, specify: _____

Pregnancy History

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

1) If Yes, in what week of pregnancy did the stillbirth or miscarriage occur? _____ week

2) Was there any birth defect noted? Specify: _____

Relevant Medical History			
	DATE OF DIAGNOSIS		DATE OF DIAGNOSIS
Cancer ☐ No ☐ Yes, if yes, specify			

Social History	
ALCOHOL ☐ NO ☐ YES, IF YES, AMOUNT/UNIT CONSUMED PER DAY:	
TOBACCO ☐ NO ☐ YES	IV OR RECREATIONAL DRUG USE ☐ NO ☐ YES, SPECIFY:
Family History: CONGENITAL ABNORMALITIES ☐ NO ☐ YES, SPECIFY:	

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

DRUG	START DATE	STOP DATE/ ONGOING	INDICATION

Adverse Event(s) During Pregnancy

EVENT(S)	SERIOUS		SERIOUS CRITERIA[1]	START DATE	STOP DATE	CAUSAL RELATIONSHIP TO CELGENE PRODUCT		
	NO	YES				YES	NO	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:** _____

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Version 3.0
30Jan2015/CC

MCN:

Event-Specific Questionnaire for Patient or Male Patient of Pregnant Partner– Pregnancy Background

Telephone: _____
Fax: _____
Email: Drugsafety@celgene.com

Date: _____

Name of Patient or Name of Male Patient of Partner: _____

For a better understanding of pregnancy among patients or partners of patients on REVLIMID®, please complete the following questions.

1. What forms of birth control have you been using while on REVLIMID® before you/ your partner got pregnant? Please check all that apply.

- ☐ Tubal ligation
- ☐ IUD
- ☐ Hormonal (birth control pills, hormonal patches, injections, vaginal rings, or implants)
- ☐ Partner's vasectomy
- ☐ Male latex or synthetic condom
- ☐ Diaphragm
- ☐ Cervical cap or shield
- ☐ Spermicide or sponge
- ☐ Withdrawal

2. Were you or your partner at any time during use of REVLIMID® without contraception for even one day?

- ☐ No, please proceed to Question 5
- ☐ Yes, please answer Question 3, Question 4, Question 5, and Question 6

3. How often did you have unprotected sexual intercourse?

- ☐ Multiple times
- ☐ Once a week
- ☐ Once every 2 weeks
- ☐ Once a month
- ☐ Not at all
- ☐ Other, specify _____

4. Why did you or your partner interrupt or stop using contraception?

- ☐ Wanted a child
- ☐ Partner disapproved

MCN:

☐ Side effects
☐ Health concerns
☐ Inconvenient to use
☐ Other, specify _____

5. Did you receive the REVLIMID® Medication Guide?
☐ No, please proceed to Question 6
☐ Yes, please answer the following question

5.1 Did you read the REVLIMID® Medication Guide?
☐ No, please proceed to Question 6
☐ Yes, please answer the following question

5.2 Did you understand the information in the REVLIMID® Medication Guide?
☐ No
☐ Yes

6. Where did most of your knowledge about contraception during REVLIMID® use come from?
☐ Physician who prescribed REVLIMID®
☐ REVLIMID® Medication Guide
☐ Other, specify: _____

7. Do you feel you and/ or your partner had a good understanding of the risk of pregnancy during REVLIMID® use.
☐ Yes
☐ No
☐ Don't know

MCN:

Event-Specific Questionnaire for HCP – Pregnancy Follow-up
(Patient or Partner of Patient)
Telephone: (908) 673-9667
Fax: (908) 673-9115
Email: Drugsafety@celgene.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	

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

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

DRUG	START DATE	STOP DATE/ CONTINUING	INDICATION

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MCN:

Adverse Event(s) During Pregnancy								
EVENT(S)	SERIOUS		SERIOUS CRITERIA[1]	START DATE	STOP DATE	CAUSAL RELATIONSHIP TO CELGENE PRODUCT		
	NO	YES				YES	NO	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:** _____

Revlimid®

MCN:

Event-Specific Questionnaire for HCP – Pregnancy Outcome
(Patient or Partner of Patient)
Telephone: (908) 673-9667
Fax: (908) 673-9115
Email: Drugsafety@celgene.com

Reporter Information			
REPORTER NAME:			
ADDRESS:		CITY, STATE, ZIP, COUNTRY:	
PHONE NO.:		FAX NO.:	
Patient Information			
PATIENT ID:	DATE OF BIRTH:	ETHNICITY: ☐ WHITE ☐ AFRICAN-AMERICAN ☐ OTHER, SPECIFY:	
Partner of Patient Information ☐ Not applicable			
DATE OF BIRTH:	ETHNICITY: ☐ WHITE ☐ AFRICAN-AMERICAN ☐ OTHER, SPECIFY:		
Pregnancy Outcome			
DATE OF DELIVERY:			GESTATION AGE AT DELIVERY:
	NO	YES	
Normal	☐	☐	
C-section	☐	☐	
Induced	☐	☐	
Ectopic pregnancy	☐	☐	
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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MCN:

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 Outcome			
	NO	YES	
Live Normal Infant	☐	☐	
Fetal Distress	☐	☐	
Intra-uterine Growth Retardation	☐	☐	
Neonatal Complications*	☐	☐	If Yes, please specify:
Birth Defect Noted?	☐	☐	If Yes, please specify:

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

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

SIGNATURE OF PERSON COMPLETING THIS FORM: _____ DATE: _____

Event-Specific Questionnaire for Patient or Male Patient of Pregnant Partner–
Pregnancy Outcome
Telephone: (908) 673-9667
Fax: (908) 673-9115
Email: Drugsafety@celgene.com

Date: _____

Name of Patient or Name of Male Patient of Partner: _____

Please provide the outcome of your or your partner's pregnancy

☐ Normal baby

☐ Abnormal baby, please specify defect _____

☐ Therapeutic abortion, please specify any abnormality of the fetus if known: _____

_____

☐ Spontaneous abortion or miscarriage, please specify any abnormality of the fetus if known:

_____

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MCN:

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

Telephone: (908) 673-9667
Fax: (908) 673-9115
Email: Drugsafety@celgene.com

Date:	_____
Name of Patient or Name of Male Patient of Partner (Mother):	_____
Name of Infant (if known):	_____
Please provide information for the period from **[Date]** to **[Date]**	_____ to _____

Anomalies Diagnosed Since Initial Report:	_____
☐ None	
Developmental Assessment:	_____
☐ Normal	
☐ Abnormal, specify	_____

Infant Illnesses, Hospitalizations, Drug Therapies:

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

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

Revlimid®

MCN:

NEUTROPENIA

1) On or about *[DDMMYYYY]*, your patient was reported to have experienced neutropenia. Please provide the following lab values at baseline, onset of the event (worst), and recovery:

Test	Range w/ Units	Baseline/ Date	Worst/ Date	Recovery/ Date
WBC				
ANC				

2) What treatments were given for the neutropenia? Please include dates.

3) Did your patient experience an infection in association with the neutropenia? ☐**Yes** ☐ **No**

4) If yes, please provide location of the infection.

5) Does the patient have a history of recurrent infection? Please explain.

6) Please provide the stage/classification of the patient's disease [*specify*] at the time of the infection.

7) Please include culture / serology / bone marrow studies / x-ray results for the event of infection.

Work aid: Target Questions for Follow-up on EOI Version 3.0 – 03Sep2013

Acute Myeloid Leukemia (AML)

1) Provide bone marrow results as well as cytogenetics at baseline and at the time of transformations (to MDS high risk and AML).

2) Specify AML type if not included in the bone marrow or cytogenetics documents.

3) Please provide the date MDS was initially diagnosed with stage (FAB or other classification).

4) Please provide information regarding environmental exposure, if any.

5) Relevant medical history including familial history of malignancies and previous antineoplastic treatments the patient may have received including radiotherapy with radiation zone and cumulative dose if any.

6) Other concomitant medications (administered prior to the event) including indications, therapy dates and dosing information.

Version 1.0 – 09Jun10

AML or MDS in Non-MDS Indication

- *This Work Aid is to be use for events of MDS or AML where the therapy indication is not MDS.*
- *Use this Work Aid for any product, especially IMIDs.*
- *Tailor your follow-up questions based in existing information in the case report.*
- *Utilize medical judgment as always in developing targeted questions. Consult a medical reviewer if in doubt.*

1) Please provide the date [*Celgene drug indication, e.g., AML or MDS*] was initially diagnosed with stage/classification.

2) Please provide full bone marrow results as well as full cytogenetics at baseline and at the time of diagnosis of [*MDS or AML*) with dates. Please specify if this information is not available or not evaluable.

3) Please specify AML type if not included in the bone marrow or cytogenetics documents. Please specify if this information is not available or not evaluable.

4) Please also provide the [*Celgene drug indication*] stage/classification at the time of the MDS or AML diagnosis. Please specify if this information is not available or not evaluable. Is there evidence of progression of underlying disease? Please explain.

5) Please provide relevant medical history including familial history of malignancies, environmental exposure, blood transfusion dependence status.

6) Please provide changes in transfusion dependence status during disease (*Celgene drug indication)* treatment with corresponding dates.

7) Please provide information on any antineoplastic treatments the patient may have received including radiotherapy with radiation zone for any malignant neoplasm, specifying the indication for this. Please provide duration of treatment with dates and also cumulative dose if available.

8) Please provide all concomitant medications including indications, therapy dates and dosing information. These should include concurrent anti-myeloma therapy, colony-stimulating factors, and/or ESAs.

9) Please provide [*Celgene drug*] dosing regimen with dates and dose.

10) Please specify what treatment was received for the AML/MDS.

11) What was the outcome of AML/MDS? If fatal outcome, please provide circumstances surrounding the death.

Work aid: Target Questions for Follow-up on EOI Version 3.0 – 03Sep2013

CARDIAC FAILURE

1) Did the cardiac failure occur prior to therapy? ☐ Yes ☐ No

a. If the cardiac failure occurred prior to therapy, would you consider it an exacerbation? ☐ Yes ☐ No

b. Please provide the date the exacerbation was diagnosed_____

2) Please provide results for EKG, echocardiogram and ejection fraction including baseline data and dates.

3) Did the patient receive any recent blood transfusions or IV infusions? ☐ Yes ☐ No
a. If yes, please specify what was transfused and provide the amount transfused with dates.

b. Please provide CBC results.

4) Please provide additional laboratory tests surrounding the event, particularly calcium and magnesium, serial Total CPK, CK-MB, troponins, and BNP with dates.

5) Does the patient have other cardiac history including coronary artery disease, cardiac stents, myocardial infarction, valvular heart disease, cardiomyopathy, other chemotherapy (previous and ongoing) etc? Please specify.

6) Please provide any associated risk factors including history of hyperlipidemia, obesity, hypertension, COPD, renal disease, diabetes, sepsis, substance abuse etc.

7) Are there any concurrent events that contributed or led up to the cardiac failure? Please specify.

8) What treatments/interventions were provided to the patient for the cardiac failure?

Version 1.0 – 09Jun10

Cardiac Arrhythmia & ECG Changes

In addition to collecting routine information for this adverse event, please ensure the following additional information is provided and/or confirmed.

Please provide brief description of the cardiac arrhythmia, or ECG change, including the type and the clinical signs/symptoms observed, including start and stop dates:

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 in box below. 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 in the box below. If no, please state

Medical History (Diagnosis)	Onset Date /Duration

Please provide all relevant concomitant medications, including antiemetics (use separate sheet if necessary)

Medication	Start date	End date	Dose/Route/Frequency	Indication

Version 2.0 – 18 March 2011

Please provide the available results of the diagnostic workup (use separate sheet if necessary)

Test	Baseline		Event Onset / Worst		Recovery / Latest	
	Date	Results	Date	Results	Date	Results
EKG findings						
Echocardiogram						
Chest x-ray						
Holter, Stress Test						

Please provide the available results of the diagnostic workup (always ask for the results of serum potassium and magnesium studies – use separate sheet if necessary)

Laboratory Testing	Reference range	At Baseline		At Event Onset / Worst		Recovery / Latest	
		Date	Value	Date	Value	Date	Value
CK CK-MB							
Troponin							
RBC							
Hemoglobin							
Metabolic Panel (specify)							
Serum K+							
Serum Mg 2+							

Please describe specific treatments and interventions of the arrhythmia

What was the outcome of the event?

Version 2.0 – 18 March 2011

MYOCARDIAL INFARCTION

1. Did the patient have a history of cardiac disease such as coronary artery disease, myocardial infarction, arrhythmia, or congestive heart failure? Please provide the onset dates of diagnosis.

2. Please provide any risk factors for the myocardial infarction. (hyperlipidemia, hypercholesterolemia, obesity, hypertension, COPD, renal disease, diabetes, sepsis, substance abuse, sedentary life style, immobility, dehydration, etc.).

3. Please provide the following laboratory data: serial CPK and MB, troponin, BNP, Blood cell counts, Hgb, Hct, electrolytes including Mg, and Ca. Please include baseline, worst, and recovery values and dates drawn.

4. Please provide the following diagnostic results including the baseline and the most recent EKG, echocardiogram, stress test, and cardiac catheterization, if available.

5. Please provide the treatment and interventions that were administered due to the myocardial infarction.

Work aid: Target Questions for Follow-up on EOI Version 2.0 – 03Sep2013

MYOCARDIAL INFARCTION

6. Please provide RELEVANT concomitant medications including indications, dosage, and therapy dates. Please include erythropoietin and thromboprophylactic medications and others as appropriate.

7. Please provide concurrent events/circumstances surrounding the MI.

8. Did the patient have a history of chest pain?

9. Was the patient receiving thromboprophylaxis? If yes, which type and dose?

10. Did the patient have a history of thromboembolic events? If yes, please specify type.

SECOND PRIMARY MALIGNANCIES (SPM)

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 treatment in regards to the event
2. Dates of the underlying disease's diagnosis
3. Stage of the underlying disease treated with [*Celgene product*] at baseline, the end of treatment if applicable, and at the time of the event with supportive documentation if available
4. Previous history of malignancies (personal/familial) with estimated dates
5. Underlying medical history and concomitant diseases
6. 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
7. Environmental exposure e.g. atmospheric pollutants/toxic chemicals (pesticides, herbicides, benzene, solvents); occupation/hobbies
8. Tobacco, alcohol abuse?
9. Date of diagnosis of SPM (*specify malignancy or diagnosis if known*). Please provide date of first clinical symptoms of SPM.
10. Full SPM (*specify malignancy or diagnosis if known*) biopsy reports with exact stage. If not available please provide the detailed results
11. Treatment of SPM (*specify malignancy or diagnosis if known*)

In addition to the Core Questions specific information should be requested based on the risk factors for individual types of cancer

Lung Cancer:
- Smoking history – length of time, number of cigarettes/day, age at starting, gender, Product smoked and depth of inhalation
- Pre-existing pulmonary disease
- Family history of lung cancer

Lymphoma:
- Medical conditions that compromise the immune system – HIV/AIDS, autoimmune diseases, diseases requiring immune suppressive therapy-organ transplant
- Infection with HIV, Epstein-Barr virus+++, Helicobacter pylori, hepatitis B or C, human T-lymphotrophic virus type I, Burkitt's lymphoma

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

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
- Ethnic group, economic status and dietary iodine deficiency

Ovarian Cancer:
- Number of pregnancies and childbearing status
- History of hormone replacement therapy

Work aid: Target Questions for Follow-up on EOI Version 2.0 – 03Sep2013 1

SECOND PRIMARY MALIGNANCIES (SPM)

- 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, chronic fistulas, irradiated anal skin, leukoplakia, lymphogranulomatoma venereum, condyloma acuminatum
- HIV status

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

Oesophageal Cancer:
- Genetic causes - tylosis (hyperkeratosis palmaris et plantaris)
- 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
- Alcohol use
- Hepatitis B, C
- Hemochromatosis
- Indigestion of food contaminated with fungal aflatoxins (in subtropical regions)

Pancreatic Cancer:
- Smoking,
- Obesity
- Diet (red meat)
- History of chronic pancreatitis or long-standing diabetes mellitus (primarily in women).
- Inherited predisposition hereditary pancreatitis, familial adenomatous poliposis)

Renal Cancer (renal cell carcinoma):
- Smoking

Work aid: Target Questions for Follow-up on EOI Version 2.0 – 03Sep2013 2

SECOND PRIMARY MALIGNANCIES (SPM)

- 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 VHL disease (von Hippel-Lindau disease), Adult polycystic kidney disease, Tuberous sclerosis

Bladder Cancer:
- Smoking
- 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:
- Ethnic group
- 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:
- Smoking and alcohol use
- Prolonged sun exposure
- Exposure to Human papilloma virus (HPV) or Epstein-Barr virus (EBV)
- Ethnic group
- History of poor oral hygiene and/or poor nutrition
- Exposure to asbestos, wood dust, paint fumes or chemicals
- History of Gastroesophogeal reflux disease (GERD) or laryngopharyngeal reflux disease (LPRD)

Brain tumors (gliomas and menigiomas):
- Exposure to radiation
- Exposure to vinyl chloride, Pesticides
- Immune system disorders
- Hormone replacement therapy

Larynx Cancer:
- Smoking history, alcohol use
- 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

Mouth and Oropharyngeal Cancer:
- Smoking

Work aid: Target Questions for Follow-up on EOI Version 2.0 – 03Sep2013 3

SECOND PRIMARY MALIGNANCIES (SPM)

- alcohol use
- 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:

- 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,
- Exposure to arsenic, coal tar or creosote
- For eye localization : history of oculodermal melanocytosis or Dysplastic nevus syndrome
- Ethnic group
- History of prolonged sun exposure (UV radiation)

TUMOR FLARE REACTION (TFR)

In addition to collecting routine information for this adverse event, please ensure the following information is provided and/or confirmed.

1. Provide Celgene product dosing with therapy start date, all doses prior to the event.

2. Please confirm the chemotherapy indication.

3. Tumor burden (to specify) or disease stage at baseline and at the time of the event.

4. Details on the associated symptoms : (Fever <please provide temperature value> , pain <to specify>, rash <details on zones>, tender lymph nodes/ swelling <specify location>, tender liver or spleen, elevated WBC counts, other <to specify>).

5. Any complication (to specify).

6. Imagery results (CT scan/MRI) at baseline and at the time of the event.

7. Infections work-up (serologies, cultures – blood/urine/sputum/stools), chest Xray.

8. Provide laboratory data: baseline (prior to initiating drug), at onset of TFR, at recovery:

Laboratory Test	Reference range with Units	At Baseline		At Event Onset / Worst		Recovery / Latest	
		Date	Value	Date	Value	Date	Value
WBC							
ANC							
LYMPHOCYTES							
Hb							
PLATELETS							
LDH							
Creatinine							
Calcium							
Phosphorus							

Work aid: Target Questions for Follow-up on EOI Version 1.0 – 27May2014- ID

TUMOR FLARE REACTION (TFR)

Albumin							
CRP							

9. Concomitant therapies with dates (including at least other chemotherapies, higher dose chemotherapy, treatment with immuno-modulator, hormonotherapy). Include drug name, dosing, start/end dates.

10. Medical history with diseases and dates

11. Does this patient have a history of previous tumor flare?
☐ Yes
☐ No
☐ Unknown
If yes, please describe

12. Provide the action taken with Celgene drug:

☐ None
☐ Permanently Discontinued Stop date: _____
☐ Temporarily Interrupted Stop date: _____
☐ Dose Reduced Date and new dose:_____
☐ Dose Increased Date and new dose:_____

13. Did the event abate after discontinuing Celgene drug? ☐ Yes ☐ No

14. Was Celgene product re-introduced? ☐ Yes ☐ No

- Provide restart date and dosing:

15. Provide the action taken with concomitant chemotherapy (to specify):_____

☐ None
☐ Permanently Discontinued Stop date: _____
☐ Temporarily Interrupted Stop date: _____
☐ Dose Reduced Date and new dose:_____
☐ Dose Increased Date and new dose:_____

16. Did the event abate after discontinuing concomitant chemotherapy? ☐ Yes ☐ No

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TUMOR FLARE REACTION (TFR)

17. Was concomitant chemotherapy re-introduced? ☐ Yes ☐ No

    - Provide restart date and dosing:

18. Treatment of the tumor flare (details).

19. Response to treatment

ANNEX 5: PROTOCOLS FOR PROPOSED AND ONGOING STUDIES IN RMP PART IV

Not applicable.

ANNEX 6: DETAILS OF PROPOSED ADDITIONAL RISK MINIMISATION ACTIVITIES (IF APPLICABLE)

Direct Healthcare Professional Communications

The Direct Healthcare Professional Communication prior to launch shall consist of two parts:

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

The Educational Healthcare Professional's Kit

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

- Brief background on lenalidomide and its licensed indication
- Posology
- Maximum duration of prescription
  - 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 lenalidomide in animals and the expected teratogenic effect of lenalidomide in humans including a summary of the results of Study CC-5013-TOX-004
- Obligations of the health care professional in relation to the prescribing of Revlimid
  - Need to provide comprehensive advice and counselling to patients
  - That patients should be capable of complying with the requirements for the safe use of Revlimid
  - Need to provide patients with appropriate patient educational brochure and patient card
- Safety advice relevant to all patients
  - Disposal of unwanted medicine
  - Local country specific arrangements for a prescription for Revlimid to be dispensed
  - Description of risk of tumour flare reaction in MCL and FL patients
  - Description of the risk of progression to AML in MDS patients including incidence rates from clinical trials
  - Description of risk of SPM

- Description of the PPP and categorisation of patients based on sex and childbearing potential
  - Algorithm for implementation of PPP
  - Definition of women of childbearing potential (WCBP) and actions the physician should take if unsure
- Safety advice for women of childbearing potential
  - The need to avoid foetal exposure
  - Description of the PPP
  - Need for adequate contraception (even if woman has amenorrhoea) and definition of adequate contraception
  - Pregnancy test regime
    - Advice on suitable tests
    - Before commencing treatment
    - During treatment based on method of contraception
    - After finishing treatment
  - Need to stop Revlimid immediately upon suspicion of pregnancy
  - Need to tell treating doctor immediately upon suspicion of pregnancy
- Safety advice for men
  - The need to avoid foetal exposure
  - The need to use condoms if sexual partner is pregnant or a WCBP not using effective contraceptions (even if man has had a vasectomy)
    - During Revlimid treatment
    - For 7 days following final dose.
  - That if his partner becomes pregnant whilst he is taking Revlimid or shortly after he has stopped taking Revlimid he should inform his treating doctor immediately
- Requirements in the event of pregnancy
  - Instructions to stop Revlimid immediately upon suspicion of pregnancy, if women of childbearing potential
  - Need to refer to physician specialised or experienced in dealing with teratology and its diagnosis for evaluation and advice
  - Local contact details for reporting of any suspected pregnancy
  - Pregnancy reporting form

- Check list for physicians ensuring that patients receive the appropriate counselling concerning the treatment, contraceptive methods and pregnancy prevention appropriate for their sex and childbearing status
- Details on the MDS PASS emphasizing that prior to prescribing Revlimid, the healthcare professionals should enrol MDS patients into the PASS.
- Adverse event reporting forms

Educational Brochures for patients

The Educational brochures for patients should be of 3 types:

- Brochure for women patients of childbearing potential
- Brochure for women patients who are not of childbearing potential
- Brochure for male patients

All patient brochures should contain the following elements:

- That lenalidomide is teratogenic in animals and is expected to be teratogenic in humans
- Description of the patient card and its necessity
- Disposal of unwanted medicine
- Guidance on handling lenalidomide for patients, caregivers and family members
- National or other applicable specific arrangements for a prescription for Revlimid to be dispensed
- That the patient should not give Revlimid to any other person
- That the patient should not donate blood during therapy (including during dose interruptions) and for 7 days after discontinuation of Revlimid treatment
- That the patient should tell their doctor about any adverse events
- That a study is being conducted to collect information regarding the safety of the medicinal product and to monitor its appropriate use; and that MDS patients should be included in the study prior to the start of the treatment with Revlimid

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

Brochure for women patients with childbearing potential

- The need to avoid foetal exposure
- Description of the PPP
- Need for adequate contraception and definition of adequate contraception
- Pregnancy test regime
  - Before commencing treatment
  - During treatment, every 4 weeks except in case of confirmed tubal sterilisation

  - After finishing treatment
- The need to stop Revlimid immediately upon suspicion of pregnancy
- The need to contact their doctor immediately upon suspicion of pregnancy

ANNEX 7: OTHER SUPPORTING DATA (INCLUDING REFERENCED MATERIAL)

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ANNEX 8: SUMMARY OF CHANGES TO THE RISK MANAGEMENT PLAN OVER TIME

Version	Approval Date Procedure	Changes
6.0	Submitted on 08 Jun 2007 Agreed within FUM 23. Agreed on 21 Jun 2007.	**Important Potential Risks:** Change in rate of progression of MDS to AML added **Missing Information:** Change in rate of progression of MDS to AML moved to important identified risk Use in renal failure moved to important identified risk
8.0	Submitted 25 Feb 2008 Agreed within RM2–023.1. Agreed on 29 May 2008.	**Important Potential Risks:** Tumour lysis syndrome (TLS) added Foetal exposure renamed to Teratogenicity
8.3	Submitted on 28 Apr 2008 Agreed within II/08. CHMP Opinion: 31 Jul 2008, EC Decision 04 Aug 2008.	**Important Identified Risks:** Teratogenicity moved to important potential risk
9.0	Submitted on 18 Sep 2008 Agreed within PSUR 3 (27 Dec 2007 – 26 Jun 2008). Agreed on 22 Jan 2009.	**Important Identified Risks:** Merged thrombocytopenia and bleeding Merged neutropenia and infection Allergic conditions including angioedema, Stevens-Johnson syndrome, toxic epidermal necrolysis, urticaria, hypersensitivity and rash added Diarrhoea and constipation added **Important Potential Risks:** QTc prolongation removed TLS removed Hypothyroidism removed Change in rate of progression of MDS to AML removed
10.0	Submitted on 28 Apr 2009 Agreed within RM2-032.1. Agreed on 23 Jul 2009.	**Important Identified Risks:** Hypersensitivity and angioedema added Allergic conditions renamed to cutaneous reactions **Important Potential Risks:** TLS added MDS progression to AML added MI added
11.0; 31 Aug 2009	Agreed within RM2-032.2. Agreed on 21 Jan 2010.	No changes to safety concerns.

Version	Approval Date Procedure	Changes
12.0; 01 Mar 2010	Agreed within RM2-032.3. Agreed on 24 Jun 2010 (CHMP Opinion)	**Indications: RRMM.** **Important Identified Risks:** TLS added **Important Potential Risks:** TLS moved to important identified risk Pneumonitis added
16.0; 19 Sep 2011 (Closing Sequence)	Agreed within Art 20. Agreed on 22 Sep 2011 (CHMP Opinion) 13 Jan 2012 (EC Decision)	**Indications: RRMM.** **Since Approved Version 12.0:** **Important Identified Risks:** Cutaneous reactions including Stevens-Johnson syndrome, toxic epidermal necrolysis, urticaria and rash renamed to Cutaneous reactions. **Important Potential Risks:** Myocardial infarction renamed as ischaemic heart disease Pneumonitis renamed to interstitial lung disease SPM added MDS transformation to AML removed as it has been repositioned under SPM Liver function laboratory abnormalities added **Pharmacovigilance Activities** It was clarified that the PASS was for RRMM. **Additional Pharmacovigilance Activities**: • Solicited reporting and long-term follow-up of SPM in clinical studies. • Upgrading of invasive SPM to SUSARs.
22.0W; 10 May 2013 (Closing Sequence)	Agreed within II/56 (MDS). Agreed on 25 Apr 2013 (CHMP Opinion) 13 Jun 2013 (EC Decision)	**Indications: RRMM, MDS.** **Since Approved Version 16.0:** **Important Identified Risks:** Venous thromboembolism renamed to Thromboembolic events. Ischaemic heart disease (previously myocardial infarction) renamed Ischaemic heart disease (including myocardial infarction). AML and B-cell malignancies and NMSC added for the indications of NDMM and RRMM, respectively. Liver function laboratory abnormalities renamed to hepatic disorders and moved to important potential risks. **Important Potential Risks** SPM into the risks of AML and B-cell malignancies, NMSC and Other SPM. Hepatic disorders added Off label use added

Version	Approval Date Procedure	Changes
		Additional Pharmacovigilance Activities: • Pending EU approval, institute MDS PASS. • US CONNECT MDS/AML Registry. • Solicited reporting and long-term follow-up of SPM in all Celgene-sponsored clinical studies. • Upgrading of invasive SPM (except NMSC) to SUSARs and reporting to regulatory authorities. **Additional Risk Minimisation**: • For the risks of NMSC, SPM and AML and B-cell malignancies, Dear HCP letter following EC approval for MDS.
24.0; 23 Feb 2015	Agreed within EMEA/H/C/000/717/X/073/G (NDMM TNE). Agreed on 18 Dec 2014 (CHMP Opinion) 19 Feb 2015 (EC Decision)	**Indications: RRMM, MDS, TNE NDMM.** **Since Approved Version 22.0W:** **Missing Information:** Paediatric use added Use in moderate and severe hepatic impairment added Use in breastfeeding added **Additional Pharmacovigilance Activities**: • Revlimid TNE NDMM Registry proposed.
29.0; 27 Jan 2016	Agreed within EMEA/H/C/000/717/II/79 (RRMCL). Agreed on 28 Jan 2016 (CHMP Opinion) 08 Jul 2016 (EC Decision).	**Indications: RRMM, MDS, TNE NDMM, MCL** **Since Approved Version 24.0:** **Important Identified Risks:** TFR added for the MCL population only. **Additional Pharmacovigilance Activities**: • Revlimid RRMCL PASS proposed.
30.0; 24 Mar 2016	Agreed within EMEA/H/C/000/717-IB/0088. Agreed on 14 Jul 2016.	**Indications: RRMM, MDS, TNE NDMM** **Since Approved Version 24.0:** Updates to Additional Educational Materials, Annex IID, and Part V Addition of capsule removal and product handling guidance.
32.0; 30 Sep 2016	Agreed within EMEA/H/C/000/717/IB/0090. Agreed on 26 Oct 2016.	**Indications: RRMM, MDS, TNE NDMM, MCL.** **Since Approved Version 30.0:** Updates to Additional Educational Materials and MDS PASS milestones and timelines, and consolidation of MCL data after approval.
33.0; 22 Dec 2016	Agreed within EMEA/H/C/000/717/IB/0092/G. Agreed on 31 Jan 2017.	**Indications: RRMM, MDS, TNE NDMM, MCL.** **Since Approved Version 24.0:** **Additional Pharmacovigilance Activities**: RRMCL PASS described.

Version	Approval Date Procedure	Changes
34.0; 15 Feb 2017	Agreed within EMEA/H/C/000/717/II/0089/G (NDMM TE). Agreed on 27 Jan 2017 (CHMP Opinion) 23 Feb 2017 (EC Decision)	**Indications: RRMM, MDS, TE and TNE NDMM, MCL.** **Since Approved Version 24.0:** Consolidation of previous versions (31, 31.1, 32, 33) of the RMP as the final RMP for the TE NDMM variation.
35.1; 16 Apr 2018	Agreed within EMEA/H/C/000/717/II/0089/G (NDMM TE). Agreed on 17 May 2018 (CHMP Opinion)	**Indications: RRMM, MDS, TE and TNE NDMM, MCL.** **Important identified risks no longer considered important:** • Neutropenia and Infection (new important identified risk of serious infection due to neutropenia); • Thrombocytopenia and bleeding; • Thromboembolic events; • Cutaneous reactions; • Hypersensitivity and angioedema; • Diarrhoea and constipation; • Tumour lysis syndrome. **Important potential risk reclassified as an important identified risk:** • SPM **Important potential risks no longer considered important:** • Peripheral neuropathy; • Renal failure; • Interstitial lung disease (interstitial pneumonitis); • Hepatic disorders. **Risks previously classified as missing information, removed from safety concerns:** • Paediatric use; • Use in moderate and severe hepatic impairment; • Use in breastfeeding. **Additional Pharmacovigilance Activities:** RRMM PASS complete.
36.4; 21 Mar 2019	Agreed within EMEA/H/C/000717/II/0102/G. Agreed on 28 Mar 2019 (CHMP Opinion) 13 May 2019 (EC Decision)	**Indications: RRMM, MDS, TE and TNE NDMM, MCL.** No changes to safety concerns.

Version	Approval Date Procedure	Changes
37.0; 18 Dec 2019	Agreed within EMEA/H/C/000717/II/0107. Agreed on 14 Nov 2019 (CHMP Opinion) 18 Dec 2019 (EC Decision)	Inclusion of approvedadditional indication of Revlimid in combination with rituximab (anti-CD20 antibody) for the treatment of adult patients with previously treated FL (Grade 1 - 3a). No changes to safety concerns.

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