London, 25 April 2013
EMA/297642/2013
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Invented name: Revlimid

Procedure No. EMEA/H/C/000717/II/0056

Marketing authorisation holder (MAH): Celgene Europe Ltd.

Note

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

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List of abbreviations

AE	Adverse event
AFSSAPS	Agence française de sécurité sanitaire des produits de santé
AML	Acute myeloid leukaemia
B/R	benefit-risk ratio
BM	bone marrow
CHMP	Committee for Medicinal Products for Human Use
CLcr	creatinine clearance
Cmax	maximum plasma concentration
DB	double blind treatment phase
Del 5q	deletion 5 q
DHPC	Direct Health Care Professional Communication
EMA	European Medicines Agency
ESA	erythropoiesis-stimulating agents
EU	European Union
FAB	French-American-British
GCSF	Granulocyte colony-stimulating factor
Hb	haemoglobin
HR	Hazard ratio
HSCT	Hematopoietic stem cell transplantation
IA	Interim analysis
HRQoL	health related quality of life
IPSS	International Prognostic Scoring System
IWG	International Working Group
ITT	Intent to treat
Len	Lenalidomide
MAH	Marketing authorisation holder
MDS	myelodysplastic syndromes
MITT	Modified intent to treat
MM	Multiple myeloma
OL	open label treatment phase
OS	overall survival
Pbo	Placebo
Pbo/Len	Placebo treatment switched to lenalidomide treatment
QD	each day (latin: quaque die)
RA	Refractory anaemia
RAEB	Refractory anaemia with excess blasts
RAEBt	Refractory anaemia with excess blasts in transformation
RARS	Refractory anaemia with ring sideroblasts
RBC-TI	Red blood cell – transfusion independency
RI	Renal insufficiency
RRMM	Relapsed or refractory multiple myeloma
SAE	Serious adverse event
SmPC	Summary of Product Characteristics
SPM	Second primary malignancies
21/28d	21 days on 28-day cycle
28/28d	28 days on 28-day cycle

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Celgene Europe Ltd. submitted to the European Medicines Agency on 17 February 2012 an application for a variation including an extension of indication.

This application concerns the following medicinal product:

Medicinal product:	International non-proprietary name:	Presentations:
Revlimid	lenalidomide	See Annex A

The following variation was requested:

Variation(s) requested		**Type**
C.1.6 a)	*Addition of a new therapeutic indication or modification of an approved one*	II

The MAH applied for an extension of the indication for the treatment of patients with transfusion-dependent anaemia due to low- or intermediate-1-risk myelodysplastic syndromes associated with a deletion 5q cytogenetic abnormality with or without other cytogenetic abnormalities.

The Package Leaflet and Labelling were proposed to be updated in accordance.

The variation proposed amendments to the SmPC, Labelling and Package Leaflet.

Revlimid was designated as an orphan medicinal product EU/03/03/117 on 12 December 2003, in the following indication: treatment of multiple myeloma.

The new indication, which is the subject of this application, falls within a separate orphan designation EU/03/04/192 granted on 8 March 2004. Following the CHMP positive opinion on this marketing authorisation, the Committee for Orphan Medicinal Products (COMP) reviewed the designation of Revlimid as an orphan medicinal product in the approved indication. The outcome of the COMP review can be found here.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/102/2008 on the granting of a (product-specific) waiver.

Information relating to orphan market exclusivity

Similarity

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

Derogation(s) of market exclusivity

Not applicable.

Applicant's request for consideration

Additional marketing exclusivity

The applicant requested consideration of its application in accordance with Article 14(11) of Regulation (EC) No 726/2004 - One year of market protection for a new indication.

Protocol assistance

The applicant received Protocol Assistance from the CHMP on 18 November 2004. The Protocol Assistance pertained to clinical aspects of the dossier.

1.2. Steps taken for the assessment of the product

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

Rapporteur:Pierre Demolis Co-Rapporteur: Bengt Ljunberg

Submission date:	17 February 2012
Start of procedure:	26 February 2012
Rapporteur's preliminary assessment report circulated on:	20 April 2012
CoRapporteur's preliminary assessment report circulated on:	20 April 2012
Joint Rapporteur's updated assessment report circulated on:	18 May 2012
Request for supplementary information and extension of timetable adopted by the CHMP on:	24 May 2012
MAH's responses submitted to the CHMP on:	17 August 2012
Rapporteur's preliminary assessment report on the MAH's responses circulated on:	10 October 2012
2nd Request for supplementary information and extension of timetable adopted by the CHMP on:	18 October 2012
MAH's responses submitted to the CHMP on:	18 January 2013
Rapporteur's preliminary assessment report on the MAH's responses circulated on:	13 March 2013
3rd Request for supplementary information and extension of timetable adopted by the CHMP on:	21 March 2013
MAH's responses submitted to the CHMP on:	27 March 2013
Rapporteur's assessment report on the MAH's responses circulated on:	12 April 2013
CHMP opinion:	25 April 2013

The CHMP adopted a report on similarity of Revlimid with azacitidine on: (Appendix 1)	25 April 2013
The CHMP adopted a report on the significant clinical benefit for Revlimid in comparison with existing therapies on: (Appendix 2)	25 April 2013

2. Scientific discussion

2.1. Introduction

About the disease

Myelodysplastic syndromes are a heterogeneous group of acquired clonal hematopoietic stem cell disorders that are characterised by anaemia, varying degrees of other cytopenias, and dysplasia usually in the presence of normocellular or hypercellular bone marrow (BM). They are primarily a disease of the elderly with a median age of onset between 65 and 76 years. The incidence of MDS in Europe and the US is approximately 3 to 4/100,000 per year and rises sharply above the age of 60 years, reaching up to 50/100,000 per year. The incidence of MDS is greater in men than in women.

Based on the available epidemiologic information, deletion of the long arm of chromosome 5 (5q deletion or del (5q) lesion), partial or complete, is present in 10% to 15% of patients with primary MDS and is the most frequently documented cytogenetic abnormality in MDS. The median age at diagnosis of MDS del (5q) is between 65 and 70 years and there is a female preponderance with a male to female ratio of 1:1.5.

Tumour protein 53 (p53) mutation is a well-recognized poor prognostic factor in high-risk MDS and AML, although p53 mutation has only recently been reported to be present in 20% to 25% of patients with low-risk MDS and del (5q) as detected via genomic sequencing.

Anaemia is the most common manifestation of MDS and is present in approximately 90% of MDS patients at the time of diagnosis. Elevated percent BM blasts reflecting the potential for increased proliferation and progression to acute myeloid leukaemia (AML) are present in 20% to 30% of patients at diagnosis but can increase over time due to disease progression. The majority of MDS patients develop a requirement for RBC transfusions which is often severe in patients with the deletion 5q (del 5q) cytogenetic abnormality.

The haematopoietic insufficiency and cytopenias of MDS lead to potentially serious morbidity (transfusion-dependent anaemia, bleeding manifestations, and infections) and mortality primarily as a consequence of infection or bleeding caused by BM failure.

Repeated transfusions may cause secondary haemochromatosis due to iron overload, resulting in increased risk of congestive heart failure, diabetes mellitus, and hepatocellular carcinoma.

Transfusion-dependent anaemia has also been shown to be a risk factor for progression to AML and reduction of overall survival (OS).

The only potentially curative approach that currently exists for treating MDS patients is allogeneic hematopoietic stem cell transplantation (HSCT). But because of morbidity/mortality and the lack of a suitable donor in older patients, this approach is only employed in younger patients with higher-risk disease.

As multiple transfusions are associated with morbidity such as secondary haemochromatosis and reduced health related quality of life (HRQoL), transfusion-dependent anaemia resulting from

ineffective haematopoiesis is the principal therapeutic challenge for patients with low- and intermediate 1 (INT-1)-risk MDS.

Other than transfusion support and iron chelation, the treatment options for low- or INT-1-risk MDS, include erythropoiesis-stimulating agents (ESAs) (EPO or darbepoetin-α) alone or in combination with granulocyte colony-stimulating factor (G-CSF); hypomethylating agents such as azacitidine; immunosuppressive therapies such as antithymocyte globulin or cyclosporin A. There are currently no treatments generally approved in EU for patients with low/INT-1 MDS. Moreover, these agents are generally ineffective in patients who require ≥ 2 RBC transfusions per month.

About the product

Lenalidomide is an immunomodulating agent. It is the lead member of a group of compounds known as the immunomodulatory drugs (IMiDs).

The lenalidomide mechanism of action includes anti-neoplastic, anti-angiogenic, pro-erythropoietic and immunomodulatory properties. Specifically, lenalidomide inhibits proliferation of certain haematopoietic tumour cells (including multiple myeloma (MM) plasma tumour cells and those with deletions of chromosome 5), enhances T cell- and Natural Killer (NK) cell-mediated immunity and increases the number of NK T cells, inhibits angiogenesis by blocking the migration and adhesion of endothelial cells and the formation of microvessels, augments foetal haemoglobin production by CD34+ haematopoietic stem cells, and inhibits production of pro-inflammatory cytokines (e.g., TNF-α and IL-6) by monocytes.

Lenalidomide has shown direct cytotoxicity and/or anti-proliferative effects on the MDS del (5q) clone. In addition, lenalidomide induces apoptosis through inhibition of cytokinesis. Moreover, proerythropoietic effects, immunomodulatory properties, and antiangiogenic activities of lenalidomide are also of relevance for MDS pathogenesis.

Lenalidomide was designated as an orphan medicinal product, EU/3/04/192, on 8 March 2004, for the following indication: Treatment of myelodysplastic syndromes.

Revlimid (lenalidomide) has been granted a marketing authorisation on June 2007 through the centralised procedure in the indication “Revlimid is indicated in combination with dexamethasone for the treatment of multiple myeloma (MM) patients who have received at least one prior therapy”.

The scope of this variation is to add the following new indication to Revlimid (lenalidomide):

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

Revlimid treatment should be supervised by a physician experienced in the use of anti-cancer therapies.

Lenalidomide treatment must not be started with Absolute Neutrophil Counts (ANC) < 0.5 x 10^9/l and/or platelet counts < 25 x 10^9/l.

The recommended starting dose of lenalidomide is 10 mg orally once daily on days 1-21 of repeated 28-day cycles. Dosing is continued or modified based upon clinical and laboratory findings.

2.2. Quality aspects

The proposed new myelodysplastic syndromes (MDS) indication will require the use of Revlimid 10 mg strength for initial recommended dose and 5 mg, and 2.5 mg strengths for dose reduction steps.

2.3. Non-clinical aspects

2.3.1. Introduction

To support this type II variation, the non-clinical dossier was updated to present the pharmacology of lenalidomide with particular emphasis on the mechanism of action (MOA) in del(5q) MDS. The nonclinical pharmacokinetics and toxicology data submitted and approved for lenalidomide in multiple myeloma (MM) also supports the use of lenalidomide in MDS. Therefore, the MAH cross-referred to the existing nonclinical PK and toxicology data previously submitted for approval of the MM application. In addition, an updated Environmental Risk Assessment (ERA) was submitted.

2.3.2. Pharmacology

The MAH submitted 65 published articles and 1 MAH-sponsored study to support the use of Revlimid for the treatment of patients with transfusion-dependent anaemia due to low- or intermediate-1-risk MDS associated with an isolated deletion 5q cytogenetic abnormality.

In MDS (del (5q)), lenalidomide was shown to selectively inhibit the abnormal clone by increasing the apoptosis of del (5q) cells. The sensitivity to lenalidomide in MDS del (5q) can, at least in part, be explained by the up-regulation of several tumour suppressor genes (e.g. SPARC, p21, RPS14) which have reduced expression due to haplo-insufficiency caused by del (5q).

(1) Antineoplastic effects

The ability of lenalidomide to induce complete cytogenetic responses in patients with del(5q) MDS (Ades, 2009; Fenaux, 2009; List, 2006) is most likely due to its ability to target the del(5q) clone directly. The antineoplastic effects of lenalidomide against chromosome 5-deleted hematopoietic tumours have been reported for del(5q) MDS patient cells (Gaidarova, 2008; Pellagatti, 2007; Ramsay, 2008), del(5q) AML patient cells (Wei, 2009), and various other hematopoietic tumour cell lines harbouring deletions in chromosome 5 (Gandhi, 2006). The mechanism of this tumoricidal activity in general involves cell cycle arrest in G0–G1 and/or G2– M phases, followed by apoptosis. Common features include the induction of tumour suppressor genes and the inhibition of genes or proteins required for cell cycle progression and proliferation.

Lenalidomide was shown to inhibit the growth of differentiating del(5q) erythroblasts from MDS patients, but did not affect cytogenetically normal cells from healthy donors (Pellagatti, 2007). A report evaluating baseline and post-treatment bone marrow cells of del(5q) MDS patients treated with lenalidomide demonstrated increased apoptosis in CD34+ del(5q) progenitor cells, with a concomitant expansion in erythroid progenitors (Ximeri, 2010). An increased expression of adhesion molecules on the remaining CD34+ cells was observed post-treatment, as well as increased soluble stromal derived factor-1 alpha (SDF-1α) and inter-cellular adhesion molecule 1 (ICAM-1), suggesting recovery and maintenance of the CD34+ cells through interactions between the hematopoietic and stromal cells. Thus, a significant component of the effects seen with lenalidomide on del(5q) cells is due to selective growth inhibition and direct cytotoxicity against the malignant clone.

Lenalidomide inhibited proliferation of various hematopoietic tumour cell lines with deletions in chromosome 5, including Burkitt's lymphoma, Namalwa, AML KG-1, AML UT-7, and the TALL Loucy cell lines (Gandhi, 2006). In Namalwa cells, G0–G1 cell cycle arrest is associated with induction of the cyclin-dependent kinase (CDK) inhibitor tumour suppressor p21WAF-1, thereby causing inhibition of CDK2, CDK4 and CDK6, and subsequent reduction in phosphorylation of the retinoblastoma protein (pRb), resulting in an inability to enter cell cycle S phase (Verhelle, 2007). The mechanism of p21WAF-1 gene induction was found to be dependent on demethylation of histone H3 protein by lysine-specific

demethylase-1 (LSD-1) (Escoubet-Lozach, 2009). Demethylation of histone H3 allows transcription factor binding to the GC-rich binding site on the p21 promoter for Sp-1 and early growth response (EGR) family members, including EGR1 and EGR2 (Escoubet-Lozach, 2009). Indeed, suppression of EGR1 expression in Namalwa cells caused a reduction in p21 expression. As EGR1 is encoded within the chromosome 5q31 locus, this mechanism of p21 induction would be sensitive to deletions in 5q31 with haploinsufficiency of the EGR1 gene. The effects of lenalidomide on EGR1 and other genes encoded on chromosome 5q are described below.

(2) Effects on genes in the 5q deleted regions

SPARC, or osteonectin, functions as a tumour suppressor gene in many malignancies. It has antiproliferative, anti-adhesive and anti-angiogenic effects, and is located in chromosome 5q31–32 (Barker, 2005; Chlenski, 2006; Framson, 2004). Homozygous knockout of SPARC in mice induced thrombocytopenia, reduced haemoglobin, and decreased erythroid colony formation (Lehmann, 2007). The decreased expression of SPARC, due to hemizygous deletion, is thought to play a role in the phenotype of 5q− syndrome. The effect of lenalidomide treatment on gene expression was studied in intermediate erythroblasts isolated from del(5q) MDS patients. The tumour suppressor gene SPARC was upregulated 4-fold in erythroid and non-erythroid cells from MDS patients; however, it was also increased in cells from patients with MDS without del(5q). Expression levels of SPARC in del(5q) clones were about half that of controls, suggesting that upregulation of SPARC by lenalidomide may correct a deficiency in these cells, resulting in an antiproliferative effect (Pellagatti, 2007). Knockdown experiments using small interfering RNA to SPARC led to significant resistance to lenalidomide treatment, further indicating that the antiproliferative effects of lenalidomide may be due in part to the upregulation of SPARC (Zhang, 2008).

Cdc25C and PP2A are phosphatases that regulate the cell cycle at the G2–M stage. Gene expression of these enzymes was shown to be lower in MDS and AML cells with del(5q) compared with those with alternate karyotypes. In order to mimic the haplodeficiency found in del(5q) cells, short hairpin RNA technology was used to reduce the Cdc25C and PP2A gene expression in U937 and primary non-del(5q) MDS cells. In cells in which Cdc25C and/or PP2A genes were knocked down, reduced expression of the phosphatases promoted sensitisation to lenalidomide. Lenalidomide was shown to inhibit the phosphatase activity, causing G1 and G2–M cell cycle arrest and an increase in apoptosis (Wei, 2009). These data indicate that decreased expression of these phosphatases in 5q deletions contributes to the preferential sensitivity of del(5q) MDS cells to lenalidomide (Wei, 2009).

EGR1 is a transcription factor that regulates key target genes, such as transforming growth factor beta 1 (TGFβ1), phosphatase and tensin homolog (PTEN), and p53, (Baron, 2006) suggesting a crucial role in tumour suppression. Additionally, it has been reported to regulate proliferation and localisation of bone marrow stem cells (Min, 2008). In a study of Burkitt's lymphoma cells with chromosome 5 monosomy, lenalidomide induced nuclear transport and transcriptional activation of EGR1 in a dose-dependent manner (Gandhi, 2007). The activity was possibly related to the level of EGR1 expression, which may explain why del(5q) clones are particularly sensitive to lenalidomide. In the del(5q) MDS cell line MDS-L, EGR1 expression was increased 11.5-fold by lenalidomide treatment (Matsuoka, 2010). Lenalidomide has also been shown to induce expression of EGR1 in multiple myeloma (MM) cell lines and patient-derived MM cells (Gandhi, 2010). Therefore as observed with SPARC, EGR1 induction by lenalidomide was not restricted to cells with defects in chromosome 5. However, the tumour-suppressive effects of such gene induction events may be greater in cells with haploinsufficiency for these genes.

DIAPH1 encodes mDia1, which acts as a significant integrator of multiple 5q gene products. The mDia family of formins is tightly regulated by a Rho-controlled mechanism and act as a major template for

actin polymerization and generation (Goode, 2007). Newly generated actin filaments provide the underlying structures that drive changes in cell morphology in order to facilitate events as divergent as cell division, intracellular trafficking, and chemotaxis (Chhabra, 2007). Lenalidomide has been shown to selectively activate RhoA and Rac1 within minutes following drug exposure, resulting in enhanced F-actin formation and relocalization of membrane proteins (Gaidarova, 2009; Xu, 2009). These effects have been shown to be associated with restoration of immune synapse formation and T cell activation (Ramsay, 2008; Xu, 2009). T cell responses in the mDia1 knockout mice were studied and it was shown that Factin assembly necessary for the immune synapse formation requires mDia1 (Eisenmann, 2007). Presently, the specific effects of lenalidomide on mDia1 and how these effects may play a role in the activity of lenalidomide in del(5q) MDS are unknown.

Kinesin family member 20A (KIF20A) is normally expressed during cell cycle M phase, required for cytokinesis, and located on chromosome 5q31. In the del(5q) MDS cell line MDS-L, lenalidomide inhibited expression of KIF20A and other cell cycle M phase proteins, including non-muscle myosin heavy-chain 10, polo-like kinase 1, aurora kinase B, and citron kinase (Matsuoka, 2010). In MDS-L cells, lenalidomide inhibited cytokinesis, arrested cells in M phase, induced polyploidy and multinucleated cells, and caused apoptosis (Matsuoka, 2010).

Two microRNAs (miR-145 and miR-146a) located in the ~1.5 Mb commonly deleted region on chromosome 5q were shown to be decreased in bone marrow cells from individuals with del(5q) MDS (Starczynowski, 2010). Toll–interleukin-1 receptor domain–containing adaptor protein (TIRAP) and tumour necrosis factor receptor–associated factor-6 (TRAF6) have been identified as the targets of miR-145 and miR-146a, respectively. To determine whether the lenalidomide response of myeloid cell lines was dependent on the deletion of 5q, the sensitivity to lenalidomide was evaluated in a panel of cell lines (MDS-L, KG-1, KG-1a, UT-7, and THP-1) with varied del(5q) status (BCCA-052010Karsan). Following 48 hrs of treatment with lenalidomide (10 µM), miR-145 was upregulated in the del(5q) cell lines, MDS-L and HL-60, but not in the other cell lines, including the del(5q) cell line KG-1a. MicroRNA-146a was not significantly regulated. In addition to miR-145, miR-143 and miR-16 were uniquely upregulated in MDS-L and HL-60 cells. While the miRNA response to lenalidomide did not correspond to the del(5q) status in all cell lines, the miRNA response to lenalidomide did correlate with growth arrest/cell death induced by lenalidomide (BCCA-05, Karsan 2010).

(3) Other effects

The MAH submitted a literature review showing that lenalidomide also has:

- pro-erythropoietic effects;
- immunomodulatory effects;
- anti-inflammatory effects;
- anti-angiogenic effects.

2.3.3. Ecotoxicity / environmental risk assessment

Lenalidomide (REVLIMID)			
CAS-number: 191732-72-6			
PBT screening		Result	**Conclusion**

Bioaccumulation potential- log K_{ow}	Report no. APN 148	- 0.34	Potential PBT: no
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{SURFACEWATER}$	0.003	µg/L	< 0.01 threshold

Revlimid is currently authorised for the treatment of MM, and the present type II variation aims at extending the indication to MDS patients. The MAH calculated a Phase I $PEC_{SURFACEWATER}$ for each indication. The total phase I $PEC_{SURFACEWATER}$ covering both indications is the sum of each individual $PEC_{SURFACEWATER}$. Default values were considered for WASTEWinhab (200 L/inh/day) and Dilution (10), whereas for each indication the MAH determined the DOSEai and Fpen parameters.

(1) Fpen determination

The Fpen of lenalidomide for treatment of MM was considered to be 0.00023. The Fpen value for the MM indication is not documented at all. It corresponds to the prevalence of MDS cited in the EU orphan drug designation of lintuzumab (2.3/10,000 → Fpen = 0.00023). As such this value is not acceptable since it is not justified. According to Orphanet's "Prevalence of rare disease: bibliographic data" published in November 20111, the prevalence of MM in Europe reaches 1.75/10,000. Therefore, a Fpen of 0.0002 could be used for MM indication. There is no data which indicate when 2 orphan indications are involved for the same product, the "default orphan Fpen" (0.0005) should not be taken into account for each indication.

(2) DOSEai determination

The recommended maximal daily dose for the treatment of MM is 25 mg/day from days 1-21 of repeated 28-day cycles. For the treatment of MDS, the maximal daily dose reaches 10 mg/day to be administered from days 1-21 of repeated 28-day cycles. DOSEai values were obtained for each indication by averaging the doses over the 28-day period. More precisely:

- $DOSEai_{MDS}$ = 10 x (21/28) = 7.5 mg/day
- $DOSEai_{MM}$ = 25 x (21/28) = 18.75 mg/day

(3) PECSURFACEWATER determination

$$PEC_{SW} = \frac{DOSEai \times Fpen}{WASTEWinhab \times DILUTION}$$

$$PEC_{SWtotal} = PEC_{SWMM} + PEC_{SWMDS}$$

	MM	MDS
DOSEai (mg/day)	18.75	7.5
Fpen	0.00023	0.0003
WASTEWinhab (L/day)	200	200

[1] http://www.orpha.net/orphacom/cahiers/docs/GB/Prevalence_of_rare_diseases_by_alphabetical_list.pdf

DILUTION	10	10
PEC_{SW} individual indication (µg/L)	0.0022	0.0011
$PEC_{SW\ total}$ (µg/L)	0.0033	

The $PEC_{SURFACEWATER}$ is estimated to be 0.0033 µg/L, well below the action limit of 0.01 µg/L that triggers a Phase II assessment. Use of the standard action limit is not contraindicated by any specific concerns such as bioaccumulation (low Kow), or predicted atypical ecotoxicity (lenalidomide is not genotoxic, the NOAEL is the most sensitive species reached 1 mg/kg/day, and doses of 25 mg/day inducing Cmax values approximately 130,000-fold above the calculated $PEC_{SURFACEWATER}$ are generally well-tolerated in patients.

Even using a worst-case scenario with Fpen reaching 0.0005 for each indication, and non-averaged daily dose levels as DOSEai parameters (i.e. 25 mg/day and 10 mg/day for MM and MDS, respectively), the total PECSW would reach 0.0088 µg/L which is still lower than the action limit (0.01 µg/L). Therefore, the predicted surface water concentration for lenalidomide indicates that its use in the proposed indication, in addition to the currently approved indication, should pose a negligible risk to the environment.

2.3.4. Discussion on non-clinical aspects

An extensive review of the pharmacology of lenalidomide was submitted by the MAH. Although the mechanism of action underlying the effect of lenalidomide is not fully characterised, the available data is considered as sufficient to establish proof-of-concept for the treatment of MDS del(5q) patients with lenalidomide. In MDS, Del 5q, lenalidomide was shown to selectively inhibit the abnormal clone by increasing the apoptosis of Del 5q cells.

The MAH cross-refers to the existing nonclinical PK and toxicology previously submitted for the approval of the MM application.

In view of the therapeutic indication, the lack of carcinogenicity studies was considered acceptable by the CHMP at the time of approval. This is in line with the ICH S9 guideline which mentions that carcinogenicity studies are not warranted to support marketing for the therapeutics intended to treat patients with advanced cancer. However, there are clinical concerns related to the occurrence of secondary primary malignancies in patients (see section on Clinical Safety). The mechanism underlying these lesions is not known, although it is likely to be epigenetic since lenalidomide was shown to be non-genotoxic in an ICH-compliant battery of tests. Therefore, no further information is to be gained from conducting carcinogenicity studies in animals.

Since exposure of MDS del(5q) patients to lenalidomide is not expected to be higher than that of MM patients, it is considered that cross-reference to the existing non-clinical data previously submitted for approval of MM application (notably pharmacokinetic, repeat-dose toxicity, genotoxicity, and reproduction toxicity studies) is acceptable.

Revlimid is considered to pose a negligible risk to the environment.

2.3.5. Conclusion on the non-clinical aspects

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

The main non-clinical findings are appropriately reflected in section 5.3 of the SmPC.

The most important identified risk with lenalidomide related to non-clinical findings is that of teratogenicity. Based on the review of the data on nonclinical aspects, the following statements to address the potential risk of lenalidomide in pregnant women have previously been included in section 4.6 of the SmPC:

Lenalidomide is structurally related to thalidomide. Thalidomide is a known human teratogenic active substance that causes severe life-threatening birth defects.

Lenalidomide induced in monkeys malformations similar to those described with thalidomide. Therefore, a teratogenic effect of lenalidomide is expected and lenalidomide is contraindicated during pregnancy.

Moreover, extensive additional risk minimisation activities including a pregnancy prevention programme, a controlled distribution system, a Direct Healthcare Professional Communication and patient cards are established in each EU member state prior to market launch of the medicinal product.

2.4. Clinical aspects

The present submission is based on one Phase 3 double-blind (DB) placebo-controlled study with an open-label (OL) phase (MDS-004); four Phase 2 OL studies (MDS-003, MDS-001, MDS-002, MDS-007), and one pharmacokinetic study (PK-002). MDS-004 and MDS-003 are considered the pivotal studies. MDS-001, MDS-007 and PK-002 are submitted as supportive studies.

As this submission was made in support of the use of lenalidomide for the treatment of patients with transfusion-dependent anaemia due to low- or INT-1-risk MDS associated with a del (5q) cytogenetic abnormality, with or without additional cytogenetic abnormalities, and MDS-002 enrolled MDS patients without the del [5q] abnormality), the data from MDS-002 were not included in the overall analysis of efficacy.

The clinical formulations of lenalidomide (Revlimid 5 mg and 10 mg capsules) used in the MDS clinical studies are the same as the marketed formulations. The 5-mg and 10-mg lenalidomide capsules are approved and available.

The new dosage strength, 2.5 mg capsule, has been developed for dose reduction in MDS patients. The 2.5-mg lenalidomide capsule uses the same formulation as the currently approved 5 mg and 10 mg capsules. The in vitro dissolution profile of the 2.5 mg capsule is similar to that of the 5 mg and 10 mg capsules. The 2.5-mg lenalidomide capsules have demonstrated bioequivalence to the 5-mg lenalidomide capsules in humans (CP-010), but were not yet available for use in the clinical efficacy and safety studies in this submission. Based on the in vitro and in vivo biopharmaceutical evidence and the linear PK of lenalidomide, the plasma exposure of lenalidomide at the 2.5 mg dose is expected to be proportional relative to the higher doses.

2.4.1. Introduction

GCP

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

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

- Tabular overview of clinical studies

Table 1: Overview of MDS 001, 002, 003,004, 007 and PK 002 studies

	MDS-004 (N = 205)[a]	MDS-003 (N = 148)[b]	MDS-001 (N = 45)	MDS-002 (N = 215)	MDS-007 (N = 11)	PK-002 (N = 40)
No. of subjects treated with lenalidomide	194	148	45	215	11	39
Phase of study	3	2	2	2	2	1/2
Subject population	IPSS low or INT-1 del (5q31-33) RBC transfusion-dependent	IPSS low or INT-1 del (5q31-33) RBC transfusion-dependent	RA, RARS, RAEB, RAEB-T, or CMMoL With or without del (5q)[c]	IPSS low or INT-1 without del (5q) RBC transfusion-dependent	IPSS low or INT-1 del (5q31-33) RBC transfusion-dependent or symptomatic anemia	IPSS low or INT-1 RBC transfusion-dependent or symptomatic anemia With or without del (5q)[c]
Placebo control arm	Yes	No	No	No	No	No
Dose regimen(s)	10 mg QD (21/28 days) 5 mg QD (28/28 days)	10 mg QD (21/28 days) 10 mg QD (28/28 days)	10 mg QD (21/28 days) 10 mg QD (28/28 days) 25 mg QD (28/28 days)	10 mg QD (21/28 days) 10 mg QD (28/28 days)	10 mg QD (21/28 days)	10 mg QD (28/28 days) 15 mg QD (28/28 days)
Primary purpose of study	Primary efficacy, confirmatory	Primary efficacy	Pilot, dose-finding, supportive efficacy	Primary efficacy[d]	Supportive efficacy	Primary PK, safety, and efficacy
Primary efficacy endpoint	RBC TI (≥ 182 days)	RBC TI (≥ 56 days)	Erythroid response (major and minor)	RBC TI	Erythroid response (major and minor)	PK parameters
Primary comparisons	10 mg QD (21/28 days) vs placebo 5 mg QD (28/28 days) vs placebo	NA	NA	NA	NA	del (5q) vs non-del (5q)

21/28 days = Days 1 to 21 of 28-day cycles; 28/28 days = Days 1 to 28 of 28-day cycles; CMMoL = chronic myelomonocytic leukemia; del (5q) = deletion involving the long arm of chromosome 5; INT-1 = Intermediate-1; IPSS = International Prognostic Scoring System; MDS = myelodysplastic syndromes; NA = not applicable; PK = pharmacokinetic; RA = refractory anemia; RAEB = refractory anemia with an excess of blasts; RAEB-T = refractory anemia with excess blasts in transformation; RARS = refractory anemia with ringed (or ring) sideroblasts; RBC = red blood cell; RBC TI = red blood cell transfusion independent; QD = once daily.

[a] Data cutoff date of 14 Jun 2011.

[b] Last available follow-up data for MDS-003E/MDS-009 were collected in 2010, data cutoff date of 01 Oct 2010.

[c] MDS-001: del 5(q) = 13 subjects and non-del (5q) = 32 subjects; PK-002: del 5(q) = 7 subjects and non-del (5q) = 33 subjects.

[d] Clinical data have revealed differences in outcome in MDS patients treated with lenalidomide, depending on the presence or absence of a del (5q) cytogenetic abnormality; therefore, the MDS-002 study, conducted in subjects without the del (5q) cytogenetic abnormality, is provided in support of safety only in the SCS.

Source: Report MDS-001, Report MDS-002, Report MDS-003, Report MDS-004, Report MDS-007, and Report PK-002.

2.4.2. Pharmacokinetics

For the approved multiple myeloma (MM) indications, the normal dose of lenalidomide is 25 mg daily on day 1-21 of repeated 28-day cycles. For the new MDS indication the recommended dose is 10 mg once daily on days 1-21 of repeated 28-day cycles.

Revlimid is currently available as 2.5mg, 5 mg, 7.5mg, 10 mg, 15 mg and 25 mg capsules (the 7.5 mg, 15 mg and 25 mg strengths are not intended for the MDS indication).

The pharmacokinetic data discussed by the MAH within the current application aim primarily at describing the pharmacokinetics of lenalidomide in the new patient population and to support the proposed dose adjustment in renal impairment. The latter differs from the recommendations for the multiple myeloma indications due to the lower normal dose for the MDS indication and given the development of the 2.5 mg capsule.

Two clinical pharmacology studies specific for the MDS population have been submitted with the current application:

- Study CC-5013-PK-002, a multiple dose PK and PD study of lenalidomide in MDS patients
- Study CC-5013-MDS-007, a multiple dose study to evaluate PK, efficacy and safety of lenalidomide in Japanese MDS patients

In addition, the MAH discusses data that have been previously submitted and assessed from:

- CC-5013-DMPK-007, Ex vivo protein binding of lenalidomide in plasma from patients with different renal function status
- CC-5013-PK-001, a study of lenalidomide in renal impairment
- CC-5013-PK-005, a single-dose, PK and safety study in Japanese vs. Caucasian healthy volunteers

Methods

a. Analytical methods

R- and S-lenalidomide concentrations in plasma and urine were measured by validated chiral liquid chromatography-tandem mass spectrometry (LC-MS/MS) methods. R- and S-lenalidomide concentrations in dialysate were measured using a non-validated LC-MS/MS method. Protein binding of lenalidomide was determined using a non-GLP intraday validated ultrafiltration and LC-MS/MS method.

b. Pharmacokinetic data analysis

Non-compartmental methods were used to determine pharmacokinetic parameters in the studies referred to in the current application. As the ratio between the R- and S-enantiomer has previously been shown to be unaffected by dose level, the pharmacokinetic parameters presented in the body of the study reports were for total (R+S) lenalidomide, although concentrations for the separate enantiomers had been determined.

c. Pharmacokinetics in target population

The table below summarises lenalidomide pharmacokinetic data from studies in different patient populations with a creatinine clearance above 50 ml/min:

Table 2. Comparison of lenalidomide single-dose pharmacokinetic parameters across studies

Parameter	CLcr ≥ 50 mL/min		
	CC-5013-PK-001 (Renal Study Subjects) (N = 11)	1398/271 and 1398/272 (MM Subjects)[a] (N = 36)	CC-5013-PK-002 (MDS Subjects)[a] (N = 12)
Age (year)	61 (42-76)	59 (40-71)	70 (47-85)
CLcr (mL/min)	70 (54-140)	99 (57-155)	66 (53-146)
AUC_{∞} (ng•h/mL)	2320 (35.5)	2178 (30.0)	2334 (32.6)
C_{max} (ng/mL)	617 (33.4)	490 (34.5)	448 (33.5)
t_{max} (h)	1.0 (0.5-2)	1.0 (0.42-4)	1.0 (0.5-2)
CL/F (mL/min)	180 (35.5)	191 (30.0)	179 (32.6)
$t_{1/2}$,z (h)	3.48 (21.1)	3.21 (20.9)	3.72 (19.5)
Vz/F (L)	54 (28.4)	54 (29.7)	57 (30.3)

a: AUC_{∞} and C_{max} are normalized to the levels at 25 mg lenalidomide.
Geometric mean (CV%) data are presented for all parameters except that Median (min – max) are presented for Age, CLcr and t_{max}. AUC = area under the concentration versus time curve; AUC_{∞} = AUC from time zero extrapolated to infinity; CLcr = baseline creatinine clearance, estimated by Cockcroft-Gault equation; CL/F = apparent total clearance; C_{max} = maximum concentration; $t_{1/2}$,z = terminal half-life; t_{max} = time to reach C_{max}; Vz/F = apparent volume of distribution during terminal phase.

Two studies on the pharmacokinetics of lenalidomide in MDS patients have been submitted with the current variation application. One study was performed in mainly Caucasian patients and the other in Japanese patients.

a) Study CC-5013-PK-002

This was a phase 1/2, open-label, single-centre, single arm, multiple-dose study primarily aiming at evaluating the pharmacokinetics of lenalidomide in patients with low- or intermediate-1-risk MDS. The study included 25 patients (23 Caucasians, 1 Caucasian/Asian, and 1 Caucasian/Hispanic). Twelve (12) patients received a single 10 mg dose of lenalidomide on Day -7. Twenty-four (24) patients, including 11 treated on Day -7, received multiple doses of lenalidomide, which began at a starting daily dose of 10 mg on Day 1 and continued with dose adjustment after Day 14. Serial sampling of blood and collection of total urine were performed after dosing for 24 hours on Day -7 and for 5 hours on Day 14. Afterwards, blood samples were collected at predose and 1 hour postdose every 28 days. On the PK visit days, the patients were dosed under fasted conditions.

Following a single 10 mg oral dose, lenalidomide was rapidly absorbed and eliminated, with the median tmax occurring around 1 hour postdose and the mean t1/2,z being approximately 4 hours. Urinary excretion of unchanged lenalidomide in 24 hours postdose averaged approximately 65% of the administered dose.

Multiple dosing (10 mg QD for 14 days) did not cause lenalidomide accumulation in plasma, with the limited 5-hour pharmacokinetic profile on Day 14 comparable to that observed at a single dose (Day -7). In 11 patients treated on both Days -7 and Days 1 to14, mean drug accumulation ratios, as measured by comparing the Cmax and AUC_{5hr} values of Day -7 and Day 14, were close to 1. In addition, mean dose-normalised plasma lenalidomide concentrations at 1 hour postdose were relatively stable for up to 280 days.

In the subjects with mild renal impairment (50 ≤ CLcr ≤ 80 mL/min; N=7), the mean drug exposure (Cmax and AUC∞) after a single dose was approximately 50% higher compared with the patients with normal renal function (CLcr > 80 mL/min; N=5). However, after multiple dosing for 14 days, significant difference was not observed in the limited 5-hour pharmacokinetics of lenalidomide between the two groups of MDS patients. In two patients with moderate renal impairment (30 ≤ CLcr < 50 mL/min), the 5-hour exposure (AUC) on Day 14 was increased by more than 70%, compared with the patients with normal renal function.

Overall, the study demonstrated rapid absorption and elimination of lenalidomide as well as a lack of lenalidomide accumulation in plasma upon repeated administration of daily 10 mg lenalidomide dose to MDS patients. These characteristics are consistent with those observed in previous studies in healthy patients. Mild RI appeared to have a negligible effect on the multiple-dose exposure of lenalidomide while moderate RI increased this exposure considerably.

b) Study CC-5013-MDS-007

This was a Phase 2, open-label, multicenter, single arm, multiple-dose study conducted to evaluate the safety, PK, and efficacy of lenalidomide in Japanese patients with low- or intermediate-1- risk MDS. Patients were administered lenalidomide at 10 mg QD on Days 1-21 of each 28-day cycle. The pharmacokinetics of lenalidomide was assessed in seven patients during the first five days of the treatment. Fasting prior to dosing was not required in this study. Serial sampling of blood was performed after dosing for 24 hours on Days 1 and 4 and at predose on Day 3.

Following lenalidomide administration, the median tmax was approximately 2.5 and 2.9 hours on Days 1 and 4, respectively. The slightly longer Tmax value in this study, as compared with Study CC-5013-PK-002 above, was suggested due to the non-fasting condition in this study.

Multiple doses (10 mg, QD x 4 days) did not cause lenalidomide accumulation in plasma, with the mean plasma exposure (Cmax and AUC_{tau}) comparable to that observed at a single dose. On both Days 1 and 4, lenalidomide was rapidly eliminated from the plasma with a mean t1/2,z of 3.3 to 3.6 hours and a mean CL/F of 190 mL/min. In addition, there was no meaningful difference in Vz/F of lenalidomide between Day 1 and Day 4.

In conclusion, the multiple-dose pharmacokinetics of lenalidomide in Japanese MDS patients was characterised by rapid elimination and a lack of drug accumulation, which was similar to that observed in Caucasian patients.

2.4.2.1. Special populations

a) Impaired renal function

The previously submitted study CC-5013-PK-001 in renal impairment (RI) was a single-dose study in 30 subjects (otherwise healthy) that were recruited into five different groups: Normal renal function (CLcrea >80 ml/min), mild RI (50-80 ml/min), moderate RI (30-49 ml/min), severe RI (< 30 ml/min but not on dialysis) and end-stage renal disease (ESRD) requiring dialysis. Subjects with normal renal function, mild, moderate or severe RI received a single 25-mg oral dose of lenalidomide under fasting condition on Day 1 of the study. Subjects with ESRD received two single 25 mg doses which were separated by at least 7 days. One dose was given on a non-dialysis day. The other dose was given on a dialysis day, 3 hours before a 4-hour haemodialysis period.

The results demonstrated that the differences in exposure between normal renal function and mild RI groups were minor to modest (<32%). Patients with moderate and severe RI had on average an 2.6-fold and 3.5-fold increase in AUC, a 3-fold increase in t1/2,z, and a 65% to 74% decrease in CL/F

compared to subjects with normal renal function. On a non-dialysis day, patients with ESRD had a 4.8-fold increase in AUC, 4.8-fold increase in t1/2, and an 80% decrease in CL/F compared to subjects with normal renal function. The mean dialysis clearance was estimated to be 146 mL/min. As a result, the percentage of lenalidomide in the body removed by a 4-hour hemodialysis was 31%. The t1/2,z value was unchanged on dialysis days compared to non-dialysis days (~16 hours) (Table 3 and 4).

Table 3. Pharmacokinetic parameters (geometric mean and CV%) for total lenalidomide in renally impaired subjects after a 25 mg dose (Study CC-5013-PK-001)

PK Parameter	Renal Function Group					
	Normal RF (N = 7)	Mild RI (N = 5)	Moderate RI (N = 6)	Severe RI (N = 6)	ESRD off HD (N = 6)	ESRD on HD (N = 6)
C_{max} (ng/mL)	568 (39)	684 (16)	568 (33)	761 (11)	538 (25)	370 (32)
t_{max} (h)	1.00 (0.5- 2.0)	1.00 (1.0-1.0)	1.00 (0.5-1.5)	1.50 (0.5-2.0)	1.25 (1.0-2.0)	2.00 (0.5-6.0)
AUC_t (ng•h/mL)	1977 (32)	2514 (37)	5668 (14)	7766 (19)	10346 (19)	6238 (17)
AUC_∞ (ng•h/mL)	2091 (32)	2627 (36)	5964 (16)	8088 (18)	10958 (19)	6776 (14)
CL/F (mL/min)	199 (32)	159 (36)	70 (16)	52 (18)	38 (19)	62 (14)
Vz/F (L)	56 (30)	50 (25)	60 (30)	40 (20)	51 (17)	85 (15)
$t_{1/2},z$ (h)	3.26 (23)	3.61 (20)	9.97 (44)	8.93 (29)	15.5 (7)	16.0 (11)
Urine Excretion (% dose)	84* (10)	69 (12)	38 (48)	43 (28)	NA	NA
CL_r (mL/min)	159* (36)	109 (36)	27 (63)	22 (44)	NA	NA

Geometric mean (CV%) data are presented for all parameters except that median (min – max) are presented for t_{max}.
AUC = area under the concentration versus time curve; AUC_∞ = AUC from time zero extrapolated to infinity; AUC_t = AUC from time zero to the time for the last observable concentration; CL/F = apparent total clearance; C_{max} = maximum concentration; CL_r = renal clearance; HD = hemodialysis; NA = not applicable; RF = renal function; RI = renal impairment; $t_{1/2},z$ = terminal half-life; t_{max} = time to reach C_{max}; Vz/F = apparent volume of distribution during terminal phase.
*N = 6

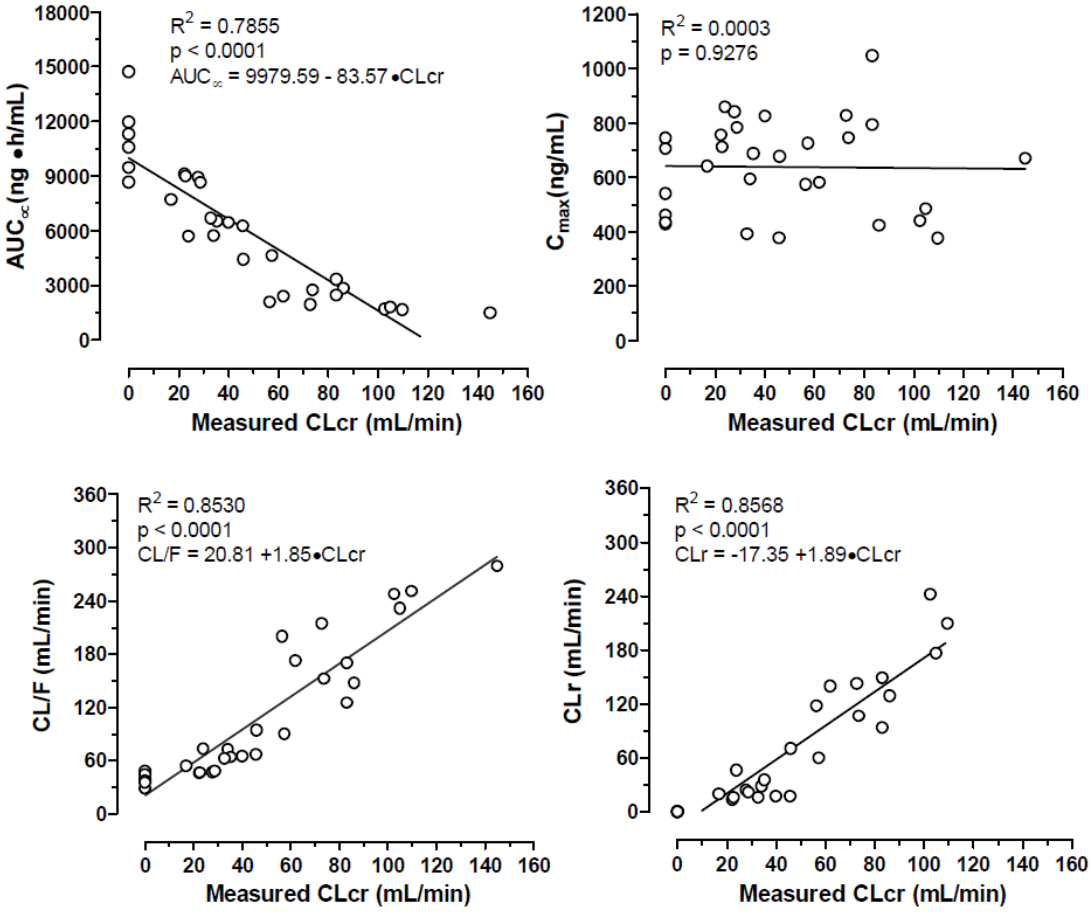
Urinary excretion of unchanged total lenalidomide was mostly completed by 24 hours postdose in all groups of subjects. Thus, the urine collection period was adequate in subjects with varying RI. Subjects with normal renal function had higher mean % dose excreted unchanged (85%), followed by subjects with mild RI (69%), subjects with moderate RI (42%), and subjects with severe RI (44%). Subjects with ESRD were not included in this analysis as they were anuric.

Table 4. Geometric mean ratio (90% CI) for lenalidomide exposure between renal function groups

Renal Function	Measured CLcr	%Geometric mean ratio (90% CI) Test/Ref = RI/(Normal + Mild RI)	
		AUC_{∞}	C_{max}
Normal + Mild	CLcr ≥ 50 mL/min	100	100
Moderate RI	30 ≤ CLcr < 50 mL/min	259 (209, 322)	93 (73, 117)
Severe RI	CLcr < 30 mL/min, not requiring dialysis	352 (284, 436)	124 (98, 157)
ESRD (off dialysis)	Requiring dialysis	477 (384, 591)	88 (70, 111)

Highly significant linear relationships were observed between AUC∞, AUCt, t1/2,z, CL/F, or CLr, and the measured CLcr. CL/F and CLr decreased as the measured CLcr declined (Figure 1). Linear regression of CL/F and CLr against the measured CLcr produced similar slopes (1.85 and 1.89, respectively). Consistent with the changes in lenalidomide clearance, AUC∞, AUCt, and t1/2,z increased with decreasing CLcr. There were no relationships between Cmax or Vz/F and the measured CLcr determined.

Figure 1. Relationship between measured creatinine clearance and lenalidomide pharmacokinetic parameters



The AUC ratio between the S- and R-enantiomer appeared to increase slightly with worsening of renal function (Table 5).

Table 5. Effects of renal impairment on the exposure to the separate R- and S-enantiomers of lenalidomide

	AUC_∞			AUCt		
Renal Function Group*	**S/R**	**S/T**	**R/T**	**S/R**	**S/T**	**R/T**
Normal	1.27	0.56	0.44	1.28	0.57	0.44
	(0.0590)	(0.013)	(0.011)	(0.0879)	(0.026)	(0.011)
Mild RI	1.26	0.56	0.44	1.26	0.56	0.45
	(0.0734)	(0.014)	(0.014)	(0.0668)	(0.018)	(0.013)
Moderate RI	1.33	0.57	0.43	1.33	0.57	0.43
	(0.0799)	(0.014)	(0.014)	(0.0779)	(0.014)	(0.014)
Severe RI	1.35	0.58	0.43	1.36	0.58	0.43
	(0.0773)	(0.012)	(0.016)	(0.0675)	(0.015)	(0.015)
ESRD (off dialysis)	1.46	0.59	0.41	1.48	0.60	0.41
	(0.138)	(0.022)	(0.023)	(0.172)	(0.038)	(0.024)
ESRD (on dialysis)	1.40	0.58	0.42	1.43	0.60	0.42
	(0.0975)	(0.018)	(0.016)	(0.150)	(0.039)	(0.017)

Note: S = S-lenalidomide, R = R-lenalidomide, T = total lenalidomide
*Renal function groups were classified based on measured CLcr.

The *ex vivo* protein binding in plasma samples from this study, as determined by ultracentrifugation at 37ºC, was 40.15 ± 4.50, 35.37 ± 4.06, 37.16 ± 6.34, 39.77 ± 6.27 and 44.31 ± 3.92 in subjects with normal renal function, mild, moderate, and severe renal impairment, and end-stage renal disease, respectively. Thus, it was concluded that renal impairment did not significantly affect protein binding of lenalidomide.

b) Dosage recommendations

For the approved multiple myeloma (MM) indications, the normal dose of lenalidomide is 25 mg daily on day 1-21 of repeated 28-day cycles. Based on the data from study CC-5013-PK-001, no dose adjustment is recommended for mild renal impairment, while a reduction by 60% to 10 mg daily at moderate impairment, by 70% to 15 mg every other day at severe impairment and by 80% to 5 mg daily in ESRD on dialysis is recommended. For moderate and severe impairment the dose may be escalated to 15 mg daily and 10 mg daily, respectively, if the patient tolerates the treatment .

For the MDS indication the normal recommended dose is 10 mg once daily on days 1-21 of repeated 28-day cycles. The MAH proposes a reduction by 50% to 5 mg daily in moderate RI, and by 75% to 2.5 mg daily in severe RI and ESRD (Table 6).

Table 6. Dosage recommendations for lenalidomide at renal impairment in patients with multiple myeloma (previously approved recommendation) and MDS (proposed recommendation)

Renal Function (CLcr)	Dose Adjustment	
	Multiple Myeloma	Myelodysplastic Syndromes (days 1-21 of repeated 28-day cycles)
Moderate renal impairment (30 ≤ CLcr < 50 ml/min)	10 mg once daily*	5 mg once daily
Severe renal impairment (CLcr < 30 ml/min, not requiring dialysis)	15 mg every other day**	2.5 mg once daily
End Stage Renal Disease (ESRD) (CLcr < 30 ml/min, requiring dialysis)	5 mg once daily. On dialysis days, the dose should be administered following dialysis.	2.5 mg once daily. On dialysis days, the dose should be administered following dialysis.

* The dose may be escalated to 15 mg once daily after 2 cycles if patient is not responding to treatment and is tolerating the treatment.

** The dose may be escalated to 10 mg once daily if the patient is tolerating the treatment

Lenalidomide displays linear pharmacokinetics in both healthy volunteers and MM patients. Although dose proportionality was not determined in MDS patients, data analysed across studies suggest that at comparable renal function there is no difference in lenalidomide pharmacokinetics between MM and MDS patients.

The steady-state plasma lenalidomide concentration-time profiles under the daily 7.5 or 2.5 mg dosing regimen were simulated using nonparametric superposition principle. The predicted lenalidomide exposure levels (AUC and Cmax) at steady-state were subsequently estimated from the simulated steady-state concentration-time profiles by non-compartmental analysis.

The simulation suggests that the steady-state daily AUC at 2.5 mg once daily in MDS patients with severe renal impairment (836 ng•h/mL) or end stage renal disease (1121 ng•h/mL) is close to that at 10 mg once daily in patients with CLcr ≥ 50 mL/min (957 ng•h/mL) (Table 7).

Table 7: Predicted lenalidomide plasma exposure at steady state

Renal Function	Dosing Regmen (Disease)	Predicted Lenalidomide Exposure	
		$AUC_{avg\ ss}$ (ng•h/mL)	$C_{max\ ss}$ (ng/mL)
CLcr ≥ 50 mL/min	25 mg q24h (MM)	2392	556
	10 mg q24h (MDS)	957	222
CLcr < 30 mL/min, not requiring dialysis (Severe renal impairment)	15 mg q48h (MM)	2507	428
	7.5 mg q24h (MM)	2506	242
	5 mg q48h (MDS)	836	143
	2.5 mg q24h (MDS)	836	81
CLcr < 30 mL/min, requiring dialysis (End stage renal disease)	5 mg 3 times a week (MDS)	960	117
	2.5 mg q24h (MDS)	1121	78

Simulation is based on nonparametric superposition principles and the data from Study CC-5013-PK-001.
$AUC_{avg\ ss}$ = average daily AUC at the steady-state; $C_{max\ ss}$ = maximum plasma concentration at the steady-state;
MDS = myelodysplastic syndromes; MM = multiple myeloma; q24h = every 24 hours; q48h = every 48 hours.

c) Race

Study CC-5013-PK-005 was an ascending single-dose, PK and safety study in Japanese and Caucasian healthy volunteers. This study was previously submitted but is briefly mentioned here, as it was discussed in the MAH's Clinical Summary supporting the MDS indication. A total of 18 healthy subjects were enrolled in 2 groups consisting of 9 Caucasian subjects and 9 Japanese subjects. Within each group of 9 subjects, 7 received lenalidomide and 2 received matching placebo. After an overnight fast, each subject received 5, 10, and 20 mg single oral doses of lenalidomide (given as multiples of 5 mg capsules) or matching placebo on 3 occasions that were separated by a washout period of at least 5 days. Serial sampling of blood was performed after each dose for 48 hours. Lenalidomide was rapidly absorbed and eliminated, with the C_{max} being reached at a median time of 0.5 to 1 hour and t1/2,z being approximately 2.5 hours. The concentration-time profiles for the Japanese and Caucasian subjects were similar for all three lenalidomide dose levels. There were no statistically significant differences ($p > 0.05$) in the pharmacokinetic parameters between Japanese and Caucasian subjects at each dose level. Cmax and AUC∞ increased proportionally with doses from 5 mg to 20 mg in both ethnic groups.

The S/R enantiomer ratio was similar across dose levels, but appeared to be somewhat lower in Japanese than in Caucasian subjects (Table 8).

Table 8. Exposure to the enantiomers of lenalidomide after a single dose to Japanese and Caucasian healthy volunteers

Dose	**S-enantiomer AUC inf (ng*hr/ml)**		**R-enantiomer AUC_{inf} (ng*hr/ml)**		**S/R ratio**	
	Japanese (n=7)	Caucasian (n=6)	Japanese (n=7)	Caucasian (n=6)	Japanese (n=7)	Caucasian (n=6)
5 mg	185	185	161	149	1.15	1.24
10 mg	391	380	337	308	1.16	1.23
20 mg	793	775	671	631	1.18	1.23

2.4.3. Pharmacodynamics

Lenalidomide is suggested to have a pleiotropic MOA, which includes direct cytotoxicity/apoptosis and/or antiproliferative effects on the del (5q) clone, pro-erythropoietic effects, immunomodulatory properties, anti-angiogenic activities, and antineoplastic properties.

The efficacy analysis of PK-002 study is based upon data from a small subset of patients (N = 7). Lenalidomide at a dose of 10 mg QD (continuous regimen) was effective in inducing an erythroid response in patients with low- or INT-1-risk MDS associated with a del (5q) cytogenetic lesion.

There was a relatively rapid onset of erythroid response (within the first 2 cycles) and the response was durable. These data are consistent with the observations of the primary and supportive MDS studies. In addition, the erythroid response rate (major or minor) achieved during the subsequent phase (Combined Treatment Phase, in combination with rhu-EPO) was 50%, suggesting that lenalidomide plus rhu-EPO can induce an erythroid response in MDS del (5q) patients who fail to respond to lenalidomide alone or who relapse following prolonged lenalidomide monotherapy.

2.4.4. Discussion on clinical pharmacology

Rapid absorption and elimination of lenalidomide as well as a lack of accumulation in plasma upon repeated administration of 10 mg lenalidomide daily dose has been demonstrated in MDS patients. These characteristics are consistent with those observed in healthy subjects. Mild RI appeared to have a negligible effect on the multiple-dose exposure of lenalidomide while moderate RI increased this exposure considerably. These results supported a starting dose adjustment in MDS patients with moderate or greater RI.

Across-study analyses demonstrate that renal function is the most important intrinsic factor affecting PK of lenalidomide in MDS patients. Effects of different disease settings, age, or gender on systemic exposure (AUC) of lenalidomide are insignificant at comparable renal function, suggesting MDS patients do not need dose reductions simply because of their disease, age, or gender. In addition, there is no racial difference in lenalidomide PK between Caucasian and Japanese healthy volunteers as well as between Caucasian and Japanese MDS patients.

A starting dose adjustment is not recommended for MDS patients with mild RI (CLcr = 50-80 mL/min). A reduction in the starting dose is recommended for MDS patients with moderate RI, severe RI, and ESRD, because the plasma lenalidomide exposure was increased significantly and the rate of SAEs tended to increase at CLcr <50 mL/min. The dose adjustment for these patients aims at approximating the daily AUC at the steady-state following administration of daily 10 mg lenalidomide to patients with CLcr ≥50 mL/min. The proposed starting doses for these patients are predicted by simulation to reach the targeted AUC range.

For dose reduction in MDS patients, the 2.5-mg QD dose and the 2.5-mg every other day dose are proposed to replace the step-down dose regimens of 5 mg every other day and 5 mg twice a week, respectively.

2.4.5. Conclusions on clinical pharmacology

The clinical pharmacology programme of Revlimid was considered acceptable.
The recommended starting dose of lenalidomide is 10 mg orally once daily on days 1-21 of repeated 28-day cycles. Dosing is continued or modified based upon clinical and laboratory findings. Dose adjustments, as summarised below, are recommended to manage grade 3 or 4 neutropenia or thrombocytopenia, or other grade 3 or 4 toxicity judged to be related to lenalidomide.

Dose reduction steps

Starting Dose	10 mg once daily on days 1-21 every 28 days
Dose Level -1	5.0 mg once daily on days 1-28 every 28 days
Dose Level -2	2.5 mg once daily on days 1-28 every 28 days
Dose Level -3	2.5 mg every other day 1-28 every 28 days

For patients who are dosed initially at 10 mg and who experience thrombocytopenia or neutropenia:

Thrombocytopenia

When platelets	Recommended Course
Fall to < 25 x 10^9/l	Interrupt lenalidomide treatment
Return to ≥ 25 x 10^9/l - < 50 x 10^9/l on at least 2 occasions for ≥ 7 days or when the platelet count recovers to ≥ 50 x 10^9/l at any time	Resume lenalidomide at next lower dose level (Dose Level -1, -2 or -3)

Neutropenia

When neutrophils	Recommended Course
Fall to < 0.5 x 10^9/l	Interrupt lenalidomide treatment
Return to ≥ 0.5 x 10^9/l	Resume lenalidomide at next lower dose level (Dose Level -1, -2 or -3)

For other grade 3 or 4 toxicities judged to be related to lenalidomide, treatment should be stopped and restarted at next lower dose level when toxicity has resolved to ≤ grade 2 depending on the physician's discretion.

Lenalidomide interruption or discontinuation should be considered for grade 2 or 3 skin rash. Lenalidomide must be discontinued for angioedema, grade 4 rash, exfoliative or bullous rash, or if Stevens-Johnson syndrome or toxic epidermal necrolysis is suspected, and should not be resumed following discontinuation from these reactions.

Patients without at least a minor erythroid response within 4 months of therapy initiation, demonstrated by at least a 50% reduction in transfusion requirements or, if not transfused, a 1g/dl rise in haemoglobin, should discontinue lenalidomide treatment.

The pharmacokinetics of lenalidomide was studied in subjects with renal impairment due to nonmalignant conditions. In this study, two methods were used to classify renal function: the urinary creatinine clearance measured over 24 hours and the creatinine clearance estimated by Cockcroft-Gault formula. The results indicate that as renal function decreases (< 50 ml/min), the total drug clearance decreases proportionally resulting in an increase in AUC. The AUC was increased by approximately 2.5, 4 and 5-fold in subjects with moderate renal impairment, severe renal impairment, and end-stage renal disease, respectively, compared to the group combining subjects with normal renal function and subjects with mild renal impairment. The half-life of lenalidomide increased from approximately 3.5 hours in subjects with creatinine clearance > 50 ml/min to more than 9 hours in subjects with reduced renal function < 50 ml/min. However, renal impairment did not alter the oral absorption of lenalidomide. The C_{max} was similar between healthy subjects and patients with renal impairment. Approximately 30% of the drug in the body was removed during a single 4-hour dialysis session. Dose adjustments in patients with impaired renal function were recommended as follows:

Renal Function (CLcr)	**Dose Adjustment**	
Moderate renal impairment (30 ≤ CLcr < 50 ml/min)	Starting dose	5 mg once daily (days 1-21 of repeated 28-day cycles)
	Dose level -1	2.5 mg once daily (days 1-28 of repeated 28-day cycles)
	Dose level -2	2.5 mg once every other day (days 1-28 of repeated 28-day cycles)
Severe renal impairment (CLcr < 30 ml/min, not requiring dialysis)	Starting dose	2.5 mg once daily (days 1-21 of repeated 28-day cycles)
	Dose level -1	2.5 mg every other day (days 1-28 of repeated 28-day cycles)
	Dose level -2	2.5 mg twice a week (days 1-28 of repeated 28-day cycles)
End Stage Renal Disease (ESRD) (CLcr < 30 ml/min, requiring dialysis)	Starting dose	2.5 mg once daily (days 1-21 of repeated 28-day cycles)
	Dose level -1	2.5 mg every other day (days 1-28 of repeated 28-day cycles)

On dialysis days, the dose should be administered following dialysis.	Dose level -2	2.5 mg twice a week (days 1-28 of repeated 28-day cycles)

2.5. Clinical efficacy

The studies supporting the efficacy of lenalidomide at a starting dose of 10 mg once daily (QD) on Days 1 of 21 of each 28-day cycle (cyclic regimen) for the treatment of transfusion-dependent anaemia due to low- or INT-1-risk MDS associated with a deletion 5q cytogenetic abnormality with or without additional cytogenetic abnormalities, are summarised as follows:

Pivotal studies:	MDS-003 (including long-term follow-up as part of the extension protocol MDS-003E/MDS-009)
	MDS-004
Supportive studies:	MDS-001: Phase II dose-finding study also aiming at identification of subpopulations of patients with MDS who respond to lenalidomide
	MDS-007: Single arm study in Japanese patients
Other study:	PK-002: Phase I/II clinical pharmacology study

Additional supportive data are provided by the available post-marketing data and national off-label use Named Patient Programmes.

Ongoing MDS-005 study: Multicenter, randomised, double-blind, placebo-controlled, parallel-group Phase 3 study of lenalidomide vs placebo in patients with RBC transfusion-dependent anemia due to low- or INT-1-risk MDS without del (5q) and unresponsive or refractory to erythropoietin-stimulating agents (99 patients randomised). As this study is ongoing and the study remains blinded, data are not included in the application, with the exception of the description of 4 reports of second primary malignancies (SPMs).

The MDS-002 study evaluated the efficacy of lenalidomide in patients with RBC transfusion-dependent anemia due to low- or INT-1-risk MDS *without* an associated del (5q) cytogenetic abnormality. Clinical data have revealed differences in outcome in MDS patients treated with lenalidomide, depending on the presence or absence of a del (5q) cytogenetic abnormality; therefore, the MDS-002 study is provided in support of safety only.

Table 9. Overview of Studies

	MDS-004 (N = 205)[a]	MDS-003 (N = 148)[b]	MDS-001 (N = 45)	MDS-002 (N = 215)	MDS-007 (N = 11)	PK-002 (N = 40)
No. of subjects treated with lenalidomide	194	148	45	215	11	39
Phase of study	3	2	2	2	2	1/2
Subject population	IPSS low or INT-1 del (5q31-33) RBC transfusion-dependent	IPSS low or INT-1 del (5q31-33) RBC transfusion-dependent	RA, RARS, RAEB, RAEB-T, or CMMoL With or without del (5q)[c]	IPSS low or INT-1 without del (5q) RBC transfusion-dependent	IPSS low or INT-1 del (5q31-33) RBC transfusion-dependent or symptomatic anemia	IPSS low or INT-1 RBC transfusion-dependent or symptomatic anemia With or without del (5q)[c]
Placebo control arm	Yes	No	No	No	No	No
Dose regimen(s)	10 mg QD (21/28 days) 5 mg QD (28/28 days)	10 mg QD (21/28 days) 10 mg QD (28/28 days)	10 mg QD (21/28 days) 10 mg QD (28/28 days) 25 mg QD (28/28 days)	10 mg QD (21/28 days) 10 mg QD (28/28 days)	10 mg QD (21/28 days)	10 mg QD (28/28 days) 15 mg QD (28/28 days)
Primary purpose of study	Primary efficacy, confirmatory	Primary efficacy	Pilot, dose-finding, supportive efficacy	Primary efficacy[d]	Supportive efficacy	Primary PK, safety, and efficacy
Primary efficacy endpoint	RBC TI (≥ 182 days)	RBC TI (≥ 56 days)	Erythroid response (major and minor)	RBC TI	Erythroid response (major and minor)	PK parameters
Primary comparisons	10 mg QD (21/28 days) vs placebo 5 mg QD (28/28 days) vs placebo	NA	NA	NA	NA	del (5q) vs non-del (5q)

21/28 days = Days 1 to 21 of 28-day cycles; 28/28 days = Days 1 to 28 of 28-day cycles; CMMoL = chronic myelomonocytic leukemia; del (5q) = deletion involving the long arm of chromosome 5; INT-1 = Intermediate-1; IPSS = International Prognostic Scoring System; MDS = myelodysplastic syndromes; NA = not applicable; PK = pharmacokinetic; RA = refractory anemia; RAEB = refractory anemia with an excess of blasts; RAEB-T = refractory anemia with excess blasts in transformation; RARS = refractory anemia with ringed (or ring) sideroblasts; RBC = red blood cell; RBC TI = red blood cell transfusion independent; QD = once daily.

[a] Data cutoff date of 14 Jun 2011.

[b] Last available follow-up data for MDS-003E/MDS-009 were collected in 2010, data cutoff date of 01 Oct 2010.

[c] MDS-001: del 5(q) = 13 subjects and non-del (5q) = 32 subjects; PK-002: del 5(q) = 7 subjects and non-del (5q) = 33 subjects.

[d] Clinical data have revealed differences in outcome in MDS patients treated with lenalidomide, depending on the presence or absence of a del (5q) cytogenetic abnormality; therefore, the MDS-002 study, conducted in subjects without the del (5q) cytogenetic abnormality, is provided in support of safety only in the SCS.

2.5.1. Dose response studies

The lenalidomide doses of 10 mg and 5 mg were selected based on the results of phase 2 studies (MDS-001 and MDS-003) which showed that a dose of 10 mg once daily was a safe and effective initial dose regimen, when administered either daily for 21-of-28 day cycles, or for 28-of-28 day cycles.

The 10-mg dose using the 21-of-28 day cycle was chosen because grade 4 neutropenia was reported less frequently with this regimen, while the RBC-transfusion independence rate was still comparable to

that for the 28-of-28 day cycle regimen (Study MDS-003). Study MDS -001 also demonstrated that this dose and regimen of lenalidomide produced erythroid responses in patients with low- to intermediate -1 risk.

The lower 5-mg dose (using the 28-of-28 day cycle) was included to refine the dosing schedule and determine whether this lower starting dose/regimen would be sufficient to provide adequate benefit, with potentially lesser toxicity.

MDS-001

13 patients were initially treated with lenalidomide 25 mg QD, a dose that was chosen based on the findings of an earlier Phase 1 study of lenalidomide in patients with MM (CDC-501-001). However, while this dose of lenalidomide produced major erythroid responses in 30.8% of patients within 16 weeks, a significant percentage of patients (31%) could not tolerate more than 30 days of continuous exposure to 25 mg lenalidomide. For this reason the protocol was amended and an additional 32 patients were enrolled to explore a reduced dose of 10 mg QD under continuous (12 patients) and cyclic (20 patients) regimens. A total of 42% and 33% of patients in the ITT population achieved a major erythroid response under the continuous and cyclic regimens, respectively. All responders had IPSS low- or INT-1-risk MDS and the majority (69.2%) of patients who achieved a major erythroid response had the del (5q) cytogenetic abnormality. Overall, the results of this study suggested that lenalidomide, administered at a dose of 10 mg QD, under either a continuous or cyclic regimen, was an effective treatment for patients with low- or INT-1-risk MDS and an associated del (5q31-33) cytogenetic abnormality. The MDS-001 data prompted the initiation of MDS-003.

Table 10. Summary of Efficacy Parameters in subjects with Low- or Intermediate-1-risk MDS associated with a Del (5q) cytogenetic abnormality (Study MDS-001)

	MDS-001		
Efficacy parameter	**Lenalidomide 25 mg QD 28/28 days (N = 4)**	**Lenalidomide 10 mg QD 28/28 days (N = 3)**	**Lenalidomide 10 mg QD 21/28 days (N = 4)**
RBC TI[a,b]	75% (3/4)	100% (3/3)	75% (3/4)
Hgb[c] Median (g/dL) Min, Max	 4.7 4.1, 6.5	 7.2 4.2, 8.7	 5.3 4.0, 7.2
Cytogenetic Response[d]			
Major	75% (3/4)	100% (3/3)	75% (3/4)
Minor	0% (0/4)	0% (0/3)	0% (0/4)

[a] Response rate for RBC TI ≥ 56 days.
[b] RBC TI was defined as the absence of any RBC transfusion during any consecutive rolling 56 days in the evaluation period and an increase in Hgb of at least 1 g/dL from the minimum during the 56 days prior to the maximum during the RBC TI period, excluding the first 30 days after the last transfusion before the transfusion-free period.
[c] Change from Hgb concentration at baseline to maximum concentration during RBC TI response period.

Study MDS-003 is described in the main studies supporting this application.

2.5.2. Main studies

Table 11. Summary of Efficacy and Safety Studies MDS 003 and MDS 004 (transfusion-dependent patients with low- or Intermediate-1-risk MDS associated with a Del (5q) cytogenetic abnormality)

Type Of Study	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Efficacy/ Safety	CC-5013-MDS-004	Compare 2 doses of lenalidomide to placebo	Randomized, double-blind, placebo controlled	Oral lenalidomide 10mg once daily on Days 1–21 every 28 days, 5mg once daily, or placebo	205	Transfusion-dependent MDS patients with lower intermediate-1-risk associated with a deletion (del) 5q[31] cytogenetic abnormality	up to 156 weeks in total (including up to 52 weeks in double-blind, followed by open-label)	Complete: Full
Efficacy/ Safety	CC-5013-MDS-003	Efficacy of lenalidomide in achieving hematopoietic improvement	Single-arm, open-label	Oral, once daily doses. Initially 10mg on Days 1 to 21 of a 28-day cycle, amended to a regimen of 10mg on Days 1-28 of a 28-day cycle	148	RBC Transfusion-dependent patients with INT1 Low risk MDS associated with a Del (5q) cytogenetic abnormality	Maximum of 24 cycles	Complete; Full

CC-5013-MDS-003 (MDS 003)

This was a multicentre, single-arm, open-label study of the efficacy and safety of lenalidomide monotherapy in red blood cell transfusion-dependent patients with Myelodysplastic Syndromes associated with a del (5q) cytogenetic abnormality

Methods

Study participants

Inclusion criteria

Patients had to fulfil all of the following criteria for inclusion in the study:

- Patients had to understand and voluntarily sign an informed consent form.
- Aged ⩾ 18 years at the time of signing the informed consent form.
- Patients had to be able to adhere to the study visit schedule and other protocol requirements.
- Diagnosis of low- or intermediate-1-risk MDS associated with a del (5q) cytogenetic abnormality. The cytogenetic abnormality of chromosome 5 had to involve a deletion between bands q31 and q33. The del (5q) cytogenetic abnormality could either have been an isolated cytogenetic finding (the 5q- syndrome) or been associated with other cytogenetic abnormalities.
- RBC-transfusion-dependent anaemia defined as receiving ⩾ 2 units of RBCs within 8 weeks of the first day of study treatment. Patients must have received at least 2 transfusions in each of

the 8-week periods during the 16-week pre-treatment period and must not have been transfusion free for any 56 consecutive days during the 16-week pre-treatment period.

- ECOG performance status score of 0, 1, or 2.

- Females of childbearing potential (FCBP) must have had a negative serum or urine pregnancy test within 7 days of starting study drug. In addition, sexually active FCBP had to agree to use adequate contraceptive methods (oral, injectable, or implantable hormonal contraceptive; tubal ligation; intra-uterine device; barrier contraceptive with spermicide; or vasectomized partner) while on study drug. FCBP also had to agree to have pregnancy tests every 4 weeks while on study drug. A FCBP was defined as a sexually mature woman who had not undergone a hysterectomy or bilateral oophorectomy, or who had not been naturally postmenopausal for at least 24 consecutive months, ie had had menses at any time in the preceding 24 consecutive months before study entry.

Exclusion criteria

Any of the following was regarded as a criterion for exclusion from the study:

- Any serious medical condition, laboratory abnormality, or psychiatric illness that prevented the patient from signing the informed consent form, placed the patient at an unacceptable risk if he/she were allowed to participate in the study, or confounded the interpretation of the study data.

- Pregnant or lactating females.

- Prior therapy with lenalidomide.

- Inability to aspirate bone marrow (dry tap).

- Proliferative chronic myelomonocytic leukemia (CMML), defined as a white blood cell (WBC) count of ⩾ 12,000/μL.

- Any of the following laboratory abnormalities:
  - Absolute neutrophil count (ANC) of < 500 cells/mm3 (0.5 x 109/L)
  - Platelet count of < 50,000/mm3 (50 x 109/L)
  - Serum creatinine of > 2.5 mg/dL (221 μmol/L)
  - Serum alanine aminotransferase (ALT/SGPT) or aspartate aminotransferase (AST/SGOT) > 3 times the upper limit of normal (ULN)
  - Serum direct bilirubin of > 2.0 mg/dL (34 μmol/L)

- Prior ⩾ grade 3 (NCI CTC) allergic reaction/hypersensitivity to thalidomide

- Prior ⩾ grade 3 (NCI CTC) rash or any desquamation (blistering) while taking thalidomide.

- Clinically significant anaemia due to factors such as iron, B12, or folate deficiencies, autoimmune or hereditary haemolysis, or gastrointestinal bleeding (if a marrow aspirate was not evaluable for storage iron, the transferrin saturation must have been ⩾ 20%, and the serum ferritin must not have been < 50 ng/mL).

- Use of hematopoietic growth factors within 7 days of the first day of study lenalidomide treatment.

- Chronic use (> 2 weeks) of greater than physiologic doses of a corticosteroid agent (dose equivalent to > 10 mg/day of prednisone) within 28 days of the first day of study lenalidomide treatment.

- Use of experimental or standard drugs (chemotherapeutic, immunosuppressive, and cytoprotective agents) for the treatment of MDS within 28 days of the first day of study lenalidomide treatment.

- Prior history of malignancy other than MDS (except basal cell or squamous cell carcinoma or carcinoma in situ of the cervix or breast) unless the patient had been free of disease for ≥ 3 years.
- Use of any other experimental therapy within 28 days of the first day of study lenalidomide treatment.

Treatments

Patients received treatment with 10mg of lenalidomide orally once daily.

The protocol initially employed a syncopated dosage regimen of 10 mg lenalidomide taken orally once daily on Days 1 to 21 of a 28-day cycle.

The protocol was subsequently amended to employ a continuous dosage regimen in which 10 mg of lenalidomide was taken orally once daily without a planned rest period.

Patients who began therapy on the syncopated regimen and who did not experience dose-limiting adverse events (AEs) were allowed to switch to the continuous regimen after initiation.

Dose reductions were made based on the severity and type of the AEs that occurred; dose escalation above 10 mg daily was not allowed.

Treatment continued until unacceptable AEs occurred, bone marrow disease progression was documented, progression or relapse following erythroid improvement was documented, or for a maximum of 24 cycles, whichever occurred first.

Objectives

Primary objective:

- To evaluate the efficacy of lenalidomide for achieving hematopoietic improvement in patients with an IPSS (Greenberg, 1997) diagnosis of low- or intermediate-1-risk MDS associated with a del 5 (q31-33) cytogenetic abnormality

Secondary objectives:

- to evaluate the safety of lenalidomide in this patient population

Outcomes/endpoints

Primary endpoint

RBC-transfusion independence, defined as the absence of an intravenous infusion of any RBC transfusion during any consecutive 56 days during the treatment period (eg, Days 1 to 56, Days 2 to 57, Days 3 to 58, etc), accompanied by at least a 1 g/dL increase from screening/baseline in Hgb.

The 1 g/dL increase from screening/baseline in Hgb only had to be measured once at any point during the 56 day period of RBC-transfusion independence.

Secondary endpoints

Secondary efficacy endpoints included:

- Frequency of patients with a ≥ 50% decrease from baseline in RBC transfusion requirements over any consecutive 56 days during the evaluation period;
- duration of response (transfusion independence), as determined by IWG criteria;

- time to response (transfusion independence);
- platelet response;
- neutrophil response;
- bone marrow response (improvement and progression);
- cytogenetic response.

Sample size

In the design of the protocol, a 1-stage hypothesis-testing model was used to estimate a sample size that would provide adequate statistical power to determine if the treatment was worthy of further study. When applying this design, the largest proportion that would suggest that the drug not be studied further was set to be 30%, and the smallest proportion that would suggest that the drug is worthy of further study was set to be 60%.

In the 1-stage design selected for this study, a sample of 30 patients who completed 6 cycles or dropped out early was adequate to test response rates of 30% versus 60% with acceptable error rates.

For an N of 30 patients, an exact 2-sided 95% CI for the observed response rate will fail to include 30% at least 80% of the time if the true percentage of patients who become RBC-transfusion independent is 60%. Recognizing that 30 patients, while meeting the statistical requirements, would not provide enough information to adequately assess safety, additional patients were studied both to provide additional safety data and also to provide more precise estimates of the response rates.

Randomisation

Not applicable.

Blinding (masking)

The study was open-label.

Statistical methods

The primary efficacy analyses were performed on the MITT population, which included all patients who met all of the following conditions:

- Had a diagnosis of low- or intermediate-1-risk MDS associated with a del (5q31-33) cytogenetic abnormality based on confirmation by the central hematologic and cytogenetic reviewers
- Received at least 2 transfusions in each of the 8-week periods during the 16 week pre-treatment period. In addition, patients were not to have been transfusion-free for any 56 consecutive days during the 16-week pre-treatment period.
- Received at least 1 dose of study medication

Response rates (number and percentage of patients) together with 2-sided exact 95% confidence intervals (CIs) were provided for all study endpoints based on categorized responses.

Kaplan-Meier estimates were provided for duration of response for those patients who became RBC-transfusion independent. If a patient who responded had not received an RBC-transfusion at the time of analysis, then duration of response was censored at the time of last follow-up.

Summary statistics (mean, standard deviation [SD], minimum [Min], maximum [Max]) were provided for the transfusion requirements at baseline, time to response, and duration of response, as well as observed values and changes from baseline for relevant laboratory parameters used in the determination of response, including in particular Hgb concentration. Paired t-tests (or nonparametric analogues) were to be used to test the significance of changes from baseline.

Results

Participant flow

Figure 2. Disposition of Patients in the Study

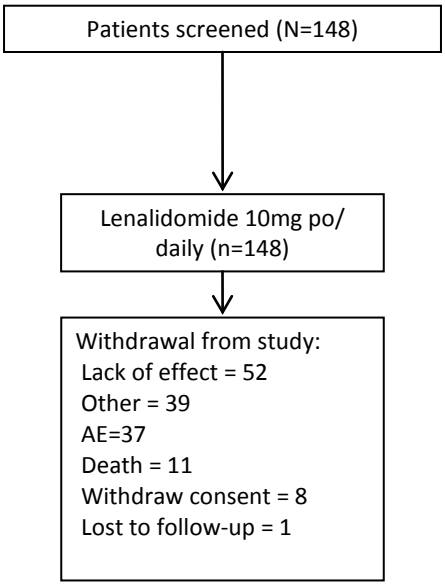


Table 12. Disposition of Patients by Initial Lenalidomide Regimen and Overall

	10 mg Cont. (N = 102)		10 mg Sync. (N = 46)		Overall (N = 148)	
Disposition / Reason	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Number of patients in the ITT population	102	(100.0)	46	(100.0)	148	(100.0)
Patients who completed ≥ 24 cycles on-study	42	(41.2)	19	(41.3)	61	(41.2)
Patients withdrawn from the study	102	(100.0)	46	(100.0)	148	(100.0)
Withdrew prior to 24 weeks of study	20	(19.6)	14	(30.4)	34	(23.0)
Withdrew after 24 weeks of study	82	(80.4)	32	(69.6)	114	(77.0)
Primary reason for discontinuation						
Lack of therapeutic effect	41	(40.2)	11	(23.9)	52	(35.1)
Other	30	(29.4)	9	(19.6)	39	(26.4)

	10 mg Cont. (N = 102)		10 mg Sync. (N = 46)		Overall (N = 148)	
Disposition / Reason	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
AE	22	(21.6)	15	(32.6)	37	(25.0)
Death	5	(4.9)	6	(13.0)	11	(7.4)
Patient withdrew consent	3	(2.9)	5	(10.9)	8	(5.4)
Patient lost to follow-up	1	(1.0)	0	(0.0)	1	(0.7)

AE = Adverse event; ITT = Intent to treat.

Recruitment

The study (period from 24 July 2003 to 27 August 2008 (date of data cut-off)) was conducted at 32 study sites in the United States and I study site in Germany.

Conduct of the study

There were 6 amendments of the study protocol (data not shown).

The following change from the analyses described in the clinical study protocol was made in this study:

- An efficacy evaluable population was defined in the protocol; however, this analysis population was not used in the statistical analysis of the data from this study, as this is very similar to the MITT population. The efficacy evaluable population was defined as a subset of the MITT population, i.e., those patients who met all the requirements for whom response could be fairly assessed, that is patients who withdrew from the study before completing 6 cycles for non-treatment related reasons without responding were not to be included in the denominator used in the response estimates. Patients who withdrew for treatment related reasons (AEs, lack of response based on clinical judgment) were to be categorised as non-responders in this analysis.
- The criteria for the eligibility of patients for the analysis of cytogenetic response were updated during the course of the trial. In the SAP, patients were eligible to be evaluated for a cytogenetic response if at least 2 abnormal metaphases were observed at baseline; in the updated eligibility criteria for this assessment, patients were eligible to be evaluated for a cytogenetic response if ≥ 20 metaphases were analysed at baseline.

Baseline data

Demographic and Baseline Characteristics (MITT population)
The baseline demographic and disease-related characteristics for the 94 patients in the MITT population are presented by initial dosing regimen and overall in the tables below.

Table 13. Baseline Demographic and Disease-Related Characteristics by Initial Lenalidomide Regimen and Overall (MITT Population)

Parameter	10 mg Cont. (N = 63)	10 mg Sync. (N = 31)	Overall (N = 94)
Age (years)			
n	63	31	94

Parameter	10 mg Cont. (N = 63)		10 mg Sync. (N = 31)		Overall (N = 94)	
Mean (SD)	69.6 (11.29)		73.1 (9.13)		70.7 (10.71)	
Median	71.0		73.0		71.5	
Min, Max	41.0, 95.0		60.0, 91.0		41.0, 95.0	
Age Distribution	n	(%)	n	(%)	n	(%)
≤ 65 years	23	(36.5)	8	(25.8)	31	(33.0)
> 65 years	40	(63.5)	23	(74.2)	63	(67.0)
Sex	n	(%)	n	(%)	n	(%)
Male	21	(33.3)	11	(35.5)	32	(34.0)
Female	42	(66.7)	20	(64.5)	62	(66.0)
Race	n	(%)	n	(%)	n	(%)
White	62	(98.4)	29	(93.5)	91	(96.8)
Hispanic	1	(1.6)	1	(3.2)	2	(2.1)
Asian/Pacific Islander	0	(0.0)	1	(3.2)	1	(1.1)
Duration of MDS (years)						
n	63		31		94	
Mean (SD)	4.0 (3.88)		3.4 (3.05)		3.8 (3.62)	
Median	3.1		2.0		3.1	
Min, Max	0.2, 20.7		0.3, 14.4		0.2, 20.7	
5q(-) (31-33) Chromosomal Abnormality	n	(%)	n	(%)	n	(%)
Yes	63	(100.0)	31	(100.0)	94	(100.0)
No	0	(0.0)	0	(0.0)	0	(0.0)
IPSS Score (Central Review)[a]	n	(%)	n	(%)	n	(%)
Low (0)	31	(49.2)	9	(29.0)	40	(42.6)
Intermediate-1 (0.5 to 1.0)	32	(50.8)	22	(71.0)	54	(57.4)
FAB Classification (Central Hematologic Review)[b]	n	(%)	n	(%)	n	(%)
RA	39	(61.9)	20	(64.5)	59	(62.8)
RARS	11	(17.5)	3	(9.7)	14	(14.9)
RAEB	11	(17.5)	7	(22.6)	18	(19.1)
CMML	2	(3.2)	1	(3.2)	3	(3.2)

Table 14. Baseline Demographic and Disease-Related Characteristics by Initial Lenalidomide Regimen and Overall (MITT population) (Continued)

Parameter	10 mg Cont. (N = 63)		10 mg Sync. (N = 31)		Overall (N = 94)	
Cytogenetic complexity	n	(%)	n	(%)	n	(%)
Isolated 5q	55	(87.3)	21	(67.7)	76	(80.9)
Intermediate (5q + 1 abnormality)	6	(9.5)	8	(25.8)	14	(14.9)
Complex	2	(3.2)	2	(6.5)	4	(4.3)
ECOG Performance Status[c]	n	(%)	n	(%)	n	(%)
0	27	(42.9)	12	(38.7)	39	(41.5)
1	28	(44.4)	18	(58.1)	46	(48.9)
2	8	(12.7)	1	(3.2)	9	(9.6)

CMML = Chronic myelomonocytic leukemia; ECOG = Eastern Cooperative Oncology Group; FAB = French-American-British; IPSS = International prognostic scoring system; Max = Maximum; MDS = Myelodysplastic syndrome; Min = Minimum; MITT = Modified intent to treat population; RA = Refractory anemia; RAEB = Refractory anemia with excess blasts; RARS = Refractory anemia with ringed sideroblasts; SD = Standard deviation.

Demographic and Baseline Characteristics (ITT population)

The demographic and baseline characteristics of the ITT population were broadly similar to those of the MITT population. Twenty-one (14.2%) patients' IPSS scores were missing (unable to assign) at baseline and 9 (6.1%) patients in total had intermediate-2- or high-risk MDS at baseline according to the central review. Twenty (13.5%) patients' FAB classifications could not be classified by the central hematologic reviewer at baseline. One (0.7%) patient had acute leukemia at baseline according to the FAB classification performed by the central reviewer; however, according to the assessment performed by the investigator at one Site this patient had RAEB at screening/baseline and was eligible to be enrolled in the study.

In the ITT population, 110 (74.3%) patients had an MDS clone with an isolated del 5q cytogenetic abnormality, 25 (16.9%) patients had intermediate cytogenetic complexity (del 5q abnormality plus 1 additional cytogenetic abnormality), and 12 (8.1%) patients had complex cytogenetic abnormalities (an MDS clone with a del 5q abnormality and more than 1 additional cytogenetic abnormality). One patient's cytogenetic complexity was unknown at baseline.

Numbers analysed

The safety and ITT populations were used for the safety analysis, whereas the MITT and ITT populations were used for the efficacy analysis.

The ITT population included all enrolled patients (n=148). The Safety population included all patients who received at least 1 dose of study drug were included in the analyses of safety (n=148). Finally, the MITT population used for the primary efficacy analyses included 94 patients.

Outcomes and estimation

The main efficacy results are summarised in the following Table 15. Additional efficacy results are presented under the MDS-004 study.

Table 15. Summary of Efficacy Results (MITT and ITT Populations)

RBC-transfusion independence[a]	Statistic	Overall MITT (N = 94)	Overall ITT (N = 148)
Response rate	Number of patients	94	148
	Number (%) transfusion independent ≥ 56 days	59 (62.8)	97 (65.5)
	Exact 95% CI	52.2, 72.5	57.3, 73.2
Hgb increase (g/dL)[b]	Number of patients	59	97
	Median	5.9	5.6
	Mean (SD)	6.1 (1.92)	6.1 (4.04)
	Min, Max	2.2, 11.4	2.2, 40.7
Time to transfusion independence (weeks)[c]	Number of patients	59	97
	Mean (SD)	6.2 (6.89)	5.5 (6.56)
	Min, Max	0.3, 49.0	0.3, 49.0
Duration of response[d]	Number of transfusion independent patients	59	97
	Number (%) who progressed (had a transfusion after response)	35 (59.3)	57 (58.8)
	Number (%) who maintained transfusion independence (censored[e])	24 (40.7)	40 (41.2)
Duration of transfusion independence response (weeks)	Median (Kaplan-Meier estimate)	97.0	114.4
	95% CI	52.9, 191.9	78.4, 153.7

CI = Confidence interval; Hgb = Hemoglobin; ITT = Intent to treat; Max = Maximum; Min = Minimum; MITT = Modified intent to treat; RBC = Red blood cell; SD = Standard deviation.

[a]The absence of the intravenous infusion of any RBC transfusion during any consecutive "rolling" 56 days during the treatment period and an increase in Hgb of at least 1 g/dL from the minimum during the screening/baseline period to the maximum during the transfusion-independent period, excluding the first 30 days after the last transfusion before the transfusion-free period.

[b]Change from baseline in Hgb concentration to maximum value during response period, where response period was defined as the time from 30 days after the last transfusion prior to achieving transfusion independence to the next transfusion or to the last assessment for patients who did not receive a subsequent transfusion during the study period.

[c]Measured from the day of the first dose of study drug to the first day of the first 56-day RBC transfusion-free period.

[d]Measured from the first of the consecutive 56 days during which the patient was free of RBC transfusions to the date of the first RBC transfusion after this period.

[e]Duration of response was censored at the date of last visit for patients who maintained transfusion independence.

Extension Study (CC-5013-MDS-003E/CC-5013-MDS-009)

CC-5013-MDS-003E/CC-5013-MDS-009 was a non-interventional, multicentre, follow-up extension study, which was conducted specifically to provide further long-term outcomes as regards overall survival/vital status and the possible occurrence of progression to AML for all patients previously enrolled in the MDS-003 study, and to further analyse these outcomes based on the long-term follow-up data obtained.

Incidence of Progression to Acute Myeloid Leukemia

One patient was diagnosed by the central cytogenetic reviewer as having AML at entry to the MDS-003 study (baseline); hence, this patient was excluded from the progression to AML analyses (N = 147). 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). Data on progression to AML are summarized in Table 16.

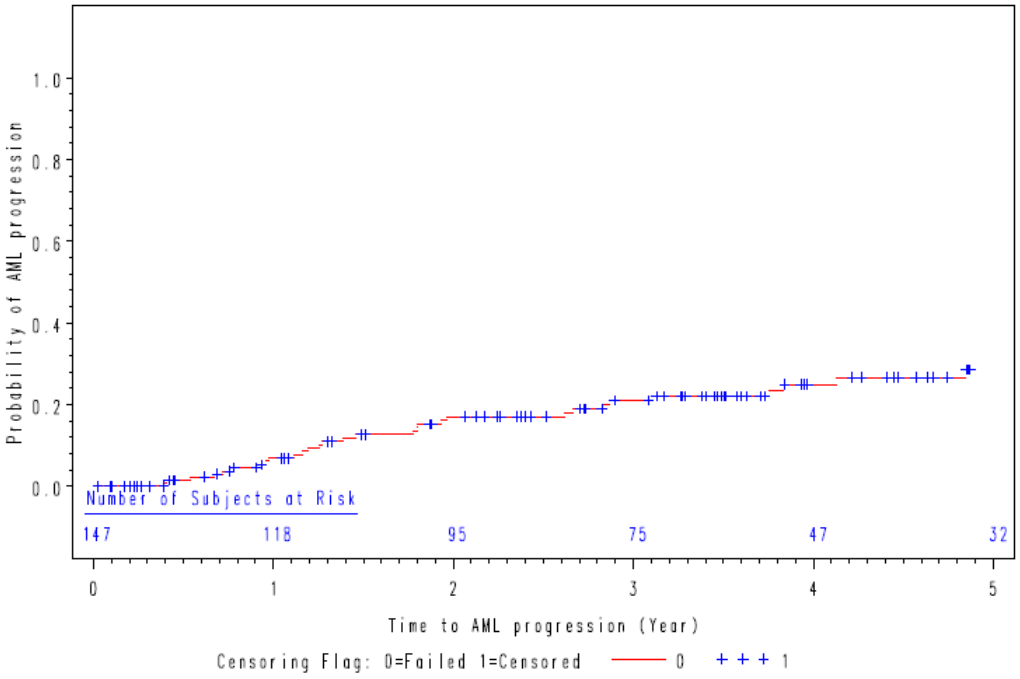
Table 16. Incidence of Progression to Acute Myeloid Leukemia (All MDS-003 Patients)

1. Progression to AML	2. Overall (N = 147)	
Number of patients that progressed to AML (n, %)	36	(24.5)
Number of patients that did not progress to AML (n, %)	86	(58.5)
Patients with unknown progression to AML status (n, %)	25	(17.0)
Cumulative incidence of progression to AML by year (%)☐ LISTNUM TableNoteAlpha * MERGEFORMAT ☐		
1-year	6.9	
2-year	17.0	
3-year	21.0	
4-year	25.0	
5-year	28.6	
All events	30.9	
Median time to progression to AML (months)	NA	

AML = acute myeloid leukemia; CI = confidence intervals; NA = not applicable.

A Kaplan-Meier plot of time to progression to AML for all MDS-003 patients is presented in Figure 3.

Figure 3. Kaplan-Meier Estimate of Time to Progression to Acute Myeloid Leukemia (All MDS-003 Patients)



Results of Cox proportional hazards ratio models are summarised in the following Table 17.

Table 17. Analysis of Progression to AML based on Cox Proportional Hazards Ratio Models (Univariate Analysis and Final Model) (All MDS-003 Patients)

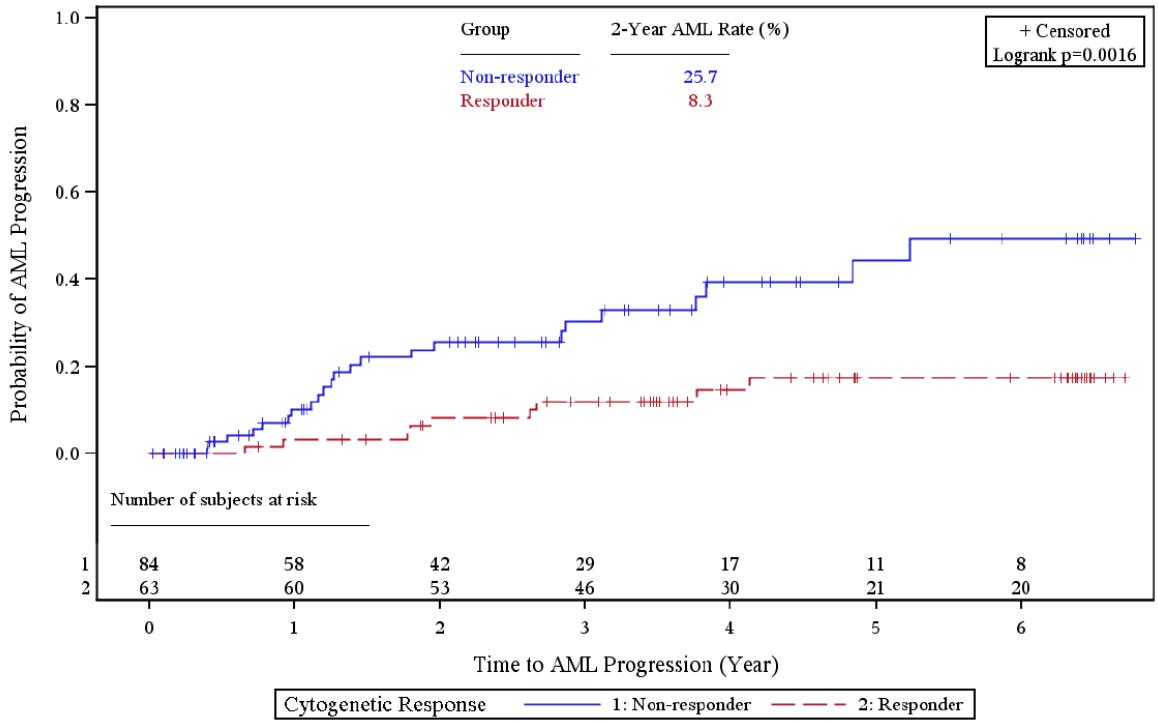
Variables[c]	Univariate Analysis[a]			Final Model[b]		
	HR	95% CI	p-value	HR	95% CI	p-value
Age (years)	0.99	0.96, 1.02	0.451			
Gender (male versus female)	1.73	0.84, 3.56	0.137			
Baseline IPSS score (INT-1, INT-2, High versus Low)	2.45	0.98, 6.11	0.055			
Baseline FAB classification (RAEB, CMMoL versus RA, RARS)	1.08	0.43, 2.71	0.864			
Time since MDS diagnosis (years)	0.95	0.84, 1.08	0.440			
Baseline transfusion burden (units/8 weeks)	1.48	0.76, 2.87	0.246			
Baseline myeloblast count (≥ 5% versus < 5%)	1.00	0.38, 2.63	0.993			
Number of cytopenias at baseline (2 or 3 versus 1)	0.90	0.43, 1.87	0.779			
Baseline platelet count (10^9/L)	1.00	1.00, 1.00	0.539			
Baseline neutrophil count (10^9/L)	1.04	0.91, 1.18	0.590			
Minimum Hgb concentration in the 8-week baseline period (g/dL)	0.88	0.64, 1.20	0.413			
Baseline cytogenetic status (intermediate or complex versus isolated del [5q])	3.32	1.58, 6.95	0.001	3.16	1.43, 6.98	0.005
WPSS risk groups (High, Very High, versus Intermediate, Low, Very Low)	1.95	0.91, 4.21	0.087			
RBC TI ≥ 182 days (time-dependent)	0.36	0.17, 0.74	0.006			

[a] The univariate analysis model included individual risk factors.
[b] The final model (stepwise selection of risk factors) included factors with a p-value < 0.15.
[c] Age, time since MDS diagnosis, baseline transfusion burden, baseline platelet count, baseline neutrophil count, and minimum Hgb at baseline were treated as continuous variables. RBC TI ≥ 182 days was treated as a time-dependent covariate. Reference groups for categorical variables were as follows: female; low IPSS; FAB Classification RA or RARS; < 5% myeloblasts; 1 cytopenia; isolated del (5q); and WPSS Intermediate, Low.
CI = confidence intervals; FAB = French-American-British; Hgb = hemoglobin; HR = hazard ratio; IPSS = International Prognostic Scoring System; MDS = myelodysplastic syndromes; RBC TI = red blood cell transfusion independence; WPSS = World Health Organization Prognostic Scoring System.
Notes: baseline characteristics were assessed at baseline of the MDS-003 study. Subject 0243010 was diagnosed by the central cytogenetic reviewer as having AML at entry to the MDS-003 study (baseline); hence, this subject was excluded from the progression to AML analyses (N = 147).

Classic 5q- syndrome yes/no was not included in the univariate analysis. In the subgroup analyses (data not shown) the classic syndrome had a relatively good prognosis AML 6/40 (yes) vs. 30/107 (no). This difference was smaller than expected, and could be partly related to longer survival, death being a competing risk and perhaps also biased bone marrow sampling.

Finally, Cytogenetic response was predictive of a lower rate of progression to AML (see Figure 4).

Figure 4. Time to AML by cytogenetic response



Overall Survival

Of the 148 patients enrolled in the MDS-003 study, approximately two-thirds were dead at the time of follow-up (101 patients; 68.2%). Twenty-nine (19.6%) patients were alive at the time of the 2010 follow-up. Vital status was unknown at the time of the 2010 follow-up in 18 (12.2%) patients who were not included in the extension study follow-up cohort. Survival information was obtained for all 54 patients included in the 2010 MDS-003E/MDS-009 extension study. Kaplan-Meier estimates of overall survival in all MDS-003 patients are presented in Table 18.

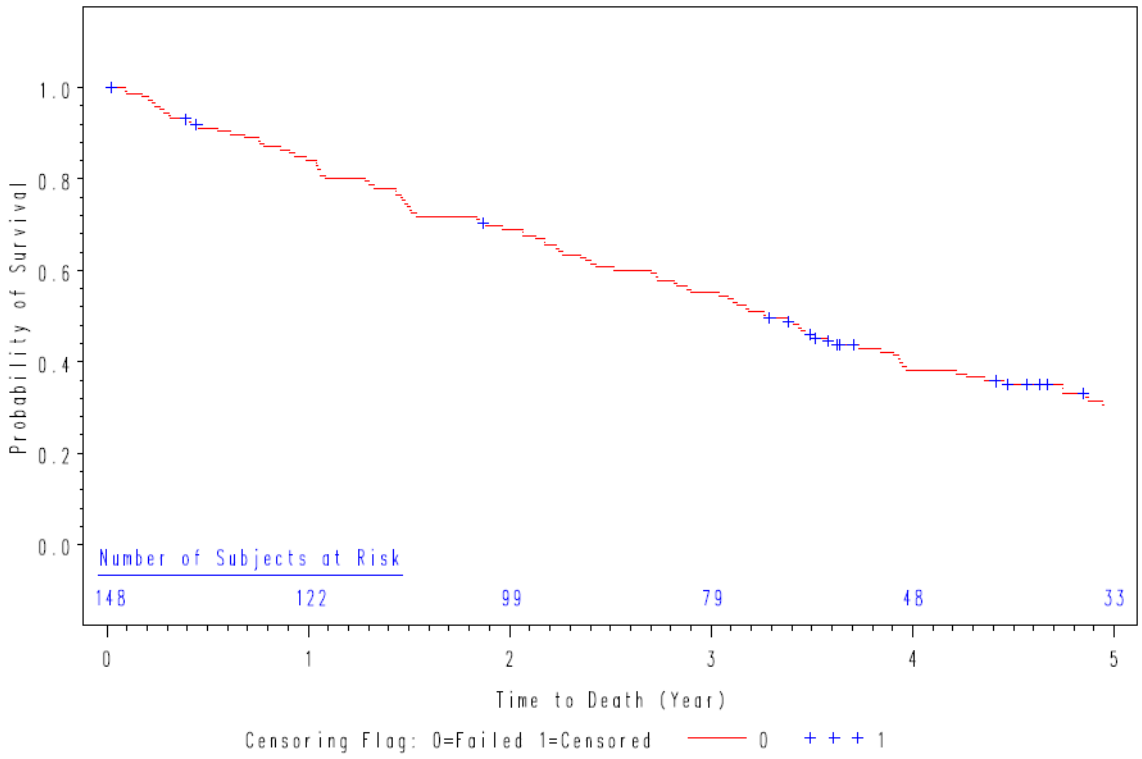
Table 18. Summary of Overall Survival (All MDS-003 Patients)

Overall survival	Overall (N = 148)	
Number of patients deceased (n, %)	101	(68.2)
Number of patients alive at 2010 follow-up (n, %)	29	(19.6)
Status unknown at time of 2010 follow-up (n, %)	18	(12.2)
Cumulative overall survival by year (%)[1]		
1-year	84.2	
2-year	69.0	
3-year	55.1	
4-year	38.1	
5-year	30.4	
Final survival	26.7	
Median survival time (months)	39.47	
95% CI	32.99, 47.14	

(1) Kaplan-Meier estimates. Patients without a reported death date were censored at the last known date they were alive. CI = confidence intervals.

A Kaplan-Meier plot of overall survival for all MDS-003 patients is presented in Figure 5. The Kaplan-Meier estimate of median overall survival time was 39.5 months (95% CI: 32.99 to 47.14 months; 3.3 years).

Figure 5. Kaplan-Meier Estimate of Overall Survival (All MDS-003 Patients)



Overall Survival by Cytogenetic Response

In all MDS-003 patients, 88 patients were evaluable for a cytogenetic response and 60 were not. The majority of evaluable patients (63 patients; 71.6%) had a major or minor cytogenetic response, whereas 25 (28.4%) evaluable patients did not.

Fewer patients who were cytogenetic responders had died at the time of follow-up (50.8%), compared with cytogenetic non-responders (80.0%) and those patients who were not evaluable for a cytogenetic response (81.7%). In the subgroup analysis of RBC TI response (≥ 182 days) by cytogenetic response, the incidence of death was lowest in patients that achieved both a RBC TI response and a cytogenetic response (47.4%), and higher in patients that achieved neither a RBC TI nor a cytogenetic response (82.4%).

Kaplan-Meier estimates of overall survival are presented for cytogenetic responders and cytogenetic non-responders in Table 18 (all MDS-003 patients).

Table 19: Overall Survival in Cytogenetic Responders and Cytogenetic Nonresponders (All MDS-003 Patients)

Cumulative overall survival by year (%)	Cytogenetic responders (N = 63)	Cytogenetic nonresponders (N = 25)
1-year	96.8	84.0
2-year	88.9	64.0
3-year	77.6	52.0
4-year	55.5	31.1
5-year	46.7	22.2
Final survival	44.5	17.8
Median survival time (months)	58.81	37.55
95% CI	43.47, NA	18.25, 47.14

Error! Reference source not found. Kaplan-Meier estimates. Patients without a reported death date were censored at the last known date they were alive.

Error! Reference source not found. Sixty patients were not evaluable for a cytogenetic response and were not included in this analysis.

CI = confidence intervals; NA = not applicable.

CC-5013-MDS-004

This was a multicentre, randomised, double-blind, placebo-controlled, 3-arm study of the efficacy and safety of 2 doses of lenalidomide versus placebo in red blood cell (RBC) transfusion-dependent patients with low or intermediate-1-risk myelodysplastic syndromes (MDS) associated with a deletion (del) 5q[31] cytogenetic abnormality.

Methods

Study participants

Inclusion criteria

Pre-randomisation Phase (Screening Phase)

Patients were required to meet all of the following inclusion criteria to be eligible for enrollment into the study:

- Must understand and voluntarily sign an informed consent form
- Must be ≥18 years of age at the time of signing the informed consent form
- Must be able to adhere to the study visit schedule and other protocol requirements
- Concurrent corticosteroids used for medical conditions other than MDS was allowed provided patient is on a stable or decreasing dose for ≥ 1 week prior to study entry
- Prior treatment with thalidomide allowed
- Investigator-documented diagnosis of MDS that met IPSS criteria for low- to intermediate-1-risk disease and has an associated del 5q[31] cytogenetic abnormality (the deleted chromosomal region must include 5q[31]. Subsequent requirement for cytogenetic confirmation by central review of patient eligibility prior to randomisation.
- RBC transfusion-dependent anemia defined as not having any consecutive 56 days (2 months) without a RBC transfusion within at least the immediate 112 days (4 months). A 112-day documented transfusion history was required for patients to enter the double-blind phase of the study.

Double-blind Treatment Phase

Patients were required to meet all of the following inclusion criteria to be eligible for enrolment into the study:

- Baseline RBC transfusion requirement calculated
- Female patients of childbearing potential were required to:
    - Understand that the study medication could have a potential teratogenic risk
    - Agree to use, and be able to comply with, effective contraception without interruption, 28 days before starting study drug, throughout study drug therapy (including dose interruptions) and for 28 days after the end of study drug therapy, even if she has amenorrhea. This applies unless the patient commits to absolute and continued abstinence confirmed on a monthly basis. The following were considered effective methods of contraception:
        - Implant
        - Levonorgestrel-releasing intrauterine system
        - Medroxyprogesterone acetate depot
        - Tubal sterilization
        - Sexual intercourse with a vasectomized male partner only; vasectomy must be confirmed by two negative semen analyses
    - Agree to have a medically supervised pregnancy test with a minimum sensitivity of 25 mIU/mL not more than 3 days from the start of study medication once the patient has been on effective contraception for at least 28 days. This requirement also applies to females of childbearing potential who practice complete and continued abstinence.

- Agree to have a medically supervised pregnancy test every 28 days including 28 days after the end of study treatment, except in the case of confirmed tubal sterilization. These tests should be performed not more than 3 days before the start of nexttreatment. This requirement also applies to females of childbearing potential who practice complete and continued abstinence.

- Male patients were required to:
  - Agree to use condoms throughout study drug therapy, during any dose interruption and for 7 days after cessation of study therapy if their partner is of childbearing potential and has no contraception
  - Agree not to donate semen during study drug therapy and for 7 days after end of study drug therapy

- All patients were required to:
  - Agree to abstain from donating blood while taking study drug therapy and for 7 days following discontinuation of study drug therapy
  - Agree not to share study medication with another person and to return all unused study drug to the investigator

Exclusion criteria

Pre-randomisation Phase

Patients who met any of the following exclusion criteria were NOT to be eligible for enrolment into the study:

- Pregnant or lactating females
- Prior therapy with lenalidomide
- Proliferative (WBC ≥ 12,000/mL) chronic myelomonocytic leukemia (CMML)
- Prior ≥ grade 2 NCI CTCAE allergic reaction to thalidomide
- Prior desquamating (blistering) rash while taking thalidomide
- Prior history of malignancy other than MDS (except basal cell or squamous cell carcinoma or carcinoma *in situ* of the cervix or breast) unless the patient had been free of disease for ≥3 years
- Use of cytotoxic chemotherapeutic agents or experimental agents (agents that are not commercially available) for the treatment of MDS within 28 days of Day 1 of the Pre Randomisation Phase
- Less than 6 months since prior allogeneic bone marrow transplantation to Day 1 of the Pre-Randomisation Phase
- Less than 3 months since prior autologous bone marrow or stem cell transplantation to Day 1 of the Pre-Randomisation Phase
- Less than 28 days since prior myelosuppressive anticancer biologic therapy to Day 1 of the Pre-Randomisation Phase
- Use of erythropoiesis stimulating growth factors (eg, recombinant human erythropoietin (rHuEPO) within 28 days or long-acting erythropoiesis stimulating growth factor (eg, darbepoetin) within 56 days of Day 1 of the Pre-Randomisation Phase
- Use of androgens other than to treat hypogonadism was prohibited

- Known HIV-1 positivity
- Any serious medical condition or psychiatric illness that would have prevented the patient from signing the informed consent form or would have placed the patient at unacceptable risk if he or she participated in the study

Double-blind Treatment Phase

Patients who met any of the following exclusion criteria were NOT to be eligible for enrolment into the study:

- Pregnant or lactating females
- Prior therapy with lenalidomide
- Proliferative (WBC ≥ 12,000/µL) CMML
- Any of the following laboratory abnormalities:
  - Absolute neutrophil count (ANC) < 500 cells/ µL (0.5 x 109/L)
  - Platelet count < 25,000/µL (25 x 109/L)
  - Serum creatinine > 2.0 mg/dL (177 mmol/L)
  - Serum aspartate aminotransferase (AST)/serum glutamic-oxaloacetic transaminase (SGOT) or alanine aminotransferase (ALT)/serum glutamate pyruvate transaminase (SGPT) > 3.0 x upper limit of normal unless it is clinically due to iron overload from blood transfusions
  - Serum total bilirubin > 1.5 mg/dL
- Prior ≥ grade-2 NCI CTCAE allergic reaction to thalidomide
- Prior desquamating (blistering) rash while taking thalidomide
- Patients with ≥ grade-2 neuropathy
- Clinically significant anemia owing to iron, B12, or folate deficiencies, or autoimmune or hereditary hemolysis or gastrointestinal bleeding (the patient must have a marrow aspirate that is evaluable for storage iron)
- Prior history of malignancy other than MDS (except basal cell or squamous cell carcinoma or carcinoma in situ of the cervix or breast) unless the patient had been free of disease for ≥ 3 years
- Use of androgens other than to treat hypogonadism was prohibited.
- Known HIV-1 positivity
- Any serious medical condition or psychiatric illness that would have prevented the patient from signing the informed consent form or would have placed the patient at unacceptable risk if he/she participated in the study

Treatments

1. Pre-randomisation phase (up to 8 weeks):

Potential protocol-eligible patients were to enter the pre-randomisation phase after signing informed consent and were evaluated for the inclusion and exclusion criteria for enrolment in the double blind treatment phase of this study.

2. Double-blind (DB) treatment phase (up to 52 weeks):

The double-blind treatment phase was to start (Day 1) within 3 days of randomisation, and could continue for up to 52 weeks (until Day 365 of the double-blind treatment phase). On Day 1, all patients began one of the following treatments:

Lenalidomide 10 mg: Oral lenalidomide 10 mg (two 5 mg capsules) once daily on Days 1–21 and two placebo capsules once daily on Days 22 – 28, every 28 days.

Lenalidomide 5 mg: Oral lenalidomide 5 mg (one 5 mg capsule) plus one placebo capsule once daily on Days 1-28, every 28 days.

Placebo: Two placebo capsules once daily on Days 1-28, every 28 days.

Study visits were to occur every 28 days (whether or not study drug had been interrupted for dose-limiting toxicity [DLT]), and serial measurements of safety and efficacy were to be performed.

The dose of lenalidomide or placebo was to be reduced if DLTs occurred, and CBCs were to be obtained weekly following the development of dose-limiting neutropenia or thrombocytopenia. The use of granulocytic growth factors were strongly encouraged for patients who developed febrile neutropenia or those who experienced ≥ grade 3 neutropenia (including those patients who had grade 3 neutropenia at baseline).

Patients who had evidence of at least a minor erythroid response after 16 weeks of treatment phase participation were able to continue therapy in the double-blind treatment phase for up to 52 weeks (Day 365 of the double-blind treatment phase) unless there was disease progression or erythroid relapse.

Patients who did not have evidence of at least a minor erythroid response after 16 weeks of double-blind treatment phase participation were to be discontinued from the double-blind treatment phase for lack of therapeutic efficacy, and unblinded.

Patients discontinued from the double-blind treatment phase of the study for disease progression were not eligible for inclusion in the open-label extension phase. Patients who had an erythroid relapse following the achievement of at least a minor erythroid response were discontinued from the double-blind treatment phase for lack of therapeutic efficacy and their assigned treatment arm was unblinded.

Patients who completed the total duration of 52 weeks in the double-blind treatment phase without disease progression or erythroid relapse were unblinded after Week 52 and entered the open-label extension phase at their current dose of lenalidomide.

3. Open-label (OL) extension phase (up week 156):

Patients were to begin treatment in the open-label extension phase within 28 days of either completing or early discontinuation from the double-blind treatment phase.

Study visits occurred every 28 days and serial measurements of safety and efficacy were performed. The dose of lenalidomide was reduced if DLTs occurred.

Patients were permitted to continue lenalidomide therapy in the open-label extension phase for up to 156 weeks of total study participation unless the following occurred:

- at least a minor erythroid response was not achieved within 16 weeks of open-label extension phase treatment;
- disease progression developed, or
- the RBC transfusion requirement returned to baseline in the absence of hypothyroidism in female patients, or hypothyroidism and/or hypogonadism in male patients.

Patients who did not achieve at least a minor erythroid response within 16 weeks of open-label extension phase treatment, or who developed an erythroid relapse without low TSH (all patients) or testosterone (male patients only) levels following the achievement of a minor or major erythroid response, were treated as follows:

- patients who started the open-label extension phase at the 10 mg dose level were discontinued from the study for lack of therapeutic efficacy;
- patients who started the open-label extension phase at the 5-mg dose level and who previously required a lenalidomide dose reduction were discontinued from the study for lack of therapeutic efficacy;
- patients who previously had tolerated lenalidomide at the 5-mg dose level without a dose reduction were permitted to escalate the dose of lenalidomide to 10 mg once daily on Days 1–21 every 28 days.

Patients who developed a decreasing blood haemoglobin (Hgb) level during a period of RBC transfusion independence were permitted to remain in the open-label extension phase until their RBC transfusion requirement returned to baseline (erythroid relapse).

Patients who discontinued the study for any reason were to be followed every 4 months (directly via telephone or information obtained from their treating physician) for survival and/or to collect any events of progression to AML.

Objectives

Primary objective:

- To compare the efficacy of 2 doses (10 mg and 5 mg) of lenalidomide to that of placebo in patients with red blood cell (RBC) transfusion-dependent low- or intermediate-1-risk IPSS MDS associated with a deletion (del) 5q[31] cytogenetic abnormality.

Secondary objectives:

To compare the safety of 2 doses of lenalidomide (10 mg and 5 mg) to that of placebo in patients with RBC transfusion-dependent low- or intermediate-1-risk IPSS MDS associated with a del 5q[31] cytogenetic abnormality.

Outcomes/endpoints

Primary endpoint

Proportion of patients achieving RBC-transfusion independence for ≥182 days (6 months).

Secondary endpoints

Secondary efficacy endpoints included:

- Erythroid response (classified as major and minor, according to International MDS Working Group Criteria)
- Duration of RBC transfusion independence, defined to be the number of days between the last transfusion prior to the start of the transfusion-free period and the first transfusion after the transfusion-free period
- Change of blood Hgb concentration from baseline in patients who achieved a major erythroid response
- Erythroid response (major and minor according to International MDS Working Group

Criteria) at one year of double-blind treatment phase participation.

- Change in platelet counts from baseline
- Change in absolute neutrophil counts from baseline
- Cytogenetic response (according to the International MDS Working Group Criteria)
- Bone marrow response (according to the International MDS Working Group Criteria)
- HRQoL assessments: the four components (Physical, Social/Family, Emotional and Functional Well-being), and total, of the 27-item FACT-G; the 13-item fatigue subscale; the total of the Additional Concerns; and the total of all items on the FACT-An (the FACT-G items plus the items under Additional Concerns and EQ-5D) (at initial visit only)
- Overall Survival (OS)
- Time to progression to AML

Sample size

A two-group continuity corrected $\chi 2$ test with a 0.025 two-sided significance level (this ensures that the type I error rate for the two comparisons to the placebo arm is bounded above by 0.05 two-sided) was calculated to have 80% power to detect the difference between a response rate of 0.400 in the active treatment group and a response rate of 0.100 in the placebo group when the sample size in each group is 45 evaluable patients for the centrally-confirmed MITT population.

Enrollment for the study was expanded from 162 patients to 205 in order to achieve the pre-specified 135 evaluable patients.

Randomisation

Patients meeting all inclusion and exclusion criteria were randomised in a 1:1:1 ratio by a validated interactive voice response system (IVRS) to receive one of three regimens.

Randomisation was stratified according to karyotype of the MDS clone (IPSS karyotype score of 0 versus score of > 0; ie, isolated del 5q[31] abnormality versus del 5q[31] abnormality plus at least one additional cytogenetic abnormality).

Blinding (masking)

The study was double-blind.

Statistical methods

The primary efficacy analyses were performed on the MITT population which included all patients with:

- a documented diagnosis of MDS that met IPSS criteria for low- to intermediate-1-risk disease and had an associated del 5q[31] cytogenetic abnormality, confirmed by central review of an evaluable bone-marrow aspirate/optional biopsy.
- RBC transfusion-dependent anemia defined as not having any 56 consecutive days (2 months) without a RBC transfusion within at least the immediate 112 days (4 months) prior to Day 1 of the Pre-Randomisation Phase
- at least 1 dose of study drug taken.

The primary comparisons of interest were the response rates of each of the active treatment groups to placebo during the double-blind treatment phase. A step-wise modified Bonferroni procedure was used to control the experiment-wide error rate. The Mantel–Haenszel procedure blocking by karyotype (IPSS

karyotype score of 0 versus greater than 0) was used to compare the response rates for 10 mg versus placebo and 5 mg versus placebo.

The Mantel–Haenszel procedure was also used to compare the secondary response measures: erythroid, cytogenetic, and bone marrow response together with the number of patients with ongoing transfusion independence at one year following initiation of treatment.

The Kaplan–Meier procedure was used to characterize the duration of response. Analyses of variance was used to analyze the changes in blood Hgb concentrations, platelet counts, and absolute neutrophil counts from baseline, and the changes in the components and total of the FACT-An HRQoL assessment, and the frequency with which transfusions were given. In these analyses, the average number of transfusions given over 56-day intervals prior to randomisation were compared to the averages over 56-day intervals during the double-blind treatment phase.

Multivariate analyses were performed to identify the prognostic variables for AML-free survival (AML or death, whichever occurs first, will be counted as the event), AML progression and overall survival. A univariate Cox proportional hazards model was used to assess the impact of the individual prognostic variables. After the potentially significant prognostic variables have been identified, a multivariate Cox proportional hazards model was used to simultaneously determine the impacts of the most important prognostic variables.

Results

Participant flow

Figure 6. Disposition of Patients Through the Double-blind and into the Open-label Phase of the Study

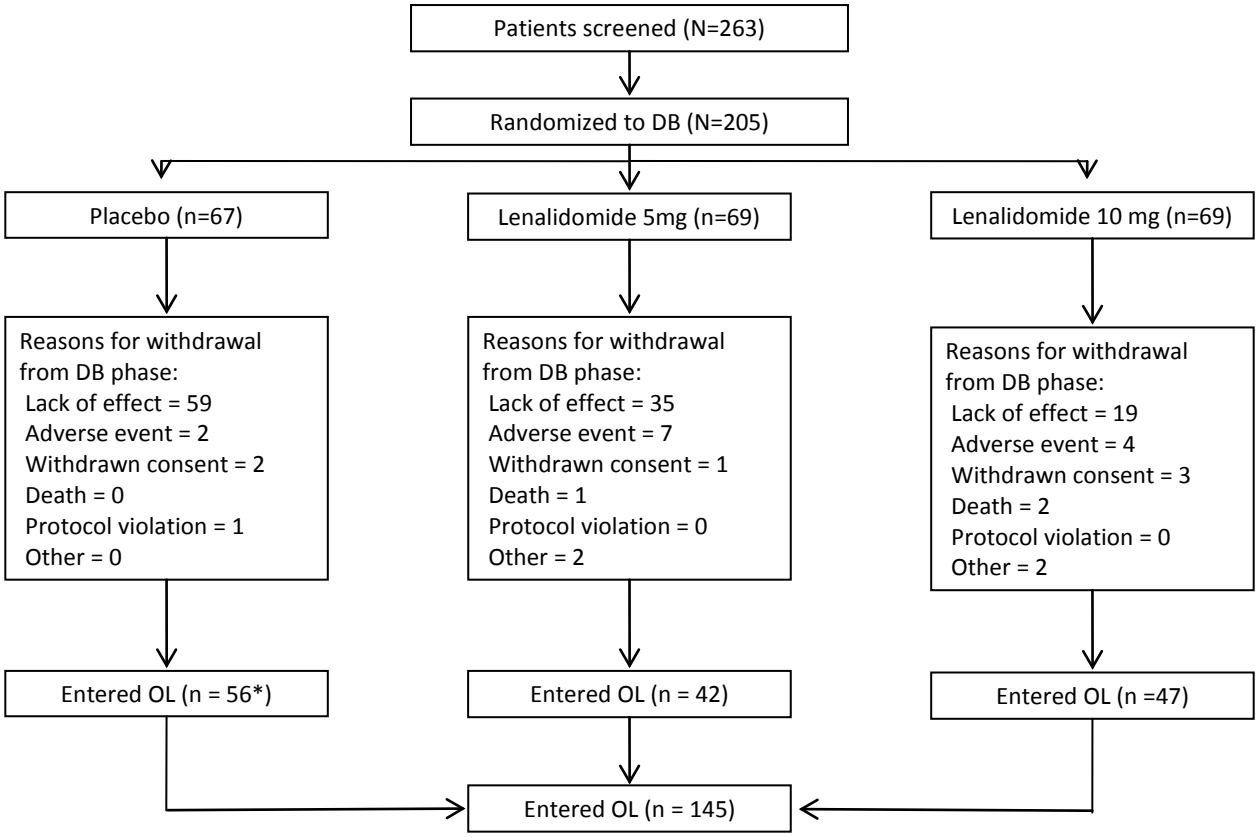


Table 20. Disposition of Patients in the Double-blind Treatment Phase by Randomised Treatment Regimen

Disposition / Reason	Placebo QD 28 of 28 Days (N=67)		Lenalidomide 5 mg QD 28 of 28 Days (N=69)		Lenalidomide 10 mg QD 21 of 28 Days (N=69)		Overall (N=205)	
	n	(%)	n	(%)	n	(%)	n	(%)
Number of Patients in the ITT Population	67	–	69	–	69	–	205	–
Patients Completed DB Phase[a]	3	(4.5)	23	(33.3)	39	(56.5)	65	(31.7)
Patients Discontinued from DB Phase[a]	64	(95.5)	46	(66.7)	30	(43.5)	140	(68.3)
Primary reason for DB discontinuation[a]								
Lack of therapeutic effect	59	(88.1)	35	(50.7)	19	(27.5)	113	(55.1)
Relapse after Erythroid response	1	(1.5)	1	(1.4)	0	(0.0)	2	(1.0)
Lack of Erythroid response	54	(80.6)	31	(44.9)	18	(26.1)	103	(50.2)
Disease progression	4	(6.0)	3	(4.3)	1	(1.4)	8	(3.9)
Adverse event	2	(3.0)	7	(10.1)	4	(5.8)	13	(6.3)
Withdrew consent	2	(3.0)	1	(1.4)	3	(4.3)	6	(2.9)
Death	0	(0.0)	1	(1.4)	2	(2.9)	3	(1.5)
Protocol violation	1	(1.5)	0	(0.0)	0	(0.0)	1	(0.5)
Other	0	(0.0)	2	(2.9)	2	(2.9)	4	(5.8)
Patients Entered Open-Label Phase[a]	56	(83.6)	42	(60.9)	47	(68.1)	145	(70.7)

Recruitment

The study (period from 08 July 2005 to 14 June 2010 (date of data cut-off)) was conducted at 38 study sites.

Conduct of the study

There were 5 amendments of the study protocol (data not shown).

Baseline data

Double-blind Treatment Phase

The baseline demographic and disease-related characteristics for the ITT population are summarised by treatment group and overall in Table 21.

Table 21. Baseline Demographic and Disease-related Characteristics by Treatment Group and Overall (ITT Population)

Parameter/Characteristic	Placebo QD 28 of 28 Days (N=67)		Lenalidomide 5 mg QD 28 of 28 Days (N=69)		Lenalidomide 10 mg QD 21 of 28 Days (N=69)		Overall (N=205)	
Age (Years)								
Mean	68.2		66.2		67.6		67.3	
Median	69.9		66.0		68.0		68.0	
Min, Max	39.0, 85.0		40.0, 86.0		36.0, 84.0		36.0, 86.0	
Sex	n	(%)	n	(%)	n	(%)	n	(%)
Male	13	(19.4)	16	(23.2)	20	(29.0)	49	(23.9)
Female	54	(80.6)	53	(76.8)	49	(71.0)	156	(76.1)
Race [a]	n	(%)	n	(%)	n	(%)	n	(%)
White	66	(98.5)	67	(97.1)	69	(100.0)	202	(98.5)
Other	1	(1.5)	2	(2.9)	0	(0.0)	3	(1.5)
Taken Prior EPO	n	(%)	n	(%)	n	(%)	n	(%)
Yes	33	(49.3)	35	(50.7)	40	(58.0)	108	(52.7)
No	34	(50.7)	34	(49.3)	29	(42.0)	97	(47.3)
Duration of MDS (Years)								
Mean	3.4		3.5		4.0		3.6	
Median	2.4		2.7		2.5		2.6	
Min, Max	0.2, 14.3		0.2, 17.1		0.2, 29.2		0.2, 29.2	
Hemoglobin (g/dL)								
Mean	8.3		8.1		8.5		8.3	
SD	1.17		1.05		1.06		1.10	
Median	8.2		8.0		8.2		8.1	
Min, Max	5.6, 11.2		5.7, 11.0		6.2, 11.2		5.6, 11.2	
5q(-) (31-33) Chromosomal Abnormality	n	(%)	n	(%)	n	(%)	n	(%)
Yes	63	(94.0)	64	(92.8)	64	(92.8)	191	(93.2)
No	1	(1.5)	2	(2.9)	1	(1.4)	4	(2.0)
Missing	3	(4.5)	3	(4.3)	4	(5.8)	10	(4.9)
Baseline Chromosomal Abnormality	n	(%)	n	(%)	n	(%)	n	(%)
Isolated del(5q)	45	(67.2)	43	(62.3)	47	(68.1)	135	(65.9)
Del(5q) + 1 additional abnormality	13	(19.4)	15	(21.7)	10	(14.5)	38	(18.5)
Del(5q) + ≥ 2 additional abnormalities	5	(7.5)	5	(7.2)	7	(10.1)	17	(8.3)
IPSS Score (Central Review)[b]	n	(%)	n	(%)	n	(%)	n	(%)
Low (0)	30	(44.8)	20	(29.0)	20	(29.0)	70	(34.1)
Intermediate-1 (0.5 – 1.0)	22	(32.8)	29	(42.0)	23	(33.3)	74	(36.1)

Table 22: Baseline Demographic and Disease-related Characteristics by Treatment Group and Overall (ITT Population) (Continued)

Parameter/Characteristic	Placebo QD 28 of 28 Days (N=67)		Lenalidomide 5 mg QD 28 of 28 Days (N=69)		Lenalidomide 10 mg QD 21 of 28 Days (N=69)		Overall (N=205)	
Intermediate-2 (1.5 – 2.0)	2	(3.0)	5	(7.2)	3	(4.3)	10	(4.9)
High Risk (≥ 2.5)	0	(0.0)	0	(0.0)	1	(1.4)	1	(0.5)
Missing	13	(19.4)	15	(21.7)	22	(31.9)	50	(24.4)
FAB Classification (Central Review)[c]	n	(%)	n	(%)	n	(%)	n	(%)
RA	37	(55.2)	38	(55.1)	32	(46.4)	107	(52.2)
RARS	8	(11.9)	7	(10.1)	9	(13.0)	24	(11.7)
RAEB	4	(6.0)	9	(13.0)	9	(13.0)	22	(10.7)
CMML	1	(1.5)	2	(2.9)	0	(0.0)	3	(1.5)
RAEB-T	1	(1.5)	0	(0.0)	0	(0.0)	1	(0.5)
CML	0	(0.0)	0	(0.0)	1	(1.4)	1	(0.5)
Specimen not adequate from diagnosis	12	(17.9)	11	(15.9)	17	(24.6)	40	(19.5)
Other or missing	4	(6.0)	2	(2.9)	1	(1.4)	7	(3.4)
Transfusion Burden (Units/8 Weeks)								
Median	6.0		6.0		6.0		6.0	
Min, Max	2.0, 12.0		1.0, 25.0		2.0, 12.0		1.0, 25.0	

[a] Percents may add up to more than 100% since patients were allowed to select more than one Race.
[b] IPSS Score = Sum of Marrow blast + Karyotype + Cytopenia Score.
[c] French-American-British (FAB) classification of MDS.

Numbers analysed

The **Intent-to-Treat (ITT) population** included all patients that were randomised to one of the three study treatments (n=205).

The **Modified Intent-to-Treat (MITT) population**, defined earlier, was the population for the primary efficacy endpoint (n= 139).

The **Safety population**: includes all randomised patients who received any study drug or placebo (205).

Outcomes and estimation (MDS 003 and MDS 004)

Primary Efficacy Endpoint

The IWG criteria define a major haematologic response as a sustained improvement of at least 8 consecutive weeks (56 days). Red blood cell transfusion independence was thus defined as a period of at least 56 consecutive days during which no transfusions were given with the additional requirement that the untransfused Hgb concentration increased by at least 1 g/dL.. In the MDS-004 study, the primary efficacy endpoint extended the RBC TI period to ≥ 182 days.

The results on the primary efficacy endpoint are summarised in the following Tables 23-25 and Figure 7.

Table 23. Red Blood Cell Transfusion Independence of at least 56 days in MDS-003 and the Double-blind Phase of MDS-004 (ITT Populations)

	MDS-003	MDS-004		
Statistic	Lenalidomide 10 mg QD 28/28 days (N = 148)	Lenalidomide 10 mg QD 21/28 days (N = 69)	Lenalidomide 5 mg QD 28/28 days (N = 69)	Placebo QD 28/28 days (N = 67)
RBC TI responders ≥ 56 days (n, %)	97 (65.5)	42 (60.9)	33 (47.8)	5 (7.5)
Exact 95% CI	57.3, 73.2	48.4, 72.4	35.6, 60.2	2.5, 16.6
P-value[a]	NA	< 0.001	< 0.001	NA

[a] P-value from Cochran-Mantel-Haenszel test stratified by IPSS score (IPSS combined score = 0 vs > 0) to compare the 2 doses of lenalidomide to placebo in MDS-004.

Note: RBC TI was defined as the absence of the intravenous infusion of any RBC transfusion during any consecutive rolling 56 days during the treatment period and an increase in Hgb of at least 1 g/dL from the minimum during the screening/baseline period to the maximum during the RBC TI period, excluding the first 30 days after the last transfusion before the transfusion-free period.

Table 24. Red Blood Cell Transfusion Independence of at least 182 days in MDS-003 and the Double-blind Phase of MDS-004 (ITT Populations)

	MDS-003	MDS-004		
Statistic	Lenalidomide 10 mg QD 28/28 days (N = 148)	Lenalidomide 10 mg QD 21/28 days (N = 69)	Lenalidomide 5 mg QD 28/28 days (N = 69)	Placebo QD 28/28 days (N = 67)
RBC TI responders ≥ 182 days (n, %)	86 (58.1)	38 (55.1)	24 (34.8)	4 (6.0)
Exact 95% CI	49.7, 66.2	42.6, 67.1	23.7, 47.2	1.7, 14.6
P-value[a]	NA	< 0.001	< 0.001	NA

[a] P-value from Cochran-Mantel-Haenszel test stratified by IPSS score (IPSS combined score = 0 vs > 0) to compare the 2 doses of lenalidomide to placebo in MDS-004.

Note: RBC TI was defined as the absence of an intravenous infusion of any RBC transfusion during any consecutive rolling 182-day period during the treatment period and an increase in Hgb of at least 1 g/dL from the minimum during the screening/baseline period to the maximum during the RBC TI period, excluding the first 7 days after the last transfusion before the transfusion-free period.

Table 25. MDS-004: Response Rate for 182+ Day RBC Transfusion Independence (MITT Population)

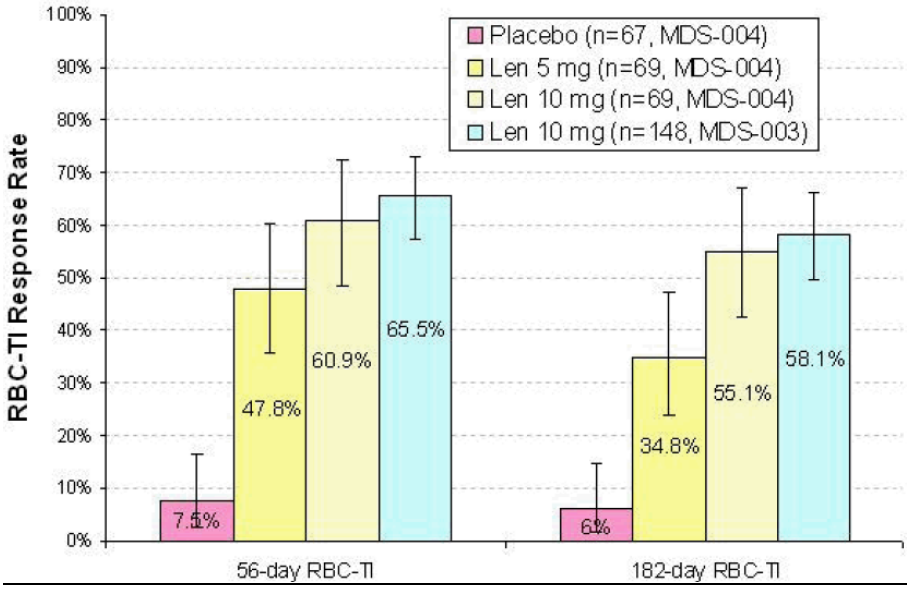
Statistic	Placebo (N=51)	Lenalidomide 5 mg/day (N=47)	Lenalidomide 10 mg/day (N=41)
Number (%) transfusion independent [a]	3 (5.9)	20 (42.6)	23 (56.1)
Exact 95% CI	1.2, 16.2	28.3, 57.8	39.7, 71.5
p-value [b]	NA	< 0.001	< 0.001
p-value [c]	NA	0.208	

[a] The absence of the intravenous infusion of any RBC transfusion during any consecutive rolling 182+ days during the treatment period and an increase in hemoglobin of at least 1 g/dL from the minimum during the screening/baseline period to the maximum during the transfusion-independent period, excluding the first 7 days after the last transfusion before the transfusion-free period.

[b] P-value from Cochran-Mantel-Haenszel (CMH) test stratified by IPSS score (IPSS combined score =0 versus >0) to compare lenalidomide treatment with placebo

[c] P-value from CMH test stratified by IPSS score (IPSS combined score =0 versus >0) to compare 5 mg lenalidomide and 10mg lenalidomide

Figure 7. Red Blood Cell Transfusion Independence Response Rates (at least 56 days and at least 182 days) in MDS-003 and the Double-blind Phase of MDS-004 (ITT Populations)



Secondary Efficacy Endpoints

Results for secondary endpoints are summarised in the following:

Minor haematologic response

Table 26. Proportion of Patients in MDS-003 and the Double-blind Phase of MDS-004 who achieved at Least a Minor Hematologic Response (ITT Populations)

	MDS-003	MDS-004		
Statistic	Lenalidomide 10 mg QD 28/28 days (N = 148)	Lenalidomide 10 mg QD 21/28 days (N = 69)	Lenalidomide 5 mg QD 28/28 days (N = 69)	Placebo QD 28/28 days (N = 67)
≥ Minor hematologic responders (n, %)[a]	113 (76.4)	49 (71.0)	42 (60.9)	16 (23.9)
Exact 95% CI	68.7, 82.9	58.8, 81.3	48.4, 72.4	14.3, 35.9

Time to Red Blood Cell Transfusion Independence

Table 27. Time to Red Blood Cell Transfusion Independence Response According to the International Working Group Criteria (at least 56 days) (ITT Populations)

	MDS-003	MDS-004		
Time to RBC TI response (Weeks)[a]	Lenalidomide 10 mg QD 28/28 days (N = 148)	Lenalidomide 10 mg QD 21/28 days (N = 69)	Lenalidomide 5 mg QD 28/28 days (N = 69)	Placebo QD 28/28 days (N = 67)
RBC TI responders (n)	97	42	33	5
Median	4.1	4.6	4.1	0.3
Mean (SD)	5.5 (6.56)	5.4 (3.74)	4.3 (3.72)	6.4 (10.33)
Min, Max	0.3, 49.0	0.3, 14.7	0.3, 12.3	0.3, 24.1

Median time to Response for 182+ Day RBC Transfusion Independence (MDS-004)

Double-blind - ITT Population: 10 mg QD (n=69), 5 mg QD (n=69), and placebo (n=67): 4.3, 3.3, and 0.3 weeks, respectively.

MITT Population:

Table 28. Median time to Response for 182+ day RBC Transfusion Independence (Study MDS-004)

Statistic	Placebo (N=51)	Lenalidomide 5 mg/day (N=47)	Lenalidomide 10 mg/day (N=41)
Number transfusion independent (responders)	3	20	23
Mean (weeks)[a]	8.2	3.5	4.5
SD	13.77	3.65	4.03
Median (weeks)[a]	0.3	3.0	4.3
Min, Max	0.3, 24.1	0.3, 12.3	0.3, 14.7

[a] Measured from the day of the first dose of study drug to the first day of the 182+ day RBC transfusion-free period.

Duration of Red Blood Cell Transfusion Independence

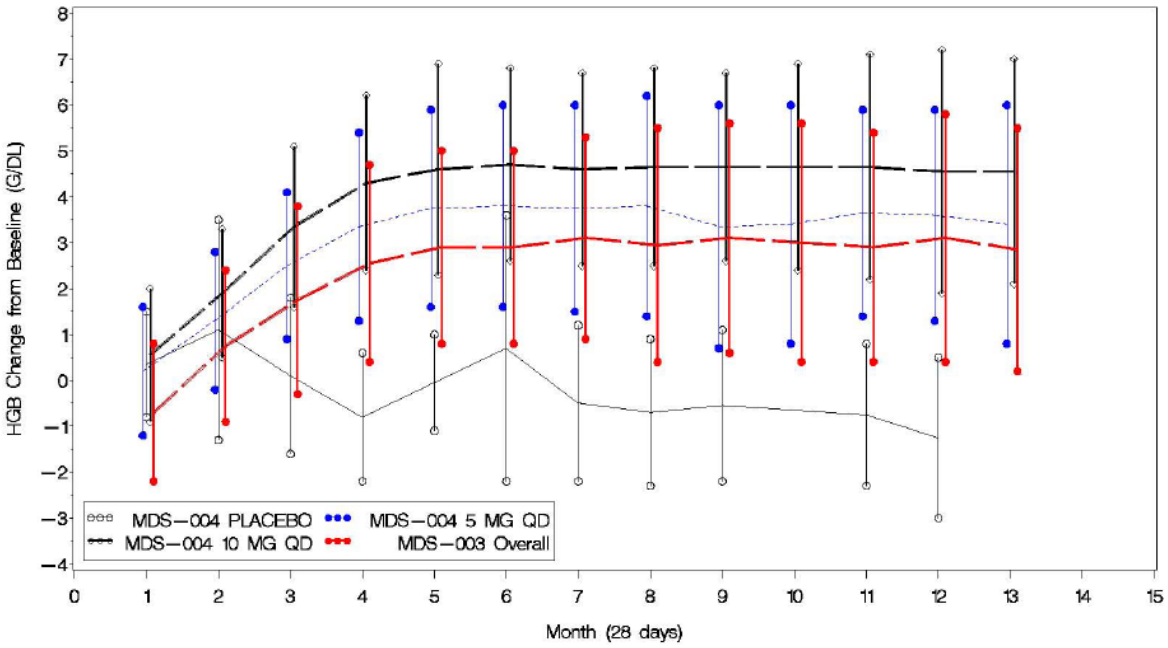
Table 29. Duration of Red Blood Cell Transfusion Independence Response According to the IWG Criteria (at least 56 days) (ITT Populations)

	MDS-003	MDS-004 (DB and OL phases)		
Kaplan-Meier Estimates[a]	Lenalidomide 10 mg QD 28/28 days (N = 148)	Lenalidomide 10 mg QD 21/28 days (N = 69)	Lenalidomide 5 mg QD 28/28 days (N = 69)	Placebo QD 28/28 days (N = 67)
Durability of RBC TI response				
RBC TI responders (n)	97	42	33	5
Subjects who had a transfusion after RBC TI response (n, %)	57 (58.8)	16 (38.1)	14 (42.4)	1 (20.0)
Subjects who maintained RBC TI response (censored)[b] (n, %)	40 (41.2)	26 (61.9)	19 (57.6)	4 (80.0)
Duration of RBC TI response (weeks)				
Median (weeks)	114.4	NE	NE	NE
95% CI	78.4, 153.7	98.3, NE	46.3, NE	9.1, NE
Summary statistics				
Mean (SD)	107.5 (82.55)	97.4 (49.53)	84.2 (58.60)	48.7 (23.94)
Min, Max	8.1, 250.9	8.0, 158.7	8.0, 157.0	9.1, 74.0

[a] Measured from the first of the consecutive 56 days during which the subject achieved RBC TI to the date of the first RBC transfusion after this period.
[b] Duration of RBC TI response was censored at the date of last visit for subjects who maintained a RBC TI response.

Change in Haemoglobin Concentration from Baseline

Figure 8. Mean Haemoglobin Change from Baseline for Patients who Achieved Red Blood Cell Transfusion Independence (at least 56 days) in MDS-003 and the Double-blind Phase of MDS-004 (ITT Populations)



Number of subjects in each month													
MDS-004 Placebo	5	5	5	5	5	5	4	4	4		4	4	
MDS-004 5 mg QD	33	33	33	32	28	26	27	27	26	26	23	21	13
MDS-004 10 mg QD (cyclic regimen)	42	42	42	42	42	40	38	39	39	39	37	37	26
MDS-003 10 mg QD (continuous regimen)	96	94	93	93	91	91	88	85	88	81	82	80	74

The median increase in Hgb concentration from baseline was 5.6 g/dL (range: 2.2 to 40.7 g/dL) for the 97 responders in the MDS-003 study and 6.4 g/dL (range: 1.8 to 10 g/dL) for the 42 responders in the 10-mg lenalidomide treatment group in the MDS-004 study.

The median Hgb increase for the 33 responders in the 5-mg lenalidomide treatment group in the MDS-004 study was 5.3 g/dL (range: 1.5 to 8.6 g/dL), approximately 2-fold higher than that for the 5 responders in the placebo group (2.6 g/dL; range: 1.5 to 4.4 g/dL).

Improved and sustained Hgb levels were seen in responders in all active treatment groups. A larger median increment was seen in the 10 mg group (6.4 g/dL) vs the 5 mg group (5.3 mg/dL) in MDS-004.

IWG-defined Hematologic Improvement: Platelet and Neutrophil Responses

Platelet response

Of the 27 evaluable patients in the ITT population of the MDS-003 study, 4 (14.8%) achieved a major platelet response. In the MDS-004 study, major platelet responses were observed in 2 of 11 (18.2%) evaluable patients in the 5-mg lenalidomide group, in 1 of 9 (11.1%) evaluable patients in the 10-mg lenalidomide group, and in none of the evaluable patients (0%) in the placebo group.

Neutrophil response

Eighteen (34.6%) of the 52 evaluable patients in the ITT population in the MDS-003 study achieved a major neutrophil response. In MDS-004, 3 (10.7%) of 28 evaluable patients in the 5-mg lenalidomide

group, 4 (14.8%) of 27 evaluable patients in the 10-mg lenalidomide group, and 2 (12.5%) of 16 evaluable patients in the placebo group had a major neutrophil response.

Bone Marrow Response (per IWG criteria)

Table 30. Bone Marrow Improvement in MDS-003 and MDS-004 (ITT Populations)

	MDS-003	MDS-004		
	Lenalidomide 10 mg QD 28/28 days (N = 148)	Lenalidomide 10 mg QD 21/28 days (N = 69)	Lenalidomide 5 mg QD 28/28 days (N = 69)	Placebo QD 28/28 days (N = 67)[a]
Response Category[b]	n (%)	n (%)	n (%)	n (%)
Complete remission	46 (31.1)	12 (17.4)	7 (10.1)	8 (11.9)[b]
Partial remission	17 (11.5)	1 (1.4)	5 (7.2)	2 (3.0)[b]
Stable disease	ND	33 (47.8)	35 (50.7)	37 (55.2)

[a] Placebo response includes responses after crossover to OL lenalidomide treatment (ITT analysis population). There were 10 responders in the placebo group who achieved their response under lenalidomide treatment after crossover to the OL phase. Subjects with a complete remission were as follows: 0014010, 0044002, 0044006, 0064001, 0144001, 0154004, 0184002, and 0384004. Subjects with a partial remission were as follows: 0034001 and 0184006 (data available upon request).
[b] Within each group, the "n" for each category does not total to "N" due to lack of sufficient BM samples to determine response.

BM improvement, partial or complete, was observed in 43% of patients in MDS-003 and in 19% in the 10 mg group and 17% in the 5 mg group in the MDS-004 study. BM improvement was induced in a little less than 20% of patients under the 10 mg cyclic regimen. The figures given under the Placebo heading refer to patients in the placebo group in the ITT population following crossover to OL lenalidomide treatment.

Cytogenetic Response (per IWG criteria)

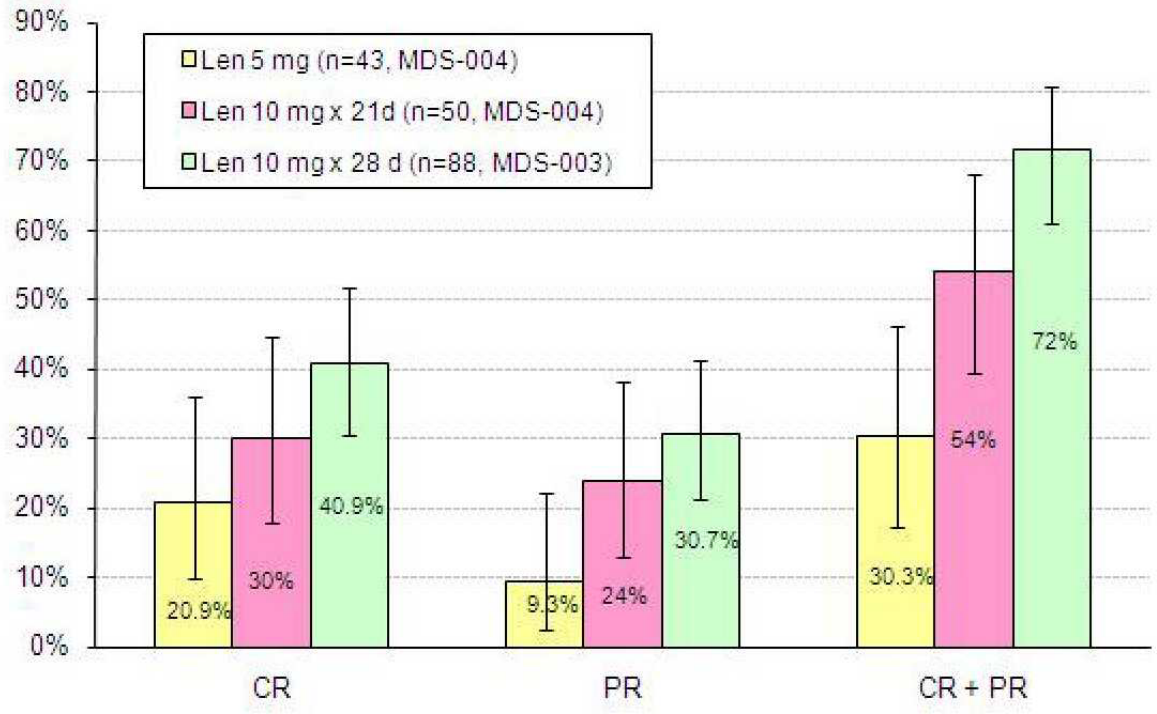
Patients were eligible to be evaluated for a cytogenetic response if ≥ 20 metaphases were analysed at baseline during the 56-day period immediately preceding the first day of study drug intake and when ≥ 20 metaphases were analysed at least once at post baseline visits using conventional cytogenetic techniques.

Table 31. Cytogenetic Response in MDS-003 and the Double-blind Phase of MDS-004 (ITT Populations)

	MDS-003	MDS-004		
Cytogenetic Response[a]	Lenalidomide 10 mg QD 28/28 days (N = 148)	Lenalidomide 10 mg QD 21/28 days (N = 69)	Lenalidomide 5 mg QD 28/28 days (N = 69)	Placebo QD 28/28 days (N = 67)
All evaluable subjects (n)[b]	**88**	**50**	**43**	**40**
Major or minor best cytogenetic response (n, %)	63 (71.6)	27 (54.0)	13 (30.2)	0 (0.0)
Major response (n, %)	36 (40.9)	15 (30.0)	9 (20.9)	0 (0.0)
Minor response (n, %)	27 (30.7)	12 (24.0)	4 (9.3)	0 (0.0)
None (n, %)	25 (28.4)	23 (46.0)	30 (69.8)	40 (100.0)
Not evaluable (n)	60	19	26	27

21/28 = Days 1 to 21 of 28-day cycles; 28/28 = Days 1 to 28 of 28-day cycles; QD = once daily.
[a] Best postbaseline response. Major response = no detectable cytogenetic abnormality if a preexisting abnormality was present. Minor response = ≥ 50% reduction in the percent of abnormal metaphases.
[b] Number of subjects who were evaluable for a cytogenetic response and who had at least 20 analyzable metaphases at baseline and at least one postbaseline visit.

Figure 9. Cytogenetic Response in Study MDS-003 and the Double-blind Phase of Study MDS-004 (Cytogenetic-evaluable Patients in ITT Populations)



CR = complete (major) response; ITT = intent to treat; Len = lenalidomide; PR = partial (minor) response.

Notes: Patients evaluable for best cytogenetic response had to have at least 20 analyzable metaphases at baseline and at

least one postbaseline visit. For Studies MDS-003 and MDS-004, the Intent-to-treat population = the treated (Safety)

population.

Study MDS-003: The study database was final on 01 Oct 2010.

Study MDS-004: Data cutoff date = 14 Jun 2010.

In the 10 mg arm major and minor cytogenetic responses were observed in 30.0% and 24.0% of patients, respectively. The achievement of transfusion independence is not dependent upon complete elimination of the malignant clone since a proportion of patients achieved transfusion independence in the absence of a cytogenetic response.

Red Blood Cell Transfusion Independence Response by Cytogenetic Response

Table 32. Association of Cytogenetic Response with Red Blood Cell Transfusion Independence Response of at least 182 days in MDS-003 and MDS-004 (ITT Populations)

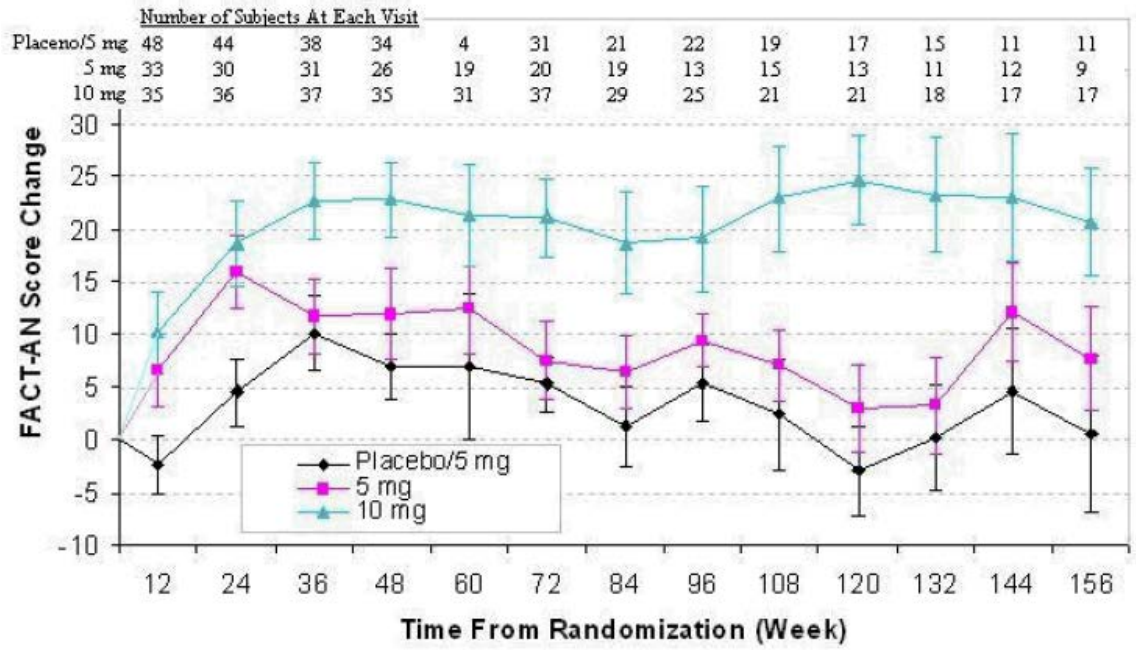
	MDS-003		MDS-004					
	Lenalidomide 10 mg QD 28/28 days (N = 148)		Lenalidomide 10 mg QD 21/28 days (N = 69)		Lenalidomide 5 mg QD 28/28 days (N = 69)		Placebo QD 28/28 days (N = 67)	
		RBC TI		RBC TI		RBC TI		RBC TI
	N[a]	n (%)	N[a]	n (%)	N[a]	n (%)	N[a]	n (%)
RBC TI ≥ 182 days	148	86 (58.1)	69	38 (55.1)	69	24 (34.8)	67	4 (6.0)
Cytogenetic response (major or minor)[b]	63	57 (90.5)	27	21 (77.8)	13	6 (46.2)	0	NA
Major cytogenetic response	36	34 (94.4)	15	12 (80.0)	9	4 (44.4)	0	NA
Minor cytogenetic response	27	23 (85.2)	12	9 (75.0)	4	2 (50.0)	0	NA
Cytogenetic Nonresponders	25	8 (32.0)	23	14 (60.9)	30	13 (43.3)	40	4 (10.0)
P-value[c]		< 0.001		0.228		1.000		NA
Not evaluable[d]	60	21 (35.0)	19	3 (15.8)	26	5 (19.2)	27	0 (0.0)

[a] Number of subjects for category of indicated cytogenetic assessment (used in percentage calculation).
[b] Percentage of subjects who were RBC TI responders and cytogenetic responders (major or minor).
[c] P-value from a 2-sided Fisher Exact test for 2 × 2 table of (cytogenetic response [major or minor] or cytogenetic nonresponse) × (RBC TI response or RBC TI nonresponse).
[d] Subjects who were evaluable for cytogenetic response had to have at least 20 analyzable metaphases at baseline and at least one postbaseline visit.

Health-related Quality of Life

The assessment of HRQoL using the FACT-An instrument was conducted using the MDS-004 ITT population. Randomised patients who completed the baseline FACT-An assessment and the FACT-An assessment at 12 weeks were included in the DB change from baseline ANOVA analyses.

Figure 10. Analysis of Mean Change from Baseline in FACT-A Total Scores during the Double-blind and Open-label Phases of MDS-004 (Weeks 12 to 156) (Safety Population)

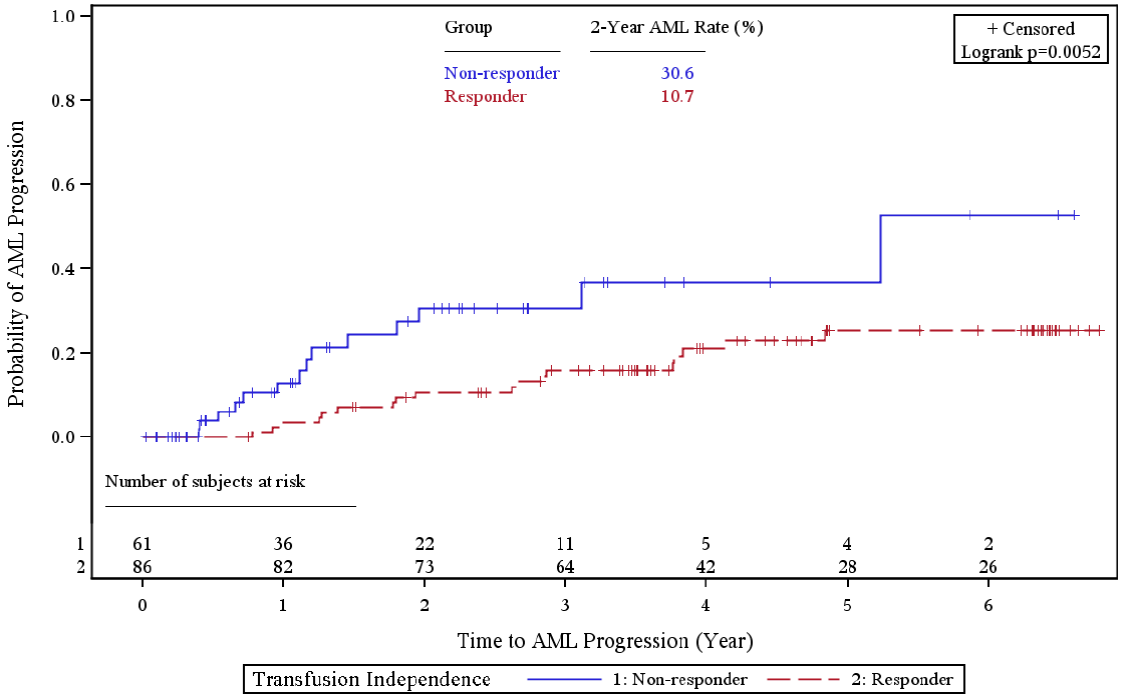


Statistically significant ($p < 0.05$) improvements of 5.9 and 5.8 points in FACT-An total scores were observed by Week 12 for patients in the 5 mg and 10 mg groups, respectively. In terms of HR QoL, more robust results were seen with the 10 mg dose.

Progression of Disease to Acute Myeloid Leukaemia (MDS-003 and MDS-004)

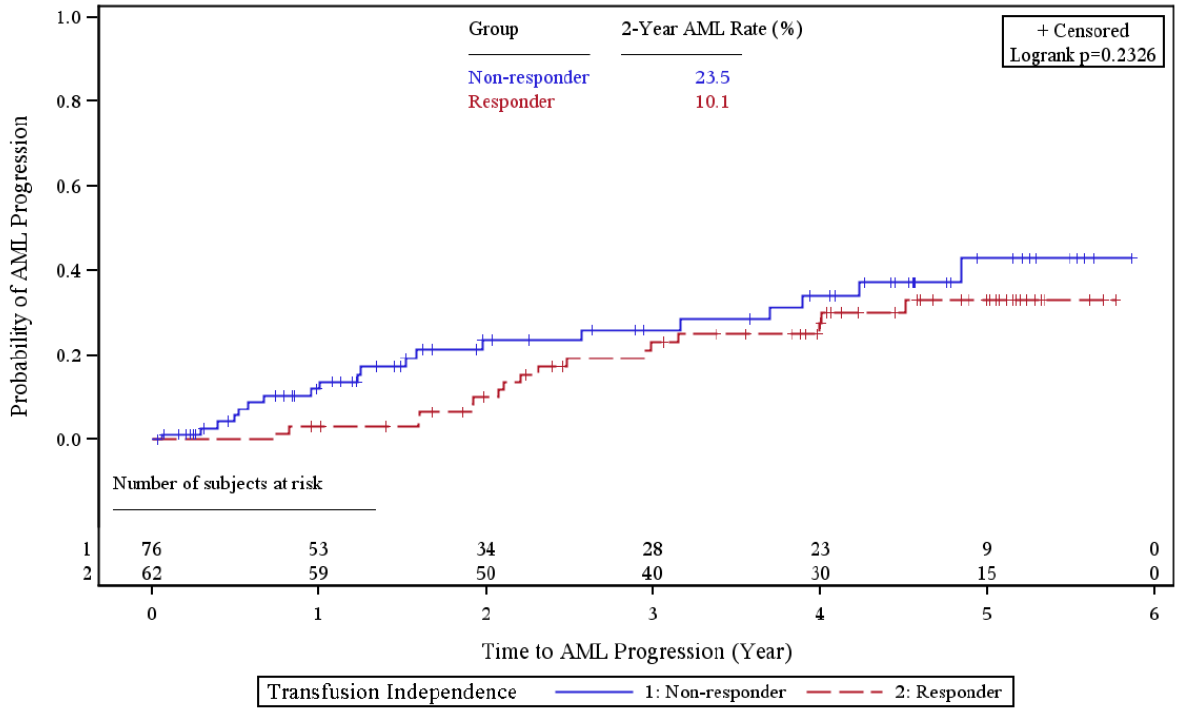
The risk of progression to AML over time in RBC TI responders (≥ 182 days) and non-responders is presented for MDS-003 (ITT population, N = 147) in Figure 11, and for MDS-004 (patients randomised to lenalidomide, N = 138) in Figure 12.

Figure 11. Kaplan-Meier Curves of Time to Progression to Acute Myeloid Leukemia in Red Blood Cell Transfusion Independence Responders (at least 182 days) and Nonresponders in MDS-003 (ITT Population)



AML = acute myeloid leukemia; ITT = intent-to-treat. Note: Patient 0243010 was diagnosed by the central cytogenetic reviewer as having AML at entry to the MDS-003 study(baseline); hence, this patient was excluded from the progression to AML analyses.

Figure 12. Kaplan-Meier Curves of Time to Progression to Acute Myeloid Leukemia in Red Blood Cell Transfusion Independence Responders (at least 182 days) and Nonresponders for Patients Randomised to Lenalidomide in MDS-004 (Double-blind Phase, Open-label Phase, and Follow-up Period; Safety Population)



AML = acute myeloid leukemia; ITT = intent-to-treat. Note: One additional patient has been included in all AML analyses for the MDS-004 study as progression to AML.

Achieving RBC TI was not associated with an increased risk of progression to AML in either pivotal study. In both pivotal studies, achieving RBC TI (≥ 182 days) was associated with a delay in the onset of AML when compared to non-responders. The 2-year risk of progression to AML was 10.7% and 10.1% for RBC TI responders in MDS-003 and MDS-004, respectively, compared to 30.6% and 23.5% for non-responders.

Table 33. Progression to Acute Myeloid Leukemia at 31 Mar 2012 and 26 Nov 2012 Data Cutoffs – Study MDS-004 (Intent-to-treat Population; Double-blind, Open-label, and Follow-up Phases)

	Placebo (N = 67)	Lenalidomide 5 mg (N = 69)	Lenalidomide 10 mg (N = 69)
Data Cutoff = 31 Mar 2012 (Day 90 First RSI)			
Progressed to AML, n (%)			
Yes	26 (38.8)	24 (34.8)	15 (21.7)
No	41 (61.2)	45 (65.2)	54 (78.3)
Time to AML from randomisation (mo)			
Median (min, max)	28.3 (2.8, 61.6)	21.6 (0.8, 65.6)	25.0 (5.9, 48.2)
Data Cutoff = 26 Nov 2012			
Progressed to AML, n (%)			
Yes	26 (38.8)	24 (34.8)	16 (23.2)
No	41 (61.2)	45 (65.2)	53 (76.8)
Time to AML from randomisation (mo)			
Median (min, max)	28.3 (2.8, 61.6)	21.6 (0.8, 65.6)	25.2 (5.9, 64.9)

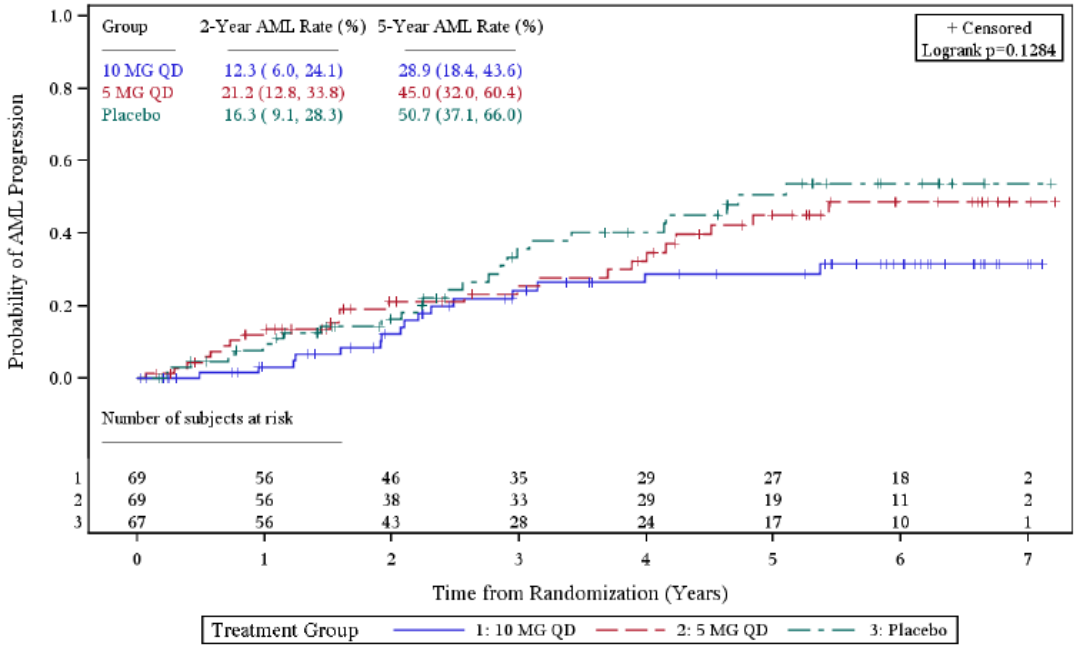
AML = acute myeloid leukemia; RSI = request for supplementary information.

[a] Revised.

Note: Intent-to-treat population = Safety population.

From the data cut-off of 31 Mar 2012 to the data cut-off of 26 Nov 2012, 1 additional patient (in the lenalidomide 10-mg group) had progression to AML. The median time to progression to AML in the lenalidomide 10-mg group was 25 months (Table 33). The 2-year rate for progression to AML remained 12.3% in the 10-mg lenalidomide group, 21.2% in the 5-mg lenalidomide group, and 16.3% in the placebo group. The respective 5-year rates were 28.9%, 45.0%, and 50.7%. (Figure 13)

Figure 13. Time to Progression to Acute Myeloid Leukemia by Randomised Treatment Group; Study MDS-004 (Double-blind Phase, Open-label Phase, and Follow-up Period; Intent-to-treat Population)



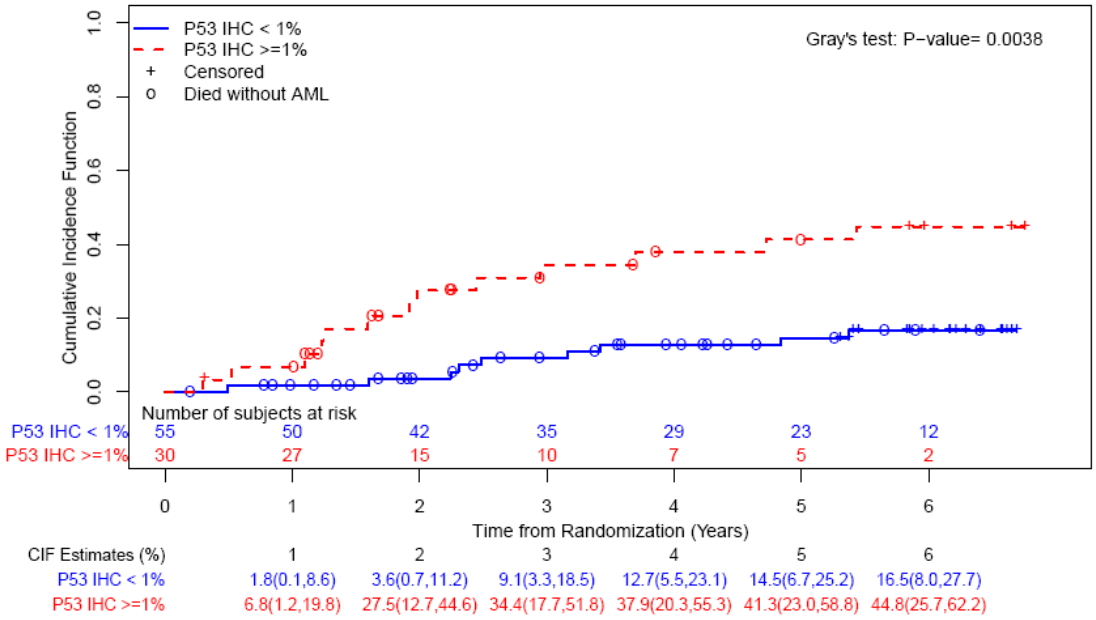
AML = acute myeloid leukemia; CI = confidence interval; QD = once daily.
Notes: Time to progression to AML was calculated from the date of randomisation. The AML rates, % (95% CI), are provided.
Data cutoff date = 26 Nov 2012.

TP53 mutational status on Progression to AML (MDS-004)(Safety Population)

Using a 1% cut-off, the 2-year cumulative incidence of progression to AML was 3.6% (95% CI = 0.7-11.2) in patients with p53-negative IHC status (ie, IHC < 1%) at baseline compared with 27.5% (95% CI = 12.7-44.6) for p53-positive patients (p = 0.004) (Figure 14).

When a 2% cut-off was used, the 2-year cumulative incidence of progression to AML was 8.7% (95% CI = 3.5-16.8) in patients with p53-negative IHC status (ie, IHC < 2%) at baseline compared with 26.3% (95% CI = 7.5-50.2) for p53-positive patients (p = 0.036).

Figure 14. Time to Progression to Acute Myeloid Leukemia Using Death Without AML as Competing Risk, by p53 IHC Status – Study MDS-004 (Safety Population; Double-blind, Open-label, and Follow-up Phases)

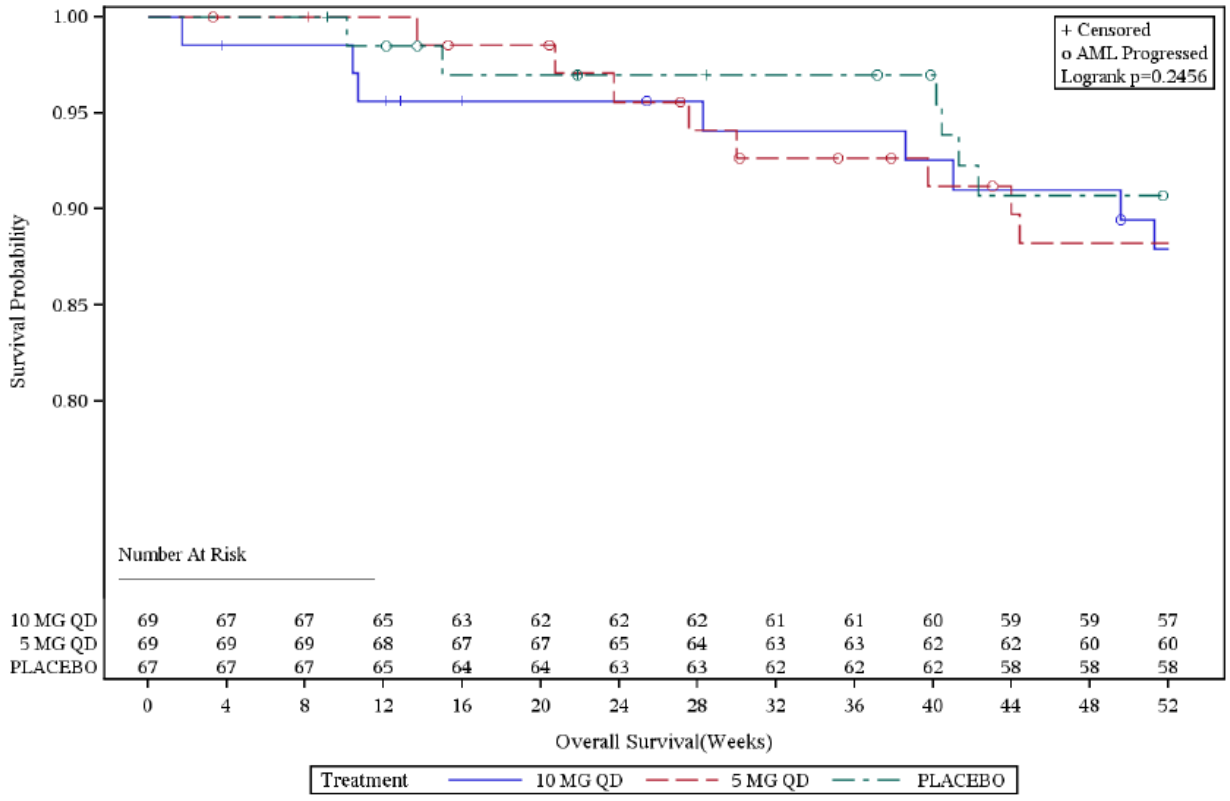


< 1% = p53 negative; ≥ 1% = p53 positive; AML = acute myeloid leukemia; CIF = cumulative incidence function; IHC = immunohistochemistry; p53 = tumor protein 53.
Notes: Time to progression to AML using death without AML as competing risk.
Data cutoff: 26 Nov 2012.

Overall Survival

The Kaplan-Meier OS curves of the first 52 weeks of study for patients in Study MDS-004 are presented by randomised treatment assignment in Figure 14. The first 52 weeks of study includes patients receiving treatment in the DB and OL phases as well as patients who have discontinued treatment and are being followed for long term outcomes. By Week 52, the median OS was not reached for any of the 3 treatment groups. There were no significant differences in OS between the placebo, 5-mg, and 10-mg treatment groups during the first 52 weeks of the study (p=0.2456).

Figure 15. Overall Survival in First 52 Weeks by Randomised Treatment Assignment (MDS-004, ITT Population)

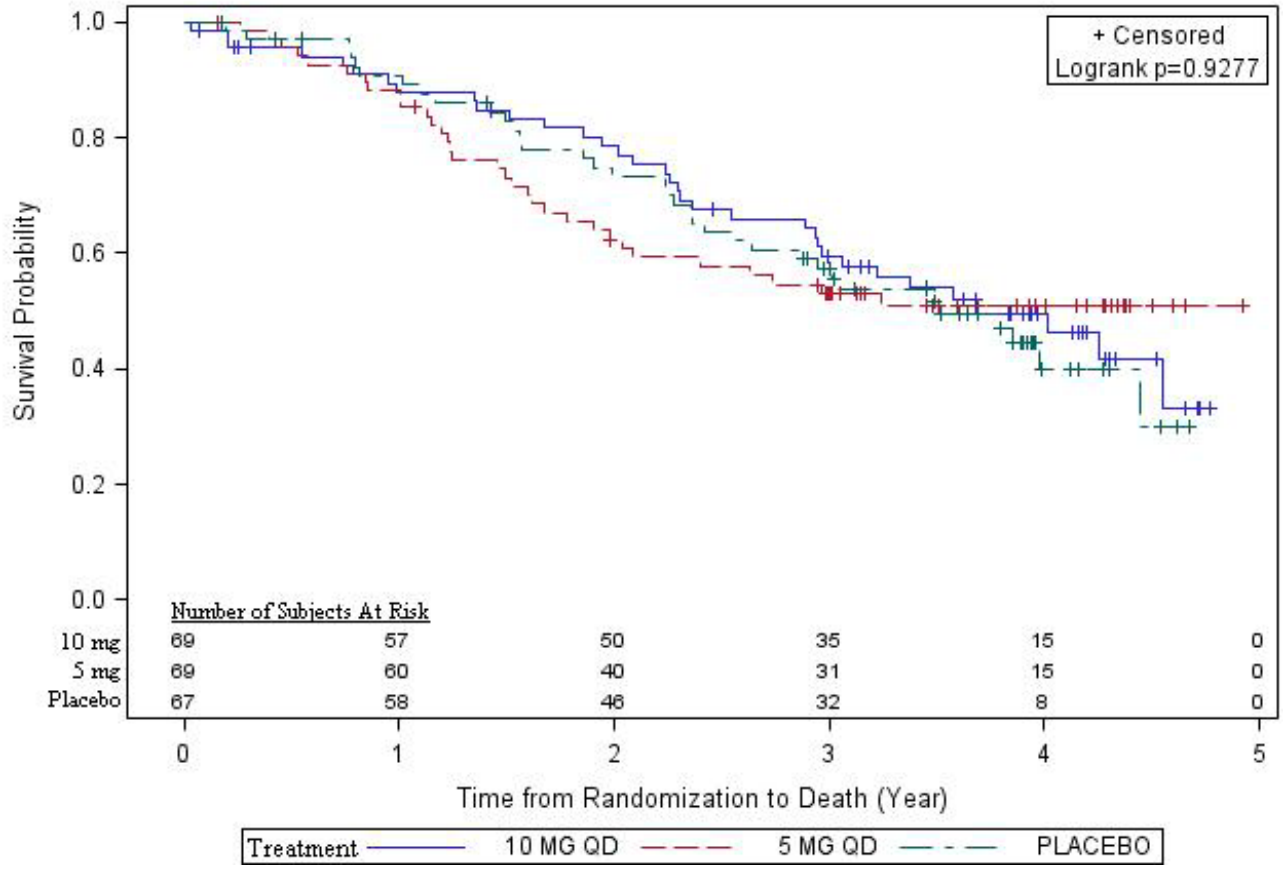


AML = acute myeloid leukemia; QD = once daily.
NOTE: each circle represents a case of progression to AML, at the time of onset.
Data Cutoff Date: 26 Nov 2012.

The median duration of follow-up for overall survival for the patients in the ITT population was approximately 36 months, with 35.9 months for placebo, 35.5 months for the 5 mg and 36.9 months for the 10 mg treatment groups, respectively.

Overall, when assessed by the ITT analysis, there was no difference in overall survival across the treatment groups (Figure 15), although the placebo group included 54 patients who crossed over to receive 5 mg after Week 16 (see disposition chart). During the first 16 weeks of the study, 1of 67 (1.5%), 1 of 69 (1.5 %) and 2 of 69 (2.9%) patients died in the placebo, 5 mg and 10 mg treatment groups.

Figure 16. Overall Survival by Randomised Treatment Group (MDS-004 ITT Population)

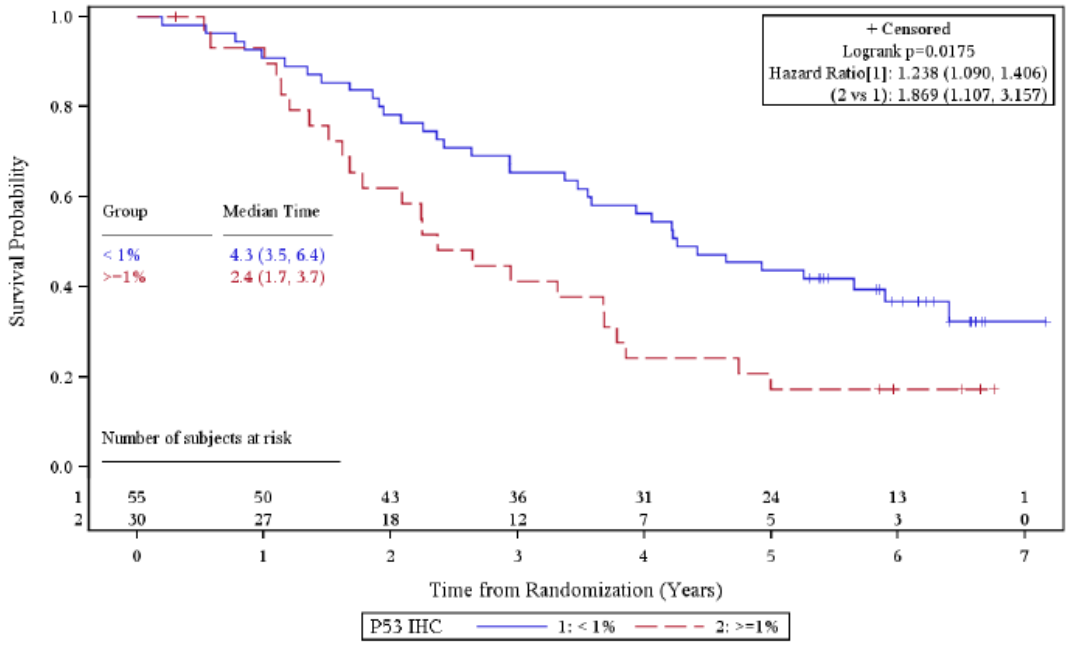


TP53 mutational status on OS (MDS-004) (Safety Population)

Using a 1% cut-off, p53-positive IHC staining at baseline was associated with reduced OS (median = 2.4 years; 95% CI = 1.7-3.7) when compared with patients with p53-negative IHC status (median = 4.3 years; 95% CI = 3.5-6.4; p = 0.0175, Figure 17).

A consistent pattern was observed when a 2% cut-off was used: OS for patients with p53-positive IHC status was reduced (median = 1.8 years; 95% CI = 1.5-3.9) compared with p53-negative IHC status (median = 3.9 years; 95% CI = 2.9-5.3; p = 0.051).

Figure 17. Kaplan-Meier Estimate of Overall Survival by p53 IHC Status – Study MDS-004 (Safety Population; Double-blind, Open-label, and Follow-up Phases)



< 1% = p53 negative; ≥ 1% = p53 positive; IHC = immunohistochemistry; p53 = tumor protein 53.

Data cutoff: 26 Nov 2012.

Ancillary analyses

Comparison of Results of Subpopulations

Subgroup analyses were performed by baseline demographic characteristics, i.e., age, gender, race, and by baseline disease characteristics, i.e., baseline IPSS score, FAB classification, del (5q) status (baseline cytogenetics), and baseline transfusion burden.

Analysis of RBC TI (≥56 days) by Baseline Demographic and Disease Characteristics (ITT populations)

Table 34. Analysis of RBC TI (≥56 days) by Baseline Demographic and Disease Characteristics (ITT populations)

		MDS-003	MDS-004		
Prognostic Variable		**Lenalidomide 10 mg QD 28/28 days (N = 148)**	**Lenalidomide 10 mg QD 21/28 days (N = 69)**	**Lenalidomide 5 mg QD 28/28 days (N = 69)**	**Placebo QD 28/28 days (N = 67)**
Age	≤ 65 years	64.6% (31/48)	65.5% (19/29)	53.1% (17/32)	4.8% (1/21)
	> 65 years	66.0% (66/100)	57.5% (23/40)	43.2% (16/37)	8.7% (4/46)
	p-value	0.856	0.619	0.474	1.000
Gender	Male	58.8% (30/51)	45.0% (9/20)	43.8% (7/16)	0.0% (0/13)
	Female	69.1% (67/97)	67.3% (33/49)	49.1% (26/53)	9.3% (5/54)
	p-value	0.275	0.107	0.78	0.574
Race	White	65.7% (94/143)	60.9% (42/69)	46.3% (31/67)	7.6% (5/66)
	Other	60.0% (3/5)	0.0% (0/0)	100% (2/2)	0.0% (0/1)
	p-value	1.000	NA	0.225	1.000
FAB Classification[a]	RA	70.5% (55/78)	68.8% (22/32)	52.6% (20/38)	8.1% (3/37)
	RARS	50.0% (8/16)	44.4% (4/9)	14.3% (1/7)	25.0% (2/8)
	RAEB	63.3% (19/30)	55.6% (5/9)	44.4% (4/9)	0.0% (0/4)
	CMMoL	66.7% (2/3)	NA (0/0)	0.0% (0/2)	0.0% (0/1)
	RAEB-T	NA (0/0)	NA (0/0)	NA (0/0)	0.0% (0/1)
	AML	0.0% (0/1)	NA (0/0)	NA (0/0)	NA (0/0)
	Other	NA (0/0)	100% (1/1)	100.0% (1/1)	0.0% (0/4)
	Unable to classify	65.0% (13/20)	52.9% (9/17)	63.6% (7/11)	0.0% (0/12)
	Missing	NA (0/0)	100.0% (1/1)	0.0% (0/1)	NA (0/0)
	p-value	0.288	0.496	0.162	0.428
IPSS Risk Category[b]	Low	69.4% (34/49)	65.0% (13/20)	50.0% (10/20)	10.0% (3/30)
	INT-1	68.1% (47/69)	56.5% (13/23)	48.3% (14/29)	9.1% (2/22)
	INT-2	28.6% (2/7)	66.7% (2/3)	20.0% (1/5)	0.0% (0/2)
	High	50.0% (1/2)	0.0% (0/1)	NA (0/0)	NA (0/0)
	Unable to assign	61.9% (13/21)	63.6% (14/22)	53.3% (8/15)	0.0% (0/13)
	p-value	0.155	0.706	0.556	1.000
WPSS Group	Low	75.0% (3/4)	100.0% (2/2)	42.9% (3/7)	0.0% (0/2)
	Intermediate	65.3% (47/72)	65.4% (17/26)	54.2% (13/24)	8.8% (3/34)
	High	69.0 (29/42)	57.9 (11/19)	39.1% (9/23)	12.5% (2/16)
	Very High	25.0% (1/4)	0.0% (0/2)	NA (0/0)	0.0% (0/1)
	Missing	65.4% (17/26)	60.0% (12/20)	53.3% (8/15)	0.0% (0/14)
	p-value	0.385	0.235	0.604	0.741
Baseline Transfusion Units	≤ 2	84.4% (27/32)	44.4% (4/9)	80.0% (4/5)	100.0% (1/1)
	> 2 to 4	64.5% (20/31)	81.3% (13/16)	50.0% (8/16)	15.8% (3/19)
	> 4	57.0% (45/79)	56.8% (25/44)	43.8% (21/48)	2.1% (1/47)
	Missing	83.3% (5/6)	NA (0/0)	NA (0/0)	NA (0/0)
	p-value	0.020	0.119	0.350	0.006

No significant differences according to age, gender, race, baseline IPSS score, or FAB classification were observed in the ITT or MITT populations. Generally, a numerically greater response was seen in females vs males (e.g. 68% vs 45% in the 10 mg group in MDS-004, p=0.107 (ITT)).

Regarding IPSS, a numerically lower response rate was seen at the 5 mg level vs the 10 mg levels in the low and INT-1 risk categories. The risk categories INT-2 and high are not evaluable due to low patient numbers.

The greatest response rates were seen in RA followed by RAEB and RARS with the 10 mg levels being numerically superior of the 5 mg level. The response rate in CMMoL is not evaluable due to low patient numbers.

Analysis of Red Blood Cell Transfusion Independence Response by Baseline Cytogenetics (ITT)

There were no significant differences in responses to lenalidomide between patients with an isolated del (5q) cytogenetic abnormality and those with del (5q) plus one or more additional cytogenetic abnormalities in any of the treatment groups in the MDS-004 study although in the 10 mg dose group, the proportion of responders with an isolated del (5q) was higher than those with additional cytogenetic abnormalities. In the MDS-003 study, a larger proportion of patients with an isolated del (5q) achieved RBC TI compared to patients who had additional cytogenetic abnormalities.

The proportion of RBC TI responders (≥182 days) in the combined lenalidomide population was statistically non-significantly higher in patients with an isolated del (5q) abnormality and in those with del (5q) plus one additional cytogenetic abnormality compared to those who had ≥ 2 additional cytogenetic abnormalities at baseline (113 of 200 patients [56.5%] and 22 of 50 patients [44%] compared to 8 of 24 patients [33.3%], respectively).

The proportion of RBC TI responders among isolated del (5q) patients with < 5% blasts at baseline was similar to those with ≥ 5% blasts at baseline (77 of 131 patients [58.8%] and 17 of 32 patients [53.1%], respectively).

Cytogenetic Response by Baseline Cytogenetics (ITT)

There were no statistically significant differences in the proportion of patients who achieved cytogenetic responses in any of the treatment groups in both studies.

In the combined lenalidomide population, the proportion of cytogenetic responders was 59.2% (77/130) among patients with isolated del (5q), 62.5% (20/32) among patients with del (5q) plus one additional cytogenetic abnormality, and 28.6% (4/14 patients) among patients with ≥ 2 additional cytogenetic abnormalities.

The proportion of cytogenetic responders was 57.8% (52/90) among patients with less than 5% blasts at baseline and 54.2% (13/24) among those who entered the study with 5% or more blasts.

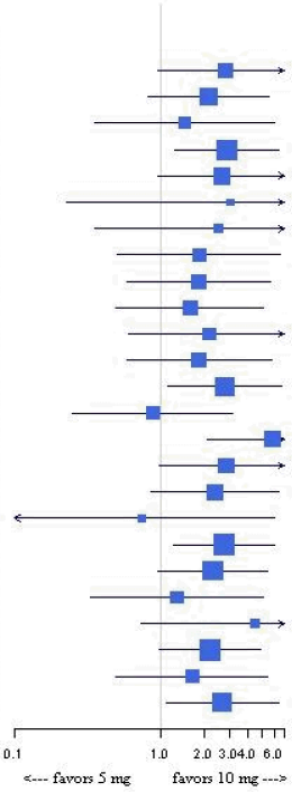
TP53 status and cytogenetic response

In the intent-to-treat analysis of all 3 arms combined, RBC-TI response ≥ 182 days was achieved by 30.0% (9/30) of p53-positive patients and 36.4% (20/55) of p53-negative patients. Among patients who received lenalidomide at a dose of 10 mg, RBC-TI response ≥ 182 days was achieved by 62.5% (5/8) of p53-positive patients and 52.0% (13/25) of p53-negative patients. Cytogenetic response (all 3 arms combined) was achieved by significantly more p53-negative patients (18/35; 51.4%) than p53-positive patients (3/21; 14.3%).

RBC TI (at least 182 days) by Treatment Group in MDS-004

Figure 18. Subgroup Analysis of 182-days Transfusion Independence Response by Treatment Group

Subgroup	RBC-TI(%) 10 mg	RBC-TI(%) 5 mg	OR
Age<=65	65.5	40.6	2.78
Age>65	47.5	29.7	2.14
Male	40.0	31.2	1.47
Female	61.2	35.8	2.83
FAB=RA	65.6	42.1	2.62
FAB=RARS	33.3	14.3	3.00
FAB=RAEB	55.6	33.3	2.50
IPSS=Low	55.0	40.0	1.83
IPSS=Intermediate-1	56.5	41.4	1.84
WPSS=Intermediate	65.4	54.2	1.60
WPSS=High	57.9	39.1	2.14
MDS Diagnosis <= 2 yrs	46.4	32.0	1.84
MDS Diagnosis > 2 yrs	61.0	36.4	2.73
EPO Level <=500 mIU/mL	39.1	42.1	0.88
EPO Level >500 mIU/mL	69.7	28.2	5.85
Prior ESA=no	69.0	44.1	2.81
Prior ESA=yes	45.0	25.7	2.36
EPO<=500 and Prior ESA=no	50.0	57.1	0.75
EPO>500 or Prior ESA=yes	53.6	29.8	2.71
Isolated Del 5q	57.4	37.2	2.28
Del 5q + >=1 additional Abn	41.2	35.0	1.30
Bsln Platelet<150x10^9/L	38.9	12.5	4.45
Bsln Platelet>=150x10^9/L	60.8	41.5	2.18
Bsln Trans Burden <= 4 units	60.0	47.6	1.65
Bsln Trans Burden > 4 units	52.3	29.2	2.66



Generally, in terms of RBC TI, the 10 mg cyclic dosing is favoured or not non-preferred. No subgroup in which the 5 mg continuous dose is superior is identified; the efficacy of lenalidomide according to baseline EPO levels is unknown.

Summary of main studies

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

For MDS 003, an interim analysis was conducted on the data captured up until 15 Sep 2004, for which clinical study report (CSR) was dated 07 Mar 2005. This report is an update with a 27 august 2008 cut off date.

Table 35. Summary of efficacy for trial MDS-003

Title: A multicenter, single-arm, open-label study of the efficacy and safety of CC-5013 monotherapy in red blood cell transfusion-dependent subjects with myelodysplastic syndromes associated with a del (5q) cytogenetic abnormality			
Study identifier	**CC-5013-MDS-003**		
Design	Phase 2, multicenter, single-arm, open-label study of the efficacy and safety of lenalidomide in patients who had an IPSS diagnosis of low- or intermediate-1-risk MDS associated with a del 5 (q31-33) cytogenetic abnormality and who had red blood cell (RBC)-transfusion-dependent anaemia. The protocol initially employed a syncopated dosage regimen in which 10 mg of lenalidomide was taken orally once daily on Days 1 to 21 of a 28-day cycle, but was subsequently amended (Amendment 1, dated 27 Aug 2003) to employ a continuous dosage regimen in which 10 mg of lenalidomide was taken without a planned rest period (28 days/28). Treatment continued until unacceptable AEs occurred, bone marrow disease progression was documented, progression or relapse following erythroid improvement was documented, or for a maximum of 24 cycles, whichever occurred first. 32 study centres in the United States and 1 study centre in Europe (Germany)		
	Duration of main phase:		24 weeks
Hypothesis	Superiority on the first 30 evaluable patients: null hypothesis (H0) response rate is ≤ 30% alternative hypothesis (H1) response rate is ≥ 60%		
Treatment	Single arm		Oral lenalidomide 10 mg (two 5 mg capsules) daily on Days 1-28 every 28 days. Patients who have been started on the syncopated regimen (Days 1-21 every 28 days) and have not experienced dose-limiting toxicity may be switched to an every day dose of 10 mg. N=148 patients (102 continuous, 46 syncopated)
Endpoints and definitions	Primary endpoint	RBC-TI	RBC-transfusion independence for at least 56 days accompanied by at least a 1 g/dL increase from screening/baseline in Hb
	Secondary endpoints		• Cytogenetic response • ≥ 50 % decrease in RBC transfusion requirements • Change of haemoglobin concentration from baseline • Safety (type, frequency, severity, and relationship of adverse events to lenalidomide) • Platelet response • Neutrophil response • Bone marrow response • Duration of response
	safety endpoint		NCI CTC
Database lock	27 august 2008		
Results and Analysis			
Analysis description	**Primary Analysis**		

Analysis population Time point description	The primary efficacy analyses were performed on the MITT population, which included all patients who met all of the following conditions: - Had a diagnosis of low- or intermediate-1-risk MDS associated with a del (5q31-33) cytogenetic abnormality based on confirmation by the central hematologic and cytogenetic reviewers - Received at least 2 transfusions in each of the 8-week periods during the 16 week pre-treatment period. In addition, patients were not to have been transfusion-free for any 56 consecutive days during the 16-week pre-treatment period. - Received at least 1 dose of study medication RBC-transfusion independence **any consecutive 56 days** during the treatment period (e.g., Days 1 to 56, Days 2 to 57, Days 3 to 58, etc), accompanied by at least a 1 g/dL increase from screening/baseline in Hb.
Descriptive statistics and estimate variability	

RBC-transfusion independence[a]	Statistic	Overall MITT (N = 94)	Overall ITT (N = 148)
Response rate	Number of subjects	94	148
	Number (%) transfusion independent	59 (62.8)	97 (65.5)
	Exact 95% CI	52.2, 72.5	57.3, 73.2
Hgb increase (g/dL)[b]	Number of subjects	59	97
	Median	5.9	5.6
	Mean (SD)	6.1 (1.92)	6.1 (4.04)
	Min, Max	2.2, 11.4	2.2, 40.7
Time to transfusion independence (weeks)[c]	Number of subjects	59	97
	Mean (SD)	6.2 (6.89)	5.5 (6.56)
	Min, Max	0.3, 49.0	0.3, 49.0
Duration of response[d]	Number of transfusion independent subjects	59	97
	Number (%) who progressed (had a transfusion after response)	35 (59.3)	57 (58.8)
	Number (%) who maintained transfusion independence (censored[e])	24 (40.7)	40 (41.2)
Duration of transfusion independence response (weeks)	Median (Kaplan-Meier estimate)	97.0	114.4
	95% CI	52.9, 191.9	78.4, 153.7

CI = Confidence interval; Hgb = Hemoglobin; ITT = Intent to treat; Max = Maximum; Min = Minimum; MITT = Modified intent to treat; RBC = Red blood cell; SD = Standard deviation.

[a]The absence of the intravenous infusion of any RBC transfusion during any consecutive "rolling" 56 days during the treatment period and an increase in Hgb of at least 1 g/dL from the minimum during the screening/baseline period to the maximum during the transfusion-independent period, excluding the first 30 days after the last transfusion before the transfusion-free period.

[b]Change from baseline in Hgb concentration to maximum value during response period, where response period was defined as the time from 30 days after the last transfusion prior to achieving transfusion independence to the next transfusion or to the last assessment for subjects who did not receive a subsequent transfusion during the study period.

[c]Measured from the day of the first dose of study drug to the first day of the first 56-day RBC transfusion-free period.

[d]Measured from the first of the consecutive 56 days during which the subject was free of RBC transfusions to the date of the first RBC transfusion after this period.

[e]Duration of response was censored at the date of last visit for subjects who maintained transfusion independence.

Sources: Table 14.2.1.1.1, Table 14.2.1.1.2, Table 14.2.2.1, Table 14.2.2.2, Table 14.2.3.1, Table 14.2.3.2, Table 14.2.4.1, and Table 14.2.4.2.

Secondary endpoints

MDS 003	Overall MITT	Overall ITT
Cytogenetic response	N=94	N=148
evaluable subjects	52	88
Major	18 (34.6)	36 (40.9)
Minor	20 (38.5)	27 (30.7)
None	14 (26.9)	25 (28.4)
Bone marrow improvement	N=94	N=148
Number (%)with adequate BM aspirate at baseline	94 (100.0)	148 (100.0)
Number (%) with baseline dysplasia in ≥ 2 cell lines	83 (88.3)	120 (81.1)
Number (%) with adequate baseline and follow-up BM aspirate and baseline dysplasia in ≥ 2 cell lines	66 (70.2)	97 (65.5)
Number (%) with no evidence of MDS	18 (19.1)	36 (24.3)
Number (%) with resolution in all 3 cell lines	19 (20.2)	33 (22.3)
Complete BM improvement	22 (23.4)	46 (31.1)
RA to no MDS	17 (18.1)	28 (18.9)
RARS to no MDS	1 (1.1)	3 (2.0)
RAEB to no MDS	2 (2.1)	5 (3.4)
CMML to no MDS	2 (2.1)	2 (1.4)
Others to no MDS		8 (5.4)
Partial Bone Marrow Improvement	15 (16.0)	17 (11.5)
RARS to RA	7 (7.4)	7 (4.7)
RAEB to RARS	1 (1.1)	2 (1.4)
RAEB to RA	7 (7.4)	8 (5.4)
Total BM Improvement (Complete and Partial)	37 (39.4)	63 (42.6)
Bone Marrow Progression		
Progressed (total n [%])	17 (18.1)	25 (16.9)
RA/RARS to RAEB	11 (11.7)	12 (8.1)
RA/RARS/RAEB to RAEB-t		3 (2.0)
RA/RARS/RAEB/RAEB-t/CMML to AML	6 (6.4)	8 (5.4)
Unable to classify to AML		2 (1.4)
Progression to AML		N=147
Updated information provided for progression to AML/survival (n, %)		136
Follow-up data for progression to AML/survival not provided (n, %)		11
No progression to AML		91 (66.9)
Unknown		14 (10.2)
Progression to AML		31 (22.8)
during treatment phase of the study plus 30 days		17 (12.5)
during follow-up		14 (10.3)
Survival		N=148
Updated information provided for progression to AML/survival (n, %)		137
Follow-up data for progression to AML/survival not provided (n, %)		11
Survival (n,%)		61 (44.5)
Death (n,%)		76 (55.5)
during treatment phase of the study plus 30 days		20 (14.6)
during follow-up		56 (40.9)
No AML at last observation prior to death		57 (41.6)
AML as the recorded cause of death		19 (13.9)
during treatment phase of the study plus 30 days		4 (2.9)
during follow-up		15 (10.9)

Table 36. Summary of efficacy for trial MDS-004

Title: Multicenter, randomised, double-blind, placebo-controlled, 3-arm study of the efficacy and safety of 2 doses of lenalidomide versus placebo in red blood cell (RBC) transfusion-dependent patients with low- or intermediate-1-risk myelodysplastic syndromes associated with a deletion (del) 5q[31] cytogenetic abnormality			
Study identifier	**CC-5013-MDS-004**		
Design	Multicenter, randomised, double-blind, placebo-controlled, 3-arm study [Lenalidomide 10 mg QD 21/28 days/ Lenalidomide 5 mg QD 28/28 days/ Placebo QD 28/28 days] administered to RBC transfusion-dependent adult patients with low- or intermediate-1-risk IPSS MDS associated with a del 5q[31] cytogenetic abnormality (patients with MDS clones that have a del 5q[31] cytogenetic abnormality with additional cytogenetic abnormalities remain eligible for enrolment into this study). This study consists of three phases: - A pre-randomisation phase - A double-blind (DB) treatment phase - An open-label (OL) extension phase		
	Duration of DB phase:		16 weeks up to 52 weeks
	Duration of total study participation:		156 weeks
Hypothesis	To refine the lenalidomide dosing schedule: compare the efficacy of 2 doses of lenalidomide (10 mg and 5 mg) to that of placebo in patients with RBC transfusion-dependent low- or int-1-risk IPSS MDS associated with a del5q[31] cytogenetic abnormality		
Treatments groups	Lenalidomide 10 mg		QD 21/28 days, 16 weeks, n= 69
	Lenalidomide 5 mg		QD 28/28 days, 16 weeks, n= 69
	Placebo		QD 28/28 days, 16 weeks, n= 67
Endpoints and definitions	Primary endpoint	RBC TI	RBC-transfusion independence for **at least 182 days**
	Secondary endpoints		- Erythroid response (major and minor according to International MDS Working Group Criteria) - Duration of RBC transfusion independence, (number of days between the last transfusion prior to the start of the transfusion-free period and the first transfusion after the transfusion-free period) - Change of blood Hb concentration from baseline in patients who achieve a major erythroid response - Change in platelet counts from baseline - Change in absolute neutrophil counts from baseline - Cytogenetic response (according to the International MDS Working Group Criteria) - Bone marrow response (according to the International MDS Working Group Criteria) - HRQoL assessments: (components and total of the FACT–An and FACT-G questionnaires) - Overall Survival (OS) - Time to progression to AML
Database lock	14 June 2010		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population	Modified Intend to treat (MITT): all ITT patients who took at least one dose of study drug, had central confirmed low/int-1 IPSS prognosis and del 5q abnormality, and had documented transfusion dependence		
Time point description	RBC-transfusion independence for at least 182 days (6 months) during the treatment phase.		

Descriptive statistics and estimate variability

Primary endpoint

MITT population	Statistic	Placebo 28d/28 N=51	Lenalidomide 5 mg/day 28d/28 N=47	Lenalidomide 10 mg/day 28d/28 N=41
Transfusion Independence [a]	Number (%) transfusion independent	3 (5.9)	20 (42.6)	23 (56.1)
	Exact 95 % CI	1.2, 16.2	28.3, 57.8	39.7, 71.5
	p-value 5 vs Pbo		<0.001	
	10 vs Pbo			<0.001
	10 vs 5		0.208	
Time to transfusion Independence (weeks) [b]	Number of subjects	3	20	23
	Mean (SD)	8.2 (13.77)	3.5 (3.65)	4.5 (4.03)
	Median	0.3	3.0	4.3
	Min, Max	0.3, 24.1	0.3, 12.3	0.3, 14.7
Duration of transfusion independence response (weeks) [c,d] Summary statistics [e]	Number of transfusion independent subjects	3	20	23
	Number (%) who progressed (had a transfusion after response)	0 (0.0)	5 (25.0)	9 (39.1)
	Number (%) who maintained transfusion independence (censored)	3 (100.0)	15 (75.0)	14 (60.9)
	Mean (SD)	61.4 (10.93)	107.7 (52.35)	108.6 (40.63)
	Median	56.1	140.9	106.0
	Min, Max	54.1, 74.0	28.3, 157.0	40.0, 158.7
Hb increase (g/dL) [f,g]	Number of subjects	4	24	25
	Mean (SD)	2.6 (1.28)	5.0 (2.00)	5.8 (2.06)
	Median	2.3	5.2	6.3
	Min, Max	1.5, 4.4	1.5, 10.8	1.8, 10.0

[a] The absence of the intravenous infusion of any RBC transfusion during any consecutive rolling 182+ days during the treatment period and an increase in haemoglobin of a least 1 g/dl, from the minimum during the screening/baseline period to the maximum during the transfusion-independent period , excluding the first 7 days after the last transfusion before the transfusion-free period. P value is from Cochran-Mantel-Haenszel test stratified by IPSS score

[b] Measured from the days of first dose of study drug to the first day of the 182+ day RBC transfusion-free period

[c] Measured from the first of the consecutive 182 days during which the patient was free of RBC transfusions to the date of the first RBC transfusion after this period.

[d] Duration of response was censored at the date of last transfusion assessment for patients who maintained transfusion independence. These values are for the double-blind phase only.

[e] Without censoring

[f] Response period for 56+ day responders is defined as the time from 7 days after the last transfusion prior to achieving transfusion independence to the next transfusion or to the last assessment for patients who did not receive a subsequent transfusion during the study period

[g] Baseline untransfused haemoglobin was calculated by taking the average of the two most recent Hb measurements prior to the start of treatment, excluding measurements within 7 days after the RBC transfusion unless within 3 days prior to another RBC transfusion

Secondary endpoints

		Placebo 28d/28 N=51	Lenalidomide 5 mg/day 28d/28 N=47	Lenalidomide 10 mg/day 28d/28 N=41
	Statistic			
Cytogenetic response [h]	Major response n(%)	0 (0.0)	5 (10.6)	10 (24.4)
	Minor response n(%)	0 (0.0)	3 (6.4)	7 (17.1)
	progression n (%)	5 (9.8)	10 (21.3)	8 (19.5)
	relapse n (%)	0 (0.0)	0 (0.0)	0 (0.0)
Bone marrow improvement	Complete remission n(%)	7 (13.7)	5 (10.6)	7 (17.1)
	Partial remission n(%)	2 (3.9)	3 (6.4)	1 (2.4)
	Stable disease n(%)	34 (66.7)	27 (57.4)	25 (61.0)
	Progression n(%)	1 (2.0)	3 (6.4)	2 (4.9)
Platelet response [i]	evaluable	3	6	4
	Major	0 (0.0)	1 (16.7)	1 (25.0)
	Minor	0 (0.0)	0 (0.0)	0 (0.0)
	None	3 (100.0)	5 (83.3)	3 (75.0)
Neutrophil response [j]	evaluable	10	18	17
	Major	1 (10.0)	3 (16.7)	2 (11.8)
	Minor	0 (0.0)	0 (0.0)	1 (5.9)
	None	9 (90.0)	15 (83.3)	14 (82.4)
Hb change for responders and non responders over 7 months (g/dl)	median (min, max)	0.3 (-1.6, 1.7)	3.8 (-1.4, 8.1)	4.3 (0.7, 10.2)
Overall survival (safety population)	evaluable	67	69	69
	Death n (%)	35 (52.2)	32 (46.4)	34 (49.3)
	Median (months) 95% CI	42.4 (31.9, NA)	NA (24.6, NA)	NA (35.5, NA)
Progression to AML	evaluable	67	69	69
	DB+OL phases n (%)	21 (31.3)	16 (23.2)	15 (21.7)
	2-year cumulative incidence rates, %	16.3	21.2	12.3
Quality of life	FACT-An Evaluable n	52/67	45/69	48/69
	Mean change (sd)	-2.5 (18.50)	5.9 (18.26)	5.8 (23.17)
	p value	-	<0.05	<0.05
	TOI-An Evaluable n	52/67	46/69	49/69
	Mean change (sd)	-1.1 (17.13)	5.6 (15.56)	4.9 (18.16)
	p value	-	0.054	0.08
	TOI-F Evaluable n	53/67	46/69	49/69
	Mean change (sd)	-0.8 (14.76)	4.8 (14.21)	3.9 (15.47)
	p value	-	0.062	0.113

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

Progression to Acute Myeloid Leukemia – Studies MDS-003 and MDS-004

In a Cox proportional hazard model comparing risk of progression to AML between the 2 cohorts without using left truncation, the same set of significant risk factors was identified: complex cytogenetics, baseline blast count, transfusion burden, and baseline hemoglobin (Table 37).

Table 37. Analysis of Progression to AML Based on Cox Proportional HR Models Without Left Truncation in Lenalidomide-treated Patients in Studies MDS-003 and MDS-004 Versus MCR Patients

Variables	Univariate Analysis[1]			Final Model[2]		
	HR	95% CI	p-value	HR	95% CI	p-value
Age (years)	0.990	0.973 – 1.008	0.278			
Gender (female)	0.746	0.476 – 1.168	0.20			
Baseline Cytogenetics: del (5q) ≥ 2 vs Isolated del (5q)	4.574	2.319 – 9.019	<0.0001	3.708	1.645 – 8.362	0.002
Baseline Cytogenetics: del (5q) + 1 vs Isolated del (5q)	1.213	0.697 – 2.111	0.495	1.006	0.522 – 1.941	0.985
Baseline Myeloblast Count (≥ 5% vs < 5%)	1.424	0.766 – 2.646	0.264	1.867	0.986 – 3.534	0.055
Baseline Transfusion Burden (units/8 weeks)	1.092	1.023 – 1.165	0.008	1.085	1.003 – 1.173	0.042
Number of Cytopenias at Baseline (1 vs 0)	0.906	0.387 – 2.120	0.820			
Number of Cytopenias at Baseline (2 or 3 vs 0)	0.929	0.387 – 2.227	0.868			
Baseline Hemoglobin (g/dL)	0.891	0.771 – 1.031	0.121	0.864	0.736 – 1.104	0.073
Baseline Platelet Count ($\times 10^9$/L)	0.999	0.998 – 1.001	0.405			
Baseline Absolute Neutrophil Count ($\times 10^6$/L)	1.000	1.000 – 1.000	0.360			
Lenalidomide Cohort vs Multicenter Registry Cohort	1.14	0.685 – 1.90	0.614	0.850	0.463 – 1.558	0.599

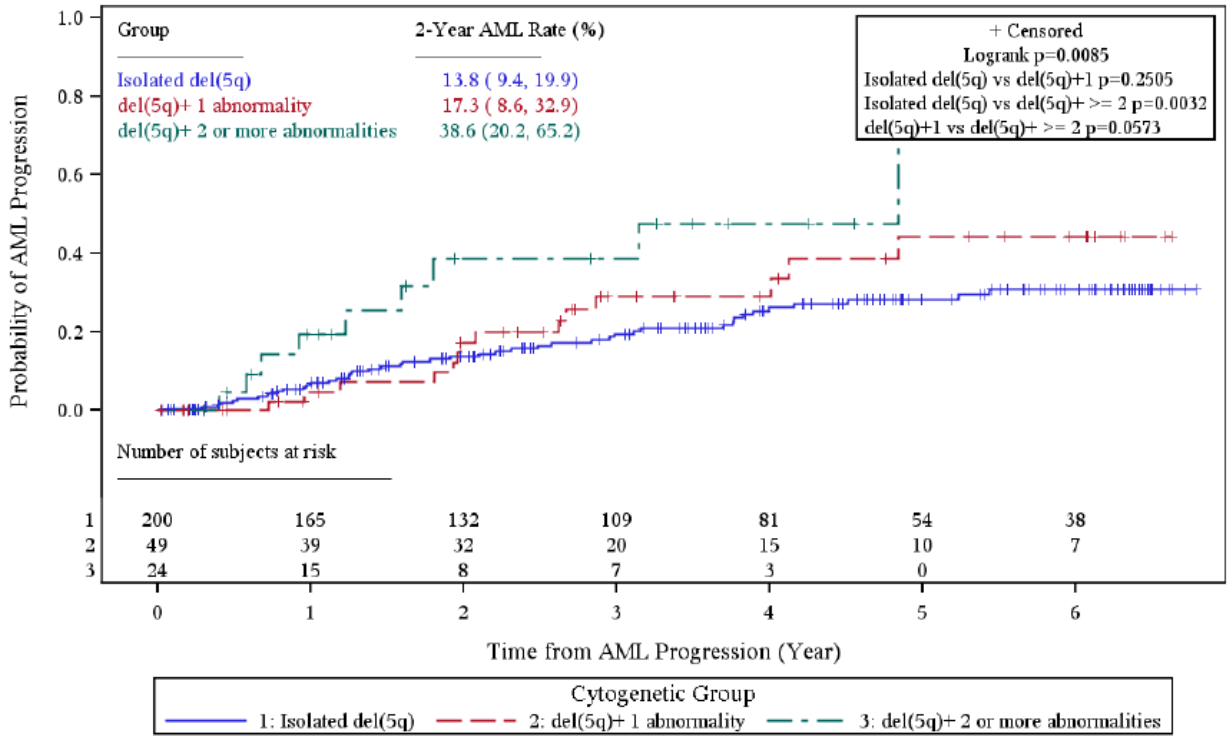
AML = acute myeloid leukemia; CI = confidence interval; del (5q) = deletion involving the long arm of chromosome 5; HR = hazard ratio; MCR = Multicenter Registry; vs = versus.

In the univariate analysis, the cumulative risk of progression to AML among patients in the MCR who were TD at initial diagnosis and TD patients in Studies MDS-003 and MDS-004 also were compared without left truncation using both the Kaplan-Meier estimator and the Fine-Gray competing-risk estimator (with death as the competing risk).

Two additional sensitivity analyses were performed to control for the influence of time from TD to treatment or enrollment in the MCR including (1) between newly diagnosed MCR patients who were TD at registry enrollment versus lenalidomide-treated patients diagnosed within 1 year of study entry and (2) between newly diagnosed MCR patients who were TD at registry enrollment, newly diagnosed MCR patients who were transfusion independent at registry enrollment but with known date of first TD after registry enrollment, and lenalidomide-treated patients (data not shown).

An extensive assessment was undertaken to evaluate the influence of known risk factors on the risk of progression to AML in the combined MDS-003/MDS-004 data sets. The influence of baseline cytogenetics is illustrated in the 2-year cumulative rates of progression to AML (see Figure 19). Patients with complex cytogenetics had the highest 2-year rate of progression to AML (38.6%; 95% CI = 20.2% – 65.2%).

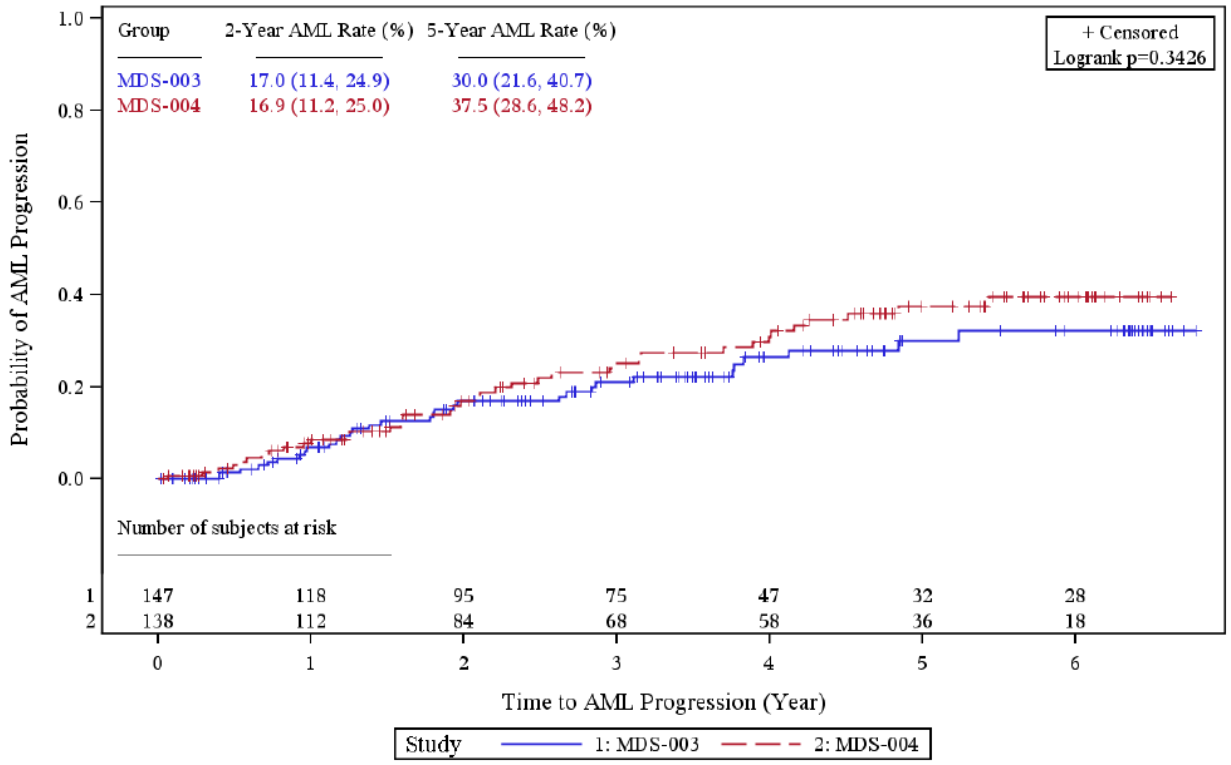
Figure 19. Time to Progression to Acute Myeloid Leukemia by Baseline Cytogenetics in Study MDS-003 and Patients Randomised to Lenalidomide in Study MDS-004 (Double-blind Phase, Open-label Phase, and Follow-up Period) (ITT Populations)



AML = acute myeloid leukemia; del (5q) = deletion involving the long arm of chromosome 5; ITT = intent to treat.
Notes: Time to progression to AML was calculated from the date of randomisation.
Study MDS-003: Follow-up was completed on 01 Oct 2010.
Study MDS-004: Data cutoff date = 31 Mar 2012.

The time to progression to AML for patients in Study MDS-003 (ITT population; N = 147) and in patients randomised to lenalidomide in Study MDS-004 (N = 138; updated data cutoff date = 31 Mar 2012) is presented in Figure 20.

Figure 20. Time to Progression to Acute Myeloid Leukemia in Study MDS-003 and Patients Randomised to Lenalidomide in Study MDS-004 (Double-blind Phase, Open-label Phase, and Follow-up Period) (ITT Populations)



AML = acute myeloid leukemia; ITT = intent to treat.
Notes: Time to progression to AML was calculated from the date of randomisation. Patient 0243010 was diagnosed by the central cytogenetic reviewer as having AML at entry to Study MDS-003 (baseline); hence, this patient was excluded from the progression to AML analyses.
Study MDS-003: Follow-up was completed on 01 Oct 2010.
Study MDS-004: Data cutoff date = 31 Mar 2012.

Overall, the 2-year cumulative incidence of progression to AML from time of study entry was approximately 17% in both studies: 17.0% (CI = 11.4% – 24.9%) for the MDS-003 ITT population and 16.9% (CI = 11.2% – 25.0%) for patients randomised to lenalidomide in Study MDS-004. Based on a median duration of follow-up of approximately 3 years, the 2-year rate (from study entry) of progression to AML of 17.0% was observed in both studies (Figure 18)

In Study MDS-004, lower 2-year cumulative rates of progression to AML (12.3% [95% CI = 6.0% – 24.1%]) were observed when starting treatment with the 10-mg dose, a dose also associated with highest rates of both cytogenetic response and RBC-TI response (Table 38)

Finally, for patients in Studies MDS-003 and MDS-004 who achieved either a cytogenetic response or RBC-TI response and who remained on treatment beyond 16 weeks, the 2-year cumulative rates of progression to AML were between 8.3% and 10.7%, and the 5-year cumulative rates were between 25.4% and 33.5%.

In contrast, the 2-year rates of progression to AML for patients who failed to achieve either cytogenetic response (19.7% – 25.7%) or attain RBC TI (23.5% – 30.6%) were 2-fold to 3-fold higher. The rates of progression to AML in these non-responding patients who received limited exposure to lenalidomide (< 16 weeks) approached the 2-year progression to AML rate (33.3%) observed for the 11 placebo patients from Study MDS-004 who did not receive lenalidomide.

Table 38. Quantitative Risk of Progression to Acute Myeloid Leukemia from Study Entry (2-Year and 5-Year Rates) – Study MDS-004 (Double-blind Phase, Open-label Phase, and Follow-up Period; ITT Population)

Population	MDS-004	
	2-Year Rate	5-Year Rate
Overall, % (CI)		
5 mg and 10 mg Lenalidomide combined	16.9 (11.2, 25.0)	37.5 (28.6, 48.2)
10 mg Lenalidomide	12.3 (6.0, 24.1)	28.9 (18.4, 43.6)
5 mg Lenalidomide	21.2 (12.8, 33.8)	45.9 (32.4, 61.7)
Placebo	16.3 (9.1, 28.3)	51.5 (37.6, 67.2)
Subgroups, %		
Time from MDS diagnosis		
< 1 Year from MDS diagnosis	9.7	36.2
≥ 1 Year from MDS diagnosis	18.4	37.8
Transfusion independent (> 182 days)		
Responder	10.1	33.5
Nonresponder	23.5	40.7
Cytogenetic response in cytogenetic response-evaluable patients[a]		
Responder	10.7	31.2
Nonresponder	19.7	40.6

CI = confidence interval; ITT = intent-to-treat; MDS = myelodysplastic syndromes.
[a] Patients evaluable for best cytogenetic response had to have at least 20 analyzable metaphases at baseline and at least one postbaseline visit.
Notes: Time to progression to acute myeloid leukemia was calculated from the date of randomisation. For Studies MDS-003 and MDS-004, the Intent-to-treat population = the Treated (Safety) population.
Study MDS-003: Follow-up was completed on 01 Oct 2010.
Study MDS-004: Data cutoff date = 31 Mar 2012.

Clinical studies in special populations

No clinical studies in special populations were submitted.

Supportive studies

In the MDS-001, MDS-002 and PK-002 supportive studies, the majority of patients (71.1% in MDS-001, 100% in MDS-002, 82.1% in PK-002) did not have the del (5q) cytogenetic abnormality unlike the primary studies, which limits the extrapolability to the targeted population.

MDS-007

This was a phase 2, multicenter, open-label, single-arm study to evaluate the safety, efficacy, and PK profile of lenalidomide in Japanese patients with an IPSS diagnosis of low- or INT-1-risk MDS associated with a del (5q) abnormality and symptomatic anaemia or RBC transfusion-dependent anaemia. The purpose of MDS- 007 was also to support the dosing regimen of 10 mg QD lenalidomide administered on Days 1 to 21 of a 28-day cycle.

All the patients enrolled in the MDS-007 study presented with the del (5q) cytogenetic abnormality at baseline. Even if patients included were exclusively Japanese, baseline characteristics were consistent with those of patients in the MDS-003 and MDS-004 studies but the small population size (11) is of limited information.

All 11 (100%) treated patients were evaluable and achieved major erythroid responses (IWG-defined criteria, RBC TI ≥ 56 days during the treatment period associated with Hgb increase of > 2 g/dL compared with baseline Hgb).

The median age of patients was 72 years, and the majority of patients were > 65 years of age (81.8%).

MDS-001 and MDS-002

In MDS-001 and MDS-002, the majority of patients were white. The MDS-007 study was conducted exclusively in Japanese patients.

The majority of patients in the MDS-001 (55.6%) and MDS-002 (64.2%) studies were male, reflecting the predominance of non-del (5q) MDS patients in these studies. As in the MDS-003 and MDS-004 studies, in the MDS-007 study where only del (5q) MDS patients were enrolled, the majority (63.6%) of patients were female patients.

The median age of patients was 72 years in each study, and the majority of patients were > 65 years of age (71.1% in MDS-001, 76.3% in MDS-002).

Duration of MDS was slightly shorter than in the primary studies (median duration ranging from 1.9 to 2.1 years).

MDS-001, 002 and 007 showed that lenalidomide is effective in producing major haematological responses (especially erythroid responses), RBC-transfusion independence in patients with low or intermediate-1-risk MDS. They allowed to orient the development towards a starting dose of 10 mg daily and to focus on subpopulation with del (5q) abnormality.

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The present submission is based on one Phase 3 double-blind, placebo-controlled study with an open-label phase (study MDS-004), four Phase 2 open label studies (studies MDS-003, MDS-001, MDS-002, and MDS-007) and one pharmacokinetic study (study PK-002). Results derive from the 2 primary studies MDS 003 and MDS 004.

The standardised French-American-British (FAB) criterion has been used to classify subtypes of MDS at diagnosis. The internationally used index IPSS has been used to determine prognostic for overall survival and transformation to AML. The primary endpoint, RBC-transfusion independence for at least 182 days, is clinically relevant. In this disease population that may survive for several years, the

International MDS Working Group (IWG) defined 2-month duration of response. A longer duration was chosen because a sustained 6-month response would be considered a more notable clinical outcome.

All secondary endpoints are measured according to MDS IWG standardized response criteria for evaluating clinically significant responses in patients in low to intermediate 1 risk disease.

One hundred and forty eight (148) patients were enrolled in the MDS-003 study. In MDS-004 study, 205 patients were enrolled, randomised to receive lenalidomide 10 mg QD under the cyclic regimen, 5 mg QD under the continuous regimen, or placebo during the double blind phase.

A total of 145 patients proceeded to the OL phase of this study.

Patients enrolled in the 2 primary studies (MDS-003 and MDS-004) had comparable baseline demographic and disease characteristics. In both studies, the median age of patients was 71 years in MDS-003 and 68 years in MDS-004, reflecting that MDS is a disease of the elderly. There was a female predominance in both studies (65.5% and 76.1%, respectively) consistent with the expected demographics for a del (5q) MDS population. Patients were predominantly white (96.6% and 98.5%, respectively).

Other disease characteristics at baseline were comparable between the 2 studies and across dosing groups. Use of anti-anaemic agents prior to inclusion was comparable across dosing groups in MDS 004.

It should be noted that:

- If the median duration of MDS at baseline is similar across the 3 arms of MDS 004 study (2 to 3 years), the ranges are different. The maximal duration of MDS for patients of Pbo arm is 14 years compared to 17 years in 5 mg arm and 29 years in 10 mg arm.

- FAB subtype was mainly RA or RARS (79% of MDS 003 population, 64% of MDS 004 population) meaning that patients were of relatively better prognosis compared to RAEB and RAEBt patients.

- For 17.3% of MDS 003 patients and 29.8% of MDS 004 patients, IPSS score was int-2, high or missing. The part of eligibility violations is non negligible. This explains the use of MITT population for evaluation of efficacy endpoints;

- An imbalance was observed within the MDS-004 study, with a slightly higher proportion of patients with 5q syndrome (usually associated with a good prognosis, a longer OS, and a lower risk of progression to AML) in the placebo group than in each of the lenalidomide groups.

Overall, the demographic characteristics and baseline disease-related characteristics are consistent with published data on MDS del (5q) population

MDS 003 is non comparative study and MDS 004 is a comparative dose refinement study. This clinical development is the reverse of a conventional scheme (dose finding study followed by a comparative confirmatory pivotal study).

The use of placebo as comparator is appropriate since there is no active reference treatment, for low to intermediate 1 risk MDS patients, with an EU marketing authorisation.

As proposed by the Applicant, the lenalidomide recommended dose is 10 mg once daily on days 1-21 of repeated 28-day cycles. MDS 003 study was not designed to prospectively compare the 10 mg continuous and 10 mg syncopated regimens, but both regimens showed impressive activity. MDS 004 objective was to refine the lenalidomide dosing schedule comparing the 10 mg 21/28d to 5 mg 28/28d and to placebo 28/28d. None of the studies was designed to compare the efficacy and safety of 10 mg lenalidomide administered on a continuous 28-days regimen vs. a 21-day cyclic regimen.

Firstly, the 10-mg dose using the 21-of-28 day cycle was chosen for MDS-004 because grade 4 neutropenia was reported less frequently with this regimen in MDS-003 study, while the RBC-transfusion independence rate was still comparable to that for the 28-of-28 day cycle regimen, duration of RBC-TI was longer even though the response is a little bit delayed compared to 10 mg 28/28d. The median dose/treatment day/cycle observed in the 10-mg dosing groups in MDS-003 (continuous regimen) and MDS-004 (cyclic regimen) suggest that the initial daily dose of 10 mg QD can be maintained for slightly longer under a cyclic regimen compared to a continuous dosing regimen. The 7-day break in treatment may confer better tolerability during the first 3 to 4 cycles of treatment.

Secondly, the MDS 004 statistical analysis plan owed both comparisons [10 mg 21/28d versus placebo 28/28d] and [5 mg 28/28d versus placebo 28/28d], on response rate for ≥182 days. Both p-values were statistically significant in favour of lenalidomide arm. Even though the study was not powered to compare 5 mg with 10 mg dose, a subgroup analysis showed that 10 mg lenalidomide was consistently associated with a higher transfusion independent response rate by 182 days of treatment compared with 5 mg regardless of baseline characteristics.

In MDS 004 study, the proportion of patients who completed the DB phase of the study was higher in the 10-mg group (56.5%), followed by the 5-mg group (33.3%), and then placebo (4.5%). Following the DB phase, patients entering the OL phase, were allowed to cross over from Pbo to 5-mg lenalidomide (called Pbo/5mg), from 5mg to 5mg, from 5mg to 10 mg, from 10 mg to 5 mg, from 10 mg to 10 mg. The proportion of lenalidomide-treated patients who completed the OL phase of the study ranged from 23.2% (in the Pbo/5mg group) to 43.8% (in the 10mg/10mg group).

Moreover, the Applicant claimed that 10-mg cyclic and 5-mg continuous regimens have similar tolerability.

But adverse events (AE) that lead to a dose reduction or interruption were more frequent (73.9%) in the 10-mg cyclic regimen than in the 5-mg continuous regimen (63.8%). The primary reason for discontinuation was lack of therapeutic effect in 52 patients (35.1%) in MDS 003 and in 113 patients (55.1%) in MDS 004 of which 50.2% for lack of erythroid response. On the other hand, AE that led to discontinuation of the study drug occurred more frequently in the 5-mg continuous regimen (17.4% vs. 8.7%) and the 2-year AML rate of progression to AML is numerically higher in 5mg arm compared to Pbo.

At the end, the lenalidomide dose 10 mg was preferred to 5 mg and the scheme of administration 21/28d preferred to 28/28d.

Treatment is to be continued until unacceptable AEs or progression/relapse. MDS 003 mentioned a maximal duration of treatment total of 24 cycles and MDS 004 a total of 156 weeks. The stopping rule has been defined, in a further step, as follows: Patients without at least a minor erythroid response within 4 months of therapy initiation demonstrated by at least a 50% reduction in transfusion requirements or, if not transfused, a 1g/dl rise in haemoglobin, should discontinue lenalidomide treatment.

Efficacy data and additional analyses

MDS 003 being a non comparative study may give essentially descriptive information on RBC-TI, OS and progression to AML.

Lenalidomide-induced RBC-transfusion independence was associated with a median increase from baseline in blood Hb concentration of 5.9 g/dL in the responders in the MITT population. Both syncopated and continuous regimens were associated with a median increase from baseline in blood Hb concentration.

Response to lenalidomide was rapid (median time to response in MITT population, 4.1 weeks) and sustained. The median duration of transfusion independence was 97.0 weeks in the MITT population and 114.4 weeks in the ITT population.

Lenalidomide therapy resulted in at least a 50% decrease from pre-treatment in RBC transfusion requirements in 74.5% (70/94) of the patients in the MITT population. The transfusion-reduction response rate was 74.6% (47/63) in the 10 mg continuous regimen and 74.2% (23/31) in the 10 mg syncopated regimen.

Major and minor cytogenetic responses were observed in 40.9% and 30.7% of patients, respectively.

The incidence of progression to acute myeloid leukemia has been explored in 147 of the 148 patients. The median duration of follow-up for all MDS-003 patients was 38.4 months (range: 0.3 to 81.9 months). Considering that data for progression to AML/survival were available for 147 patients in the ITT population, the overall 5-year cumulative incidence of progression to AML in the ITT population was 28.6%.

MDS 004 is designed as a comparative trial. It showed that lenalidomide is effective in achieving transfusion independence for ≥ 182 days in transfusion dependent patients with lower risk MDS (IPSS low or INT-1) associated with del(5q) with or without additional cytogenetic abnormalities. In the MITT population, the RBC-TI has been achieved in 56.1% (95% CI: 39.7-71.5) in the 10 mg cyclic group and 42.6% (95% CI: 28.3-57.8) in the 5 mg continuous group, both significantly better than placebo; in the ITT populations, the corresponding figures were 55.1% and 34.8%, respectively.

The transfusion independence attained was seen across all of the subgroups analyzed including baseline cytogenetics (isolated del (5q) vs. 1 or more cytogenetic abnormalities), FAB classification, IPSS and WPSS risk groups. However, the demonstration of a clinical benefit is based on a unique trial which is, as a matter of fact, not comparative.

The median durations of RBC TI for the 10 mg and 5 mg groups in MDS-004 were not reached at database lock (14 Jun 2010), but the lower bounds of the CIs are 98 weeks and 46 weeks in favour of the 10 mg dose level.

The onset of transfusion independence in response to lenalidomide treatment is based on a limited size of patients (20 patients treated with 5 mg lenalidomide, 23 with 10 mg). The initial appearance of a TI response may take some months (100% of responses becoming evident within 6 months of treatment initiation).

From a methodological point of view, the analysis of the primary efficacy endpoint (RBC-TI) is sullied by the cross over in MDS 004 study: 56 out of the 67 patients randomised to Pbo arm discontinued the DB phase of the study at week 16 due to lack of efficacy, were unblinded and switched to the 5 mg lenalidomide arm. The primary efficacy endpoint (transfusion independency) supports one single component of the benefit on a relatively short term. The MDS PASS requested aims to confirm long term benefit such as overall survival. Moreover, the switch from placebo to lenalidomide 5 mg occurred early during the DB phase. It was planned to happen after the week 16 response assessment. Nevertheless, in the DB treatment phase, the median duration of treatment with placebo was 16.0 weeks (range, 1.3 – 54.4 weeks); this means that half of patients in Pbo arm discontinued at or before the protocol-defined time.

Subgroups analyses of TI responses are of minor relevance as the size of each stratum is limited.

Approximately 50% MDS-004 patients had received a prior treatment with ESA as well-established use in the treatment of anaemia due to MDS. This questions the place of lenalidomide in the

armamentarium of MDS del 5q. The indication claimed for Revlimid cannot be as “first line” treatment (prior or instead of ESA).

Additional endpoints of the study included:

Cytogenetic response

In the 10 mg arm major and minor cytogenetic responses were observed in 30.0% and 24.0% of patients, respectively. The achievement of transfusion independence is not dependent upon complete elimination of the malignant clone since a proportion of patients achieved transfusion independence in the absence of a cytogenetic response.

Assessment of Health Related Quality of Life (HRQoL)

Improvement of Quality of Life was seen with more robust results with the 10 mg dose compared to the 5 mg dose.

Overall survival

When assessed by the ITT analysis, and over the whole study (DB plus OL phases), there was no difference in overall survival across the treatment groups (p=0.2456), although 56 patients in the placebo group crossed over to receive 5 mg of lenalidomide after Week 16. However when analysing the Kaplan Meier curve per treatment arm, it appears graphically that the 10 mg curve falls earlier than the 5 mg or the Pbo curves. Patients died as a majority from disease progression (MDS or AML progression).

A Cox proportional hazards model has showed that achieving RBC TI with duration of ≥ 182 days was associated with a significant reduction (51%) in the relative risk of death. However, the crossover design of Study MDS-004 precludes a definitive answer regarding long-term effects of lenalidomide treatment. Based on a multivariate analysis assessing the influence of prognostic factors on overall survival, patients who achieved transfusion independence had a better OS than non responding patients. Similarly, achieving a cytogenetic response to lenalidomide was associated with prolonged overall survival compared with non-response. All these statements are controversial since they do not take into account the cross over from Pbo to lenalidomide.

Progression to acute myeloid leukaemia

As of data cut-off 26 Nov 2012, the 2-year rate for progression to AML was 12.3% in the 10-mg lenalidomide group, 21.2% in the 5-mg lenalidomide group, and 16.3% in the placebo group. The respective 5-year rates were 28.9%, 45.0%, and 50.7%. Based on a multivariate analysis assessing the influence of prognostic factors on progression to AML, patients who achieved the primary end point of 26 weeks transfusion independence response had a lower cumulative incidence of progression to AML than those who did not respond with a 2-year cumulative incidence of 10.1% compared to 23.5%.

The applicant states that there was no significant difference in the risk of progression to AML over time between the 3 randomised treatment arms in the MDS-004 study but overall median time to AML has not yet been reached for the lenalidomide treatment groups, the population size in each arm of the trial is small, the duration of placebo treatment is short and the majority of patients from placebo arm switched to lenalidomide arm.

The TP53 mutation being present in 20 to 25% of lower-risk MDS Del 5q patients seems associated with a higher risk of progression to acute myeloid leukaemia (AML). In a post-hoc analysis of a clinical trial of Revlimid in low- or intermediate-1-risk myelodysplastic syndromes (MDS-004), the 2-year rate of progression to AML was 27.5 % in patients with a TP53 mutation and 3.6% in patients with no TP53 mutation (p=0.0038).

Imbalances in certain baseline disease characteristics such % bone marrow blasts, transfusion burden, cytogenetic complexity, karyotype abnormalities, prognostic score, could influence progression to AML. The sample size of each of the baseline prognostic factors subgroups is small and limits a formal analysis of the influence of any individual factor on progression to AML. Moreover, considering that the majority of MDS 004 patients of the Pbo arm (56/67) switched to lenalidomide arms, the appreciation of the risk of AML transformation is biased.

2.5.4. Conclusions on the clinical efficacy

The efficacy of lenalidomide was evaluated in patients with transfusion-dependent anaemia due to low- or intermediate-1-risk myelodysplastic syndromes associated with a deletion 5q cytogenetic abnormality, with or without additional cytogenetic abnormalities, in two main studies: a Phase III, multicentre, randomised, double-blind, placebo-controlled, 3-arm study of two doses of oral lenalidomide (10 mg and 5 mg) versus placebo (MDS-004); and a Phase II, a multicentre, single-arm, open-label study of lenalidomide (10 mg) (MDS-003).

In study MDS-004, in which 205 patients were equally randomised to receive lenalidomide 10 mg, 5 mg or placebo, the primary efficacy analysis consisted of a comparison of the transfusion-independence response rates of the 10 mg and 5 mg lenalidomide arms versus the placebo arm (double-blind phase 16 to 52 weeks and open-label up to a total of 156 weeks). Patients who did not have evidence of at least a minor erythroid response after 16 weeks were to be discontinued from treatment. Patients who had evidence of at least a minor erythroid response could continue therapy until erythroid relapse, disease progression or unacceptable toxicity. Patients, who initially received placebo or 5 mg and did not achieve at least a minor erythroid response after 16 weeks of treatment were permitted to switch from placebo to 5 mg lenalidomide or continue lenalidomide treatment at higher dose (5 mg to 10 mg).

In MDS-003, in which 148 patients received lenalidomide at a dose of 10 mg, the primary efficacy analysis consisted of an evaluation of the efficacy of lenalidomide treatments to achieve haematopoietic improvement in patients with low- or intermediate-1 risk myelodysplastic syndromes.

In MDS-004, a significant larger proportion of patients with myelodysplastic syndromes achieved the primary endpoint of transfusion independence (>182 days) on lenalidomide 10 mg compared with placebo (55.1% vs. 6.0%). Amongst the 47 patients with an isolated Del (5q) cytogenetic abnormality and treated with lenalidomide 10 mg, 27 patients (57.4%) achieved red blood cell transfusion independence.

The median time to transfusion independence in the lenalidomide 10 mg arm was 4.6 weeks. The median duration of transfusion independence was not reached in any of the treatment arms, but should exceed 2 years for the lenalidomide-treated patients. The median increase in haemoglobin (Hgb) from baseline in the 10 mg arm was 6.4 g/dL.

Additional endpoints of the study included cytogenetic response (in the 10 mg arm major and minor cytogenetic responses were observed in 30.0% and 24.0% of patients, respectively), assessment of Health Related Quality of Life (HRQoL) and progression to acute myeloid leukaemia. Results of the cytogenetic response and HRQoL were consistent with the findings of the primary endpoint and in favour of lenalidomide treatment compared to placebo.

In MDS-003, a large proportion of patients with myelodysplastic syndromes achieved transfusion independence (>182 days) on lenalidomide 10 mg (58.1%). The median time to transfusion independence was 4.1 weeks. The median duration of transfusion independence was 114.4 weeks. The

median increase in haemoglobin (Hgb) was 5.6 g/dL. Major and minor cytogenetic responses were observed in 40.9% and 30.7% of patients, respectively.

All results of the additional endpoints were consistent with the findings of the primary endpoint and in favour of lenalidomide treatment compared to placebo but the risk for progression to AML remained a safety concern.

All the investigations performed to better characterise the prognostic factors of progression to AML (such baseline endogenous EPO level or prior ESA treatment) suffer methodological limits.

The activity of lenalidomide in correcting anaemia can be established in the indication “low or int 1 – risk MDS associated with a deletion 5q cytogenetic abnormality with or without other cytogenetic abnormalities” but the extent of the clinical benefit is mitigated by the uncertainties regarding OS, transformation to AML and occurrence of SPMs and a precise estimation of the benefit risk ratio is not feasible.

Considering that (1) the risk for progression to AML has not been characterised in the target population for which an extension of the marketing authorisation was initially applied for, (2) the benefit of lenalidomide treatment is evidenced (achieving RBC-TI, cytogenetic response, durable response), the CHMP agreed to restrict lenalidomide treatment to those patients with the lowest risk among transfusion dependent del 5q MDS patients, i.e.; low or int-1 MDS associated with an isolated deletion 5q. The efficacy in the restricted indication is considered demonstrated.

2.6. Clinical safety

In the 6 completed company-sponsored MDS clinical studies considered in the overall analysis of safety, a total of 652 patients received at least one dose of lenalidomide (25 mg, 15 mg, 10 mg, or 5 mg QD), including 56 placebo-treated patients who received lenalidomide in the open-label phase of MDS-004.

In further support of the safety of lenalidomide in MDS, additional safety information is available from postmarketing surveillance activities, non-MAH sponsored clinical studies (e.g., investigator-initiated trials [IITs]), compassionate use/named patient use, or the published literature.

Patient exposure

A total of 205 patients were enrolled in study MDS-004, with 67 in the placebo arm, 69 in the 5-mg lenalidomide arm, and 69 in the 10-mg lenalidomide arm. All 205 (100%) patients were in the ITT population and the Safety population, and 139 (67.8%) were in the MITT population.

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 10-mg group, and was consistently higher in the 10-mg group. The respective median daily doses remained stable through month/cycle 12

Overall, the percentages of patients who had at least one dose reduction or interruption due to an AE were similar between the lenalidomide groups (59.4 % and 62.3% for the 5-mg and 10-mg groups, respectively) and higher than that of the placebo group (3.0%).

The median time to first dose reduction or interruption due to an AE was 43.0 days for the 5-mg group and 27.0 day for the 10-mg group; and occurred earlier compared with the placebo group (79.0 days). The median duration of the first dose interruption was 7.0 days in the placebo group, and increased with increasing dose of lenalidomide (11.0 days and 14.0 days in the 5-mg and 10-mg groups, respectively).

A total of 141 patients received at least 1 dose of open-label lenalidomide and were included in the open-label treated set of study MDS-004. Of those, 111 patients received 5-mg, including placebo patients who crossed over to 5 mg and patients randomised to 10 mg who subsequently had their dose reduced (Pbo/5mg, 5mg/5mg, and 10mg/5mg); and 30 patients received 10-mg (5mg/10mg and 10mg/10mg).

The shortest median duration of treatment was in the 5mg/10mg group (15.7 weeks; range 2.3-136.0 weeks), the group that crossed over to a higher dose at OL. This short duration may reflect patients who did not achieve transfusion independence or at least a minor erythroid response, and subsequently stopped at 16 weeks of the DB phase.

The median duration of treatment for the Pbo/5mg group (68.9 weeks; range 0.4 - 140.6 weeks) was similar to that for the 5mg/5mg group (63.0 weeks; range 3.1 - 104.9 weeks). The median duration of treatment was somewhat shorter for the 10mg/10mg group (52.4 weeks; range 7.3 weeks– 106.9 weeks).

Overall, approximately half of the patients in each group remained on OL treatment for a minimum of an additional 52 weeks with the exception of the 5mg/10mg group (where only 50% remained on treatment for at least 16 weeks).

Adverse events

The most common adverse events in studies MDS 003 and MDS 004 are summarised in the following Table 39.

Table 39. Treatment emergent Adverse Events reported in at least 10% of Patients in Any Group- Studies MDS-003 and MDS-004 (Safety Population)

	MDS-003		MDS-004 (Double-blind Phase)					
	Len 10 mg QD 28/28 days[b] (N = 148)		Len 10 mg QD 21/28 days (N = 69)		Len 5 mg QD 28/28 days (N = 69)		Placebo QD 28/28 days (N = 67)	
System Organ Class / Preferred Term[a]	n	(%)	n	(%)	n	(%)	n	(%)
Subjects with ≥ 1 Adverse Event	**148**	**(100.0)**	**69**	**(100.0)**	**69**	**(100.0)**	**64**	**(95.5)**
Blood and Lymphatic System Disorders	**128**	**(86.5)**	**59**	**(85.5)**	**59**	**(85.5)**	**21**	**(31.3)**
Neutropenia	98	(66.2)	53	(76.8)	53	(76.8)	12	(17.9)
Thrombocytopenia	96	(64.9)	34	(49.3)	30	(43.5)	2	(3.0)
Anemia	39	(26.4)	3	(4.3)	8	(11.6)	6	(9.0)
Leukopenia	20	(13.5)	6	(8.7)	11	(15.9)	3	(4.5)
Gastrointestinal Disorders	**123**	**(83.1)**	**45**	**(65.2)**	**41**	**(59.4)**	**30**	**(44.8)**
Diarrhea	90	(60.8)	26	(37.7)	22	(31.9)	12	(17.9)
Nausea	41	(27.7)	14	(20.3)	13	(18.8)	6	(9.0)
Constipation	39	(26.4)	12	(17.4)	15	(21.7)	5	(7.5)
Abdominal pain	28	(18.9)	9	(13.0)	6	(8.7)	4	(6.0)
Vomiting	21	(14.2)	7	(10.1)	6	(8.7)	4	(6.0)
Skin and Subcutaneous Tissue Disorders	**121**	**(81.8)**	**38**	**(55.1)**	**41**	**(59.4)**	**11**	**(16.4)**
Pruritus	66	(44.6)	19	(27.5)	16	(23.2)	3	(4.5)
Rash	60	(40.5)	9	(13.0)	16	(23.2)	1	(1.5)
Dry skin	21	(14.2)	7	(10.1)	7	(10.1)	1	(1.5)
Night sweats	16	(10.8)	1	(1.4)	2	(2.9)	0	(0)
General Disorders and Administration Site Conditions	**118**	**(79.7)**	**40**	**(58.0)**	**38**	**(55.1)**	**27**	**(40.3)**
Fatigue	62	(41.9)	13	(18.8)	12	(17.4)	5	(7.5)
Edema peripheral	48	(32.4)	9	(13.0)	12	(17.4)	5	(7.5)
Pyrexia	39	(26.4)	11	(15.9)	8	(11.6)	4	(6.0)
Asthenia	19	(12.8)	8	(11.6)	8	(11.6)	11	(16.4)
Edema	19	(12.8)	3	(4.3)	3	(4.3)	0	(0)

	MDS-003		MDS-004 (Double-blind Phase)					
	Len 10 mg QD 28/28 days[b] (N = 148)		Len 10 mg QD 21/28 days (N = 69)		Len 5 mg QD 28/28 days (N = 69)		Placebo QD 28/28 days (N = 67)	
System Organ Class / Preferred Term	n	(%)	n	(%)	n	(%)	n	(%)
Infections and Infestations	**117**	**(79.1)**	**45**	**(65.2)**	**41**	**(59.4)**	**23**	**(34.3)**
Upper respiratory tract infection	49	(33.1)	8	(11.6)	7	(10.1)	4	(6.0)
Nasopharyngitis	27	(18.2)	10	(14.5)	6	(8.7)	5	(7.5)
Urinary tract infection	23	(15.5)	8	(11.6)	5	(7.2)	4	(6.0)
Bronchitis	20	(13.5)	10	(14.5)	6	(8.7)	3	(4.5)
Pneumonia	20	(13.5)	3	(4.3)	2	(2.9)	3	(4.5)
Sinusitis	20	(13.5)	3	(4.3)	0	(0)	1	(1.5)
Respiratory, Thoracic, and Mediastinal Disorders	**104**	**(70.3)**	**23**	**(33.3)**	**25**	**(36.2)**	**13**	**(19.4)**
Cough	38	(25.7)	9	(13.0)	7	(10.1)	4	(6.0)
Dyspnea	38	(25.7)	5	(7.2)	6	(8.7)	5	(7.5)
Oropharyngeal pain	27	(18.2)	4	(5.8)	4	(5.8)	1	(1.5)
Epistaxis	22	(14.9)	4	(5.8)	3	(4.3)	2	(3.0)
Dyspnea exertional	16	(10.8)	0	(0)	4	(5.8)	1	(1.5)
Musculoskeletal and Connective Tissue Disorders	**101**	**(68.2)**	**41**	**(59.4)**	**28**	**(40.6)**	**15**	**(22.4)**
Back pain	40	(27.0)	6	(8.7)	7	(10.1)	4	(6.0)
Arthralgia	38	(25.7)	4	(5.8)	6	(8.7)	1	(1.5)
Muscle spasms	36	(24.3)	12	(17.4)	11	(15.9)	6	(9.0)
Pain in extremity	29	(19.6)	6	(8.7)	3	(4.3)	1	(1.5)
Musculoskeletal pain	21	(14.2)	9	(13.0)	3	(4.3)	3	(4.5)
Myalgia	19	(12.8)	5	(7.2)	2	(2.9)	2	(3.0)
Nervous System Disorders	**91**	**(61.5)**	**31**	**(44.9)**	**22**	**(31.9)**	**17**	**(25.4)**
Dizziness	37	(25.0)	8	(11.6)	6	(8.7)	3	(4.5)
Headache	33	(22.3)	10	(14.5)	10	(14.5)	6	(9.0)
Paresthesia	11	(7.4)	3	(4.3)	7	(10.1)	3	(4.5)
Metabolism and Nutrition Disorders	**71**	**(48.0)**	**17**	**(24.6)**	**16**	**(23.2)**	**13**	**(19.4)**
Decreased appetite	27	(18.2)	7	(10.1)	5	(7.2)	2	(3.0)
Hypokalemia	22	(14.9)	3	(4.3)	3	(4.3)	0	(0)
Investigations	**56**	**(37.8)**	**16**	**(23.2)**	**14**	**(20.3)**	**7**	**(10.4)**
Alanine aminotransferase increased	13	(8.8)	4	(5.8)	7	(10.1)	2	(3.0)
Injury, Poisoning, and Procedural Complications	**53**	**(35.8)**	**11**	**(15.9)**	**9**	**(13.0)**	**7**	**(10.4)**
Contusion	18	(12.2)	1	(1.4)	2	(2.9)	1	(1.5)
Fall	15	(10.1)	4	(5.8)	1	(1.4)	0	(0)
Psychiatric Disorders	**46**	**(31.1)**	**15**	**(21.7)**	**11**	**(15.9)**	**9**	**(13.4)**
Insomnia	19	(12.8)	7	(10.1)	5	(7.2)	5	(7.5)

21/28 = Days 1 to 21 of 28-day cycles; 28/28 = Days 1 to 28 of 28-day cycles; AE = adverse event; Len = lenalidomide; MedDRA = Medical Dictionary for Regulatory Activities; QD = once daily.

[a] System organ classes and preferred terms were coded using the MedDRA dictionary. System organ classes and preferred terms are listed in descending order of frequency for the first column. A subject with multiple occurrences of an AE was counted only once in the AE category.

[b] Subjects received lenalidomide 10 mg QD for 21/28 days or 10 mg QD for 28/28 days.

Note: For Studies MDS-003 and MDS-004, the Intent-to-treat population = the Treated (Safety) population.

Study MDS-003: The study database was final on 01 Oct 2010.

Study MDS-004: Data cutoff date = 14 Jun 2010.

Grade 3 / 4 AEs by Cycle

Treatment-emergent grade 3/4 AEs reported by ≥2% of the patients in any treatment group of study MDS-004 during the first 16 weeks of the double-blind phase are summarised in the table below, by descending incidence in the placebo group.

The grade 3/4 AEs with the greatest differences between the placebo group and the lenalidomide groups were: neutropenia (14.9% in the placebo group, and 73.9% in both lenalidomide groups); thrombocytopenia (1.5% in the placebo group, 31.9% in the 5-mg group, and 36.2% in the 10-mg

group); and leucopenia (no patients in the placebo group, 11.6% in the 5-mg group, and 8.7% in the 10-mg group).

Table 40. Grade 3/4 Adverse Events Reported in 2% or More of Patients in any Group During the First 16 Weeks of the Double-blind Phase (MDS 004, Double-blind phase, Safety Population)

	Placebo QD 28 of 28 Days (N=67)		Lenalidomide 5 mg QD 28 of 28 Days (N=69)		Lenalidomide 10 mg QD 21 of 28 Days (N=69)	
System Organ Class / Preferred Term[a]	n	(%)	n	(%)	n	(%)
Subjects with at Least One NCI CTC Grade 3 or 4 Adverse Event	**28**	**(41.8)**	**60**	**(87.0)**	**62**	**(89.9)**
Blood and Lymphatic System Disorders	**18**	**(26.9)**	**56**	**(81.2)**	**54**	**(78.3)**
Neutropenia	10	(14.9)	51	(73.9)	51	(73.9)
Anemia	6	(9.0)	2	(2.9)	1	(1.4)
Thrombocytopenia	1	(1.5)	22	(31.9)	25	(36.2)
Febrile neutropenia	0	(0.0)	2	(2.9)	1	(1.4)
Leukopenia	0	(0.0)	8	(11.6)	6	(8.7)
Metabolism and Nutrition Disorders	**4**	**(6.0)**	**5**	**(7.2)**	**2**	**(2.9)**
Iron overload	2	(3.0)	2	(2.9)	0	(0.0)
Infections and Infestations	**3**	**(4.5)**	**6**	**(8.7)**	**9**	**(13.0)**
Pneumonia	1	(1.5)	1	(1.4)	3	(4.3)
Bronchitis	0	(0.0)	0	(0.0)	2	(2.9)
Respiratory, Thoracic and Mediastinal Disorders	**3**	**(4.5)**	**2**	**(2.9)**	**4**	**(5.8)**
Dyspnea	2	(3.0)	1	(1.4)	2	(2.9)
Pulmonary embolism	0	(0.0)	1	(1.4)	2	(2.9)
General Disorders and Administration Site Conditions	**2**	**(3.0)**	**2**	**(2.9)**	**5**	**(7.2)**
Fatigue	1	(1.5)	0	(0.0)	2	(2.9)
Pyrexia	0	(0.0)	0	(0.0)	2	(2.9)
Neoplasms Benign, Malignant and Unspecified (Incl Cysts and Polyps)	**1**	**(1.5)**	**2**	**(2.9)**	**2**	**(2.9)**
Acute myeloid leukemia	1	(1.5)	2	(2.9)	0	(0.0)
Skin and Subcutaneous Tissue Disorders	**1**	**(1.5)**	**3**	**(4.3)**	**2**	**(2.9)**
Pruritus	0	(0.0)	0	(0.0)	2	(2.9)
Vascular Disorders	**1**	**(1.5)**	**1**	**(1.4)**	**5**	**(7.2)**
Deep vein thrombosis	1	(1.5)	1	(1.4)	3	(4.3)
Cardiac Disorders	**0**	**(0.0)**	**2**	**(2.9)**	**1**	**(1.4)**
Cardiac failure	0	(0.0)	2	(2.9)	0	(0.0)
Investigations	**0**	**(0.0)**	**2**	**(2.9)**	**4**	**(5.8)**
Alanine aminotransferase increased	0	(0.0)	2	(2.9)	1	(1.4)

[a] System organ classes and preferred terms are coded using the MedDRA dictionary, and are listed in descending order of frequency in the placebo column. A subject with multiple occurrences of an AE is counted only once in the AE category.

Drug-related Adverse Events

In study MDS-004, the drug-related AEs with the greatest differences between placebo and lenalidomide groups were: neutropenia (14.9% in the placebo group and 75.4% in both lenalidomide groups); thrombocytopenia (3.0% in the placebo group, 39.1% in the 5-mg group, and 47.8% in the 10-mg group); and pruritus (no patients in the placebo group, 17.4% in the 5-mg group, and 26.1% in the 10-mg group).

Table 41 shows all ADRs for the MDS indication, classified by treatment and severity.

Table 41. Lenalidomide ADRs in MDS uncontrolled trial MDS-003 and from placebo-controlled study MDS-004

Study	MDS-003			MDS-004					
System Organ Class/Preferred Term	All ADRs Lenalidomide 10mg (N=148) N (%)	Gr 3/4 ADRs Lenalidomide 10mg (N=148) N (%)	Serious ADRs Lenalidomide 10mg (N=148) N (%)	All ADRs * (10 and 5 mg QD) (N=138) N (%)	All ADRs * Placebo (N=67) N (%)	All Gr 3/4 ADRs # (10 and 5 mg QD) (n=138) N (%)	All Gr 3/4 ADRs # Placebo (N=67) N (%)	Serious ADRs& (10 and 5 mg QD) (n=138) N (%)	Serious ADRs & Placebo (N=67) N (%)
Gastrointestinal disorders									
Diarrhoea	90 (60.8)	10 (6.8)	4 (2.7)	48 (34.8)	12 (17.9)	4 (2.9)	0 (0.0)	2 (1.4)	0 (0.0)
Nausea	41 (27.7)	7 (4.7)	-	27 (19.6)	6 (9.0)	2 (1.4)	0 (0.0)	-	-
Constipation	39 (26.4)	-	-	27 (19.6)	5 (7.5)	-	-	-	-
Abdominal pain	28 (18.9)	-	-	15 (10.9)	4 (6.0)	-	-	-	-
Vomiting	21 (14.2)	-	-	13 (9.4)	4 (6.0)	-	-	-	-
Dry mouth	13 (8.8)	-	-	9 (6.5)	2 (3.0)	-	-	-	-
Abdominal pain upper	14 (9.5)	-	-	10 (7.2)	1 (1.5)	-	-	-	-
Dyspepsia	5 (3.4)	-	-	8 (5.8)	1 (1.5)	-	-	-	-
Toothache	-	1 (0.7)	-	-	-	3 (2.2)	0 (0.0)	-	-
Infections and infestations									
Erysipelas	-	0 (0.0)	0 (0.0)	-	-	2 (1.4)	0 (0.0)	2 (1.4)	0 (0.0)
Pneumonia @	-	14 (9.5)	15 (10.1)	-	-	4 (2.9)	1 (1.5)	4 (2.9)	1 (1.5)
Urinary tract infection	23 (15.5)	3 (2.0)	2 (1.4)	13 (9.4)	4 (6.0)	2 (1.4)	0 (0.0)	2 (1.4)	0 (0.0)
Respiratory tract infection	-	-	-	-	-	-	-	-	-
Upper respiratory tract infection	49 (33.1)	-	-	15 (10.9)	4 (6.0)	-	-	-	-
Herpes simplex	0 (0.0)	-	-	7 (5.1)	1 (1.5)	-	-	-	-
Respiratory, thoracic and mediastinal disorders									
Pulmonary embolism @	-	5 (3.4)	5 (3.4)	-	-	4 (2.9)	0 (0.0)	4 (2.9)	0 (0.0)
Nasopharyngitis	27 (18.2)	-	-	16 (11.6)	5 (7.5)	-	-	-	-
Cough	38 (25.7)	-	-	16 (11.6)	4 (6.0)	-	-	-	-
Bronchitis	20 (13.5)	1 (0.7)	-	16 (11.6)	3 (4.5)	2 (1.4)	0 (0.0)	-	-
Epistaxis	22 (14.9)	-	-	7 (5.1)	2 (3.0)	-	-	-	
Pharyngitis	0 (0.0)	-	-	13 (9.4)	1 (1.5)	-	-	-	-
General disorders & administration site conditions									
Fall	-	3 (2.0)	-	-	-	3 (2.2)	0 (0.0)	-	-
Fatigue	62 (41.9)	-	-	25 (18.1)	5 (7.5)	-	-	-	-
Oedema peripheral	48 (32.4)	-	-	21 (15.2)	5 (7.5)	-	-	-	-

Study	MDS-003			MDS-004					
System Organ Class/Preferred Term	All ADRs Lenalidomide 10mg (N=148) N (%)	Gr 3/4 ADRs Lenalidomide 10mg (N=148) N (%)	Serious ADRs Lenalidomide 10mg (N=148) N (%)	All ADRs * (10 and 5 mg QD) (N=138) N (%)	All ADRs * Placebo (N=67) N (%)	All Gr 3/4 ADRs # (10 and 5 mg QD) (n=138) N (%)	All Gr 3/4 ADRs # Placebo (N=67) N (%)	Serious ADRs& (10 and 5 mg QD) (n=138) N (%)	Serious ADRs & Placebo (N=67) N (%)
Pyrexia	39 (26.4)	5 (3.4)	-	19 (13.8)	4 (6.0)	2 (1.4)	0 (0.0)	-	-
Nervous system disorders									
Headache	33 (22.3)	-	-	20 (14.5)	6 (9.0)	-	-	-	-
Dizziness	37 (25.0)	-	-	14 (10.1)	3 (4.5)	-	-	-	-
Paraesthesia	11 (7.4)	-	-	10 (7.2)	3 (4.5)	-	-	-	-
Blood and lymphatic system disorders									
Anaemia	-	-	8 (5.4)	-	-	-	-	4 (2.9)	0 (0.0)
Febrile neutropenia @	-	11 (7.4)	8 (5.4)	-	-	3 (2.2)	0 (0.0)	3 (2.2)	0 (0.0)
Neutropenia %	98 (66.2)	96 (64.9)	10 (6.8)	106 (76.8)	12 (17.9)	103 (74.6)	10 (14.9)	8 (5.8)	0 (0.0)
Leukopenia	20 (13.5)	15 (10.1)	-	17 (12.3)	3 (4.5)	15 (10.9)	0 (0.0)	-	-
Thrombocytopenia %	96 (64.9)	81 (54.7)	6 (4.1)	64 (46.4)	2 (3.0)	51 (37.0)	1 (1.5)	8 (5.8)	0 (0.0)
Musculoskeletal and connective tissue disorders									
Back pain	40 (27.0)	9 (6.1)	1 (0.7)	13 (9.4)	4 (6.0)	3 (2.2)	0 (0.0)	2 (1.4)	0 (0.0)
Muscle spasms	36 (24.3)	-	-	23 (16.7)	6 (9.0)	-	-	-	-
Arthralgia	38 (25.7)	-	-	10 (7.2)	1 (1.5)	-	-	-	-
Myalgia	19 (12.8)	-	-	7 (5.1)	2 (3.0)	-	-	-	-
Pain in extremity	29 (19.6)	-	-	9 (6.5)	1 (1.5)	-	-	-	-
Musculoskeletal pain	21 (14.2)	-	-	12 (8.7)	3 (4.5)	-	-	-	-
Metabolism and nutrition disorders									
Hyperglycaemia %	-	1 (0.7)	0 (0.0)	-	-	2 (1.4)	0 (0.0)	2 (1.4)	0 (0.0)
Decreased appetite	27 (18.2)	3 (2.0)	-	12 (8.7)	2 (3.0)	2 (1.4)	0 (0.0)	-	-
Iron overload	4 (2.7)	-	-	7 (5.1)	2 (3.0)	-	-	-	-
Skin and subcutaneous tissue disorders									
Pruritus	66 (44.6)	4 (2.7)	-	35 (25.4)	3 (4.5)	2 (1.4)	0 (0.0)	-	-
Dry skin	21 (14.2)	-	-	14 (10.1)	1 (1.5)	-	-	-	-
Rash	60 (40.5)	10 (6.8)	-	25 (18.1)	1 (1.5)	3 (2.2)	0 (0.0)	-	-
Vascular disorders									
Deep vein thrombosis %	-	7 (4.7)	5 (3.4)	-	-	5 (3.6)	1 (1.5)	5 (3.6)	1 (1.5)
Haematoma	5 (3.4)	-	-	7 (5.1)	2 (3.0)	-	-	-	-
Hypertension	13 (8.8)	-	-	9 (6.5)	0 (0.0)	-	-	-	-
Investigations									
Alanine aminotransferase increased	13 (8.8)	5 (3.4)	-	11 (8.0)	2 (3.0)	3 (2.2)	0 (0.0)	-	-
Weight decreased	12 (8.1)	-	-	8 (5.8)	1 (1.5)	-	-	-	-

Study	MDS-003			MDS-004					
System Organ Class/Preferred Term	All ADRs Lenalidomide 10mg (N=148) N (%)	Gr 3/4 ADRs Lenalidomide 10mg (N=148) N (%)	Serious ADRs Lenalidomide 10mg (N=148) N (%)	All ADRs * (10 and 5 mg QD) (N=138) N (%)	All ADRs * Placebo (N=67) N (%)	All Gr 3/4 ADRs # (10 and 5 mg QD) (n=138) N (%)	All Gr 3/4 ADRs # Placebo (N=67) N (%)	Serious ADRs& (10 and 5 mg QD) (n=138) N (%)	Serious ADRs & Placebo (N=67) N (%)
Cardiac disorders									
Acute myocardial infarction @	-	2 (1.4)	2 (1.4)	-	-	2 (1.4)	0 (0.0)	2 (1.4)	0 (0.0)
Atrial fibrillation @	-	4 (2.7)	3 (2.0)	-	-	2 (1.4)	0 (0.0)		
Cardiac failure @	-	2 (1.4)	2 (1.4)	-	-	2 (1.4)	0 (0.0)	3 (2.2)	0 (0.0)
Renal and urinary disorders									
Renal failure @	-	3 (2.0)	2 (1.4)	-	-	2 (1.4)	0 (0.0)	2 (1.4)	0 (0.0)
Psychiatric disorders									
Mood altered	-	-	0 (0.0)	-	-	-	-	2 (1.4)	0 (0.0)

N – Number of Patients
* -MDS-004 ADRs - All treatment emergent AEs with ≥5% of Patients in lenalidomide and at Least 2% difference in proportion between the two arms by Initial Dosing Regimen (Double Blind-Safety population)
# - MDS-004 Gr 3/4 ADRs - All treatment-emergent Gr 3/4 AEs in 1% of Patients in lenalidomide and at least 1% difference in proportion between the two arms (Double Blind- Safety Population)
& - MDS-004 Serious ADRs - All treatment-emergent SAEs in 1% of Patients in lenalidomide and at least 1% difference in proportion between the two arms (Double Blind- Safety Population)
@ - ADRs where at least one resulted in a fatal outcome
% - ADRs where at least one was considered to be Life Threatening (if the outcome of the event was death, it is included with death cases)

Serious adverse event / deaths / other significant events

Death

Overall, there were 101 (49.3%) deaths during the study period, 10 of which occurred within 30 days of the last dose of study drug. The percentages of deaths, including those that occurred within 30 days of their last dose, were comparable between the placebo group and the lenalidomide groups.

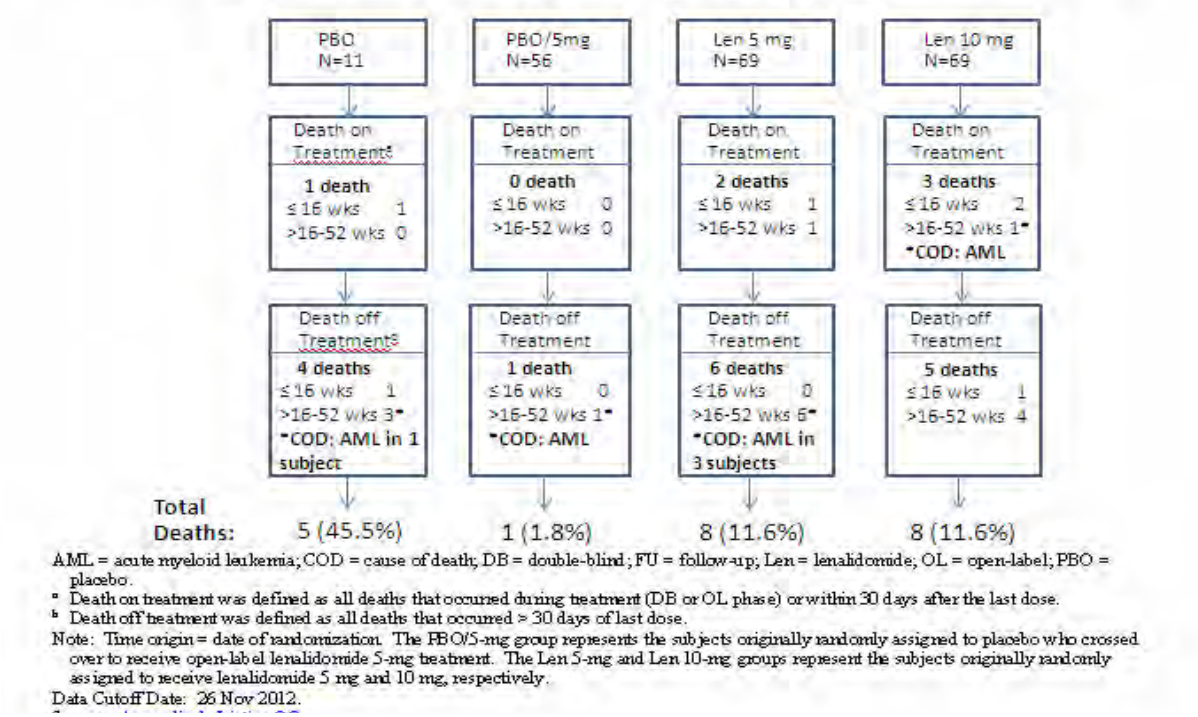
The majority of deaths, across all three treatment groups, were due to disease progression, and the numbers were comparable between the placebo group and the lenalidomide groups.

Table 42. Summary of Deaths from the Double-blind and Open-label Phases (Safety Population)

Category	Placebo QD 28 of 28 Days (N=67) n (%)	Lenalidomide 5 mg QD 28 of 28 Days (N=69) n (%)	Lenalidomide 10 mg QD 21 of 28 Days (N=69) n (%)	Overall (N=205) n (%)
All subjects who died during the study	35 (52.2)	32 (46.4)	34 (49.3)	101 (49.3)
Number of subjects who died ≤ 30 days after last dose[a]	4 (6.0)	2[b] (2.9)	4 (5.8)	10 (4.9)

a These subjects are a subset of all those who died during the study.
b The underlying AE was suspected by the investigator to be related to study drug 1 of these 2 subjects.

Figure 21. Deaths that Ocurred on and off Treatment by Treatment Group (DB, OL and FU Phases of MDS-004) During the first 52 Weeks.



AML = acute myeloid leukemia; COD = cause of death; DB = double-blind; FU = follow-up; Len = lenalidomide; OL = open-label; PBO = placebo.

[a] Death on treatment was defined as all deaths that occurred during treatment (DB or OL phase) or within 30 days after the last dose.

[b] Death off treatment was defined as all deaths that occurred > 30 days of last dose.

Note: Time origin = date of randomization. The PBO/5-mg group represents the subjects originally randomly assigned to placebo who crossed over to receive open-label lenalidomide 5-mg treatment. The Len 5-mg and Len 10-mg groups represent the subjects originally randomly assigned to receive lenalidomide 5 mg and 10 mg, respectively.

Data Cutoff Date: 26 Nov 2012.

A total of 22 (10.7%) of the 205 patients in Study MDS-004 died during the first 52 weeks of the study. Six patients died while on treatment or within 30 days of last dose of study treatment in the double-blind (DB) and open-label (OL) phases, and 16 deaths occurred during the follow-up survival phase (> 30 days after the last dose of lenalidomide).

The figure above summarizes deaths by their occurrence on treatment (while receiving drug during DB or OL phase or within 30 days of discontinuing drug) and off treatment (during follow-up >30 days of discontinuing drug).

Table 43: Analysis of Death Throughout the Study by Lenalidomide Exposure "As Treated" Analysis (Safety Population).

Summary	Placebo Never Entered Open-label [a] (N=11)	Placebo/ Lenalidomide 5 mg/day [b] (N=56)	Lenalidomide 5 mg/day [c] (N=69)	Lenalidomide 10 mg/day [a] (N=69)	Total Lenalidomide [c] (N=194)
Kaplan-Meier estimates					
Death	9 (81.8)	26 (46.4)	32 (46.4)	34 (49.3)	92 (47.4)
Median (months)	13.8	43.7	NA	44.5	44.5
95% confidence interval	9.3, 27.1	32.9, NA	24.5, NA	35.5, NA	36.9, NA

[a] Time origin is the randomization date.

[b] Time origin is the first 5 mg dosing date.

Table 44. Deaths that Ocurred During the Study or Within 30 Days After the Last Dose of Study Drug (Safety Population)

Cause of Death	Placebo QD 28 of 28 Days n	Lenalidomide 5 mg QD 28 of 28 Days n	Lenalidomide 10 mg QD 21 of 28 Days n	Total n
Disease Progression	**19**	**18**	**20**	**57**
MDS progression	5	5	6	16
AML progression	14	13	14	41
Cardiac	**4**	**4**	**3**	**11**
Cardiac heart failure	2	4	2	8
Myocardial infarction	1	0	0	1
Sudden death	1	0	1	2
Infection	**4**	**3**	**6**	**13**
Respiratory	2	2	1	5
Sepsis	2	1	4	7
Febrile pancytopenia	0	0	1	1
Hemorrhage	**2**	**2**	**0**	**4**
GI hemorrhage	0	1	0	1
Cerebral hemorrhage	2	0	0	2
Unknown origin	0	1	0	1
Neoplasm	**1**	**2**	**0**	**3**
Endometrial	1	0	0	1
Hepatocarcinoma	0	1	0	1
NSCLC	0	1	0	1
Others[a]	**5**	**3**	**5**	**13**
Total n	**35**	**32**	**34**	**101**

[a] Others: Unkown; suicide

Serious adverse events

At least one Treatment- Emergent SAE was reported in 20.9% of the patients in the placebo group, in 44.9% of the patients in the 5-mg lenalidomide group, and in 46.4% of the patients in the 10-mg group.

Table 45. Serious Adverse Events Reported in Two or More Patient in any Group (Double-blind Safety Population

System Organ Class / Preferred Term*	Placebo QD 28 of 28 Days (N=67)		Lenalidomide 5 mg QD 28 of 28 Days (N=69)		Lenalidomide 10 mg QD 21 of 28 Days (N=69)	
	n	(%)	n	(%)	n	(%)
Subjects with at Least One Serious Adverse Event	**14**	**(20.9)**	**31**	**(44.9)**	**32**	**(46.4)**
General Disorders and Administration Site Conditions	**3**	**(4.5)**	**7**	**(10.1)**	**3**	**(4.3)**
Pyrexia	2	(3.0)	4	(5.8)	1	(1.4)
Infections and Infestations	**3**	**(4.5)**	**8**	**(11.6)**	**9**	**(13.0)**
Pneumonia	1	(1.5)	2	(2.9)	2	(2.9)
Respiratory, Thoracic and Mediastinal Disorders	**3**	**(4.5)**	**4**	**(5.8)**	**3**	**(4.3)**
Pulmonary embolism	0	(0.0)	2	(2.9)	2	(2.9)
Neoplasms Benign, Malignant and Unspecified (Incl Cysts and Polyps)	**2**	**(3.0)**	**7**	**(10.1)**	**4**	**(5.8)**
Acute myeloid leukemia	2	(3.0)	4	(5.8)	2	(2.9)
Cardiac Disorders	**1**	**(1.5)**	**3**	**(4.3)**	**3**	**(4.3)**
Acute myocardial infarction	0	(0.0)	0	(0.0)	2	(2.9)
Cardiac failure	0	(0.0)	2	(2.9)	1	(1.4)
Vascular Disorders	**1**	**(1.5)**	**2**	**(2.9)**	**7**	**(10.1)**
Deep vein thrombosis	1	(1.5)	1	(1.4)	4	(5.8)
Blood and Lymphatic System Disorders	**0**	**(0.0)**	**10**	**(14.5)**	**11**	**(15.9)**
Anemia	0	(0.0)	3	(4.3)	1	(1.4)
Febrile neutropenia	0	(0.0)	2	(2.9)	1	(1.4)
Neutropenia	0	(0.0)	4	(5.8)	4	(5.8)
Thrombocytopenia	0	(0.0)	5	(7.2)	3	(4.3)
Musculoskeletal and Connective Tissue Disorders	**0**	**(0.0)**	**1**	**(1.4)**	**4**	**(5.8)**
Back pain	0	(0.0)	0	(0.0)	2	(2.9)

* System organ classes and preferred terms are coded using the MedDRA dictionary, and are listed in descending order of frequency in the placebo column. A subject with multiple occurrences of an AE is counted only once in the AE category.

Adverse Events of Special Interest

Second Primary Malignancies

Late in 2010, an increased occurrence of Second Primary Malignancies (SPMs) was noted among lenalidomide-treated patients in placebo-controlled studies in newly diagnosed multiple myeloma (NDMM), where lenalidomide was used together with melphalan or shortly following melphalan/autologous stem cell transplant therapy. Ongoing studies, including MDS-004 (where patients continue in follow-up), were amended to provide for long-term follow-up for the occurrence of SPMs.

The following analyses were conducted to analyze SPMs in the MDS del (5q) setting and are included in this application:

- The frequency of SPMs in all completed studies conducted in patients with MDS. The data cut-off dates for the MDS-001, MDS-002, MDS-003, MDS-003E/MDS-009, MDS-007, and PK-002 studies in this analysis were the respective database lock dates; the data cut-off date for MDS-004 was 22 Aug 2011.
- All AEs of SPMs by PT in all completed studies conducted in patients with MDS. The data cut-off dates for the MDS-001, MDS-002, MDS-003, MDS-003E/MDS-009, MDS-007, and PK-002 studies in this analysis were the respective database lock dates; the data cut-off date for MDS-004 was 22 Aug 2011.

- Summary of lenalidomide dosing, treatment duration and time to onset of SPMs in MDS, including postmarketing data. The data cut-off date for this analysis was 22 Feb 2011 for the MDS studies and 05 Sep 2011 for the postmarketing data; the PK-002 study was not included in this analysis.
- Summary of risk factors for developing SPMs in patients with MDS, including postmarketing data. The data cut-off date for this analysis was 22Feb2011 for the MDS studies and 05 Sep 2011 for the postmarketing data; the PK-002 study was not included in this analysis.
- A by-patient summary of SPMs, treatment, and outcome. The data cut-off dates for the MDS-001, MDS-002, MDS-003, MDS-003E/MDS-009, MDS-007, and PK-002 studies in this analysis were the respective database lock dates; the data cut-off date for MDS-004 was 22 Aug 2011.

In the 6 completed MDS studies (MDS-001, MDS-002, MDS-003, MDS-004, MDS-007, and PK-002), a total of 652 patients received at least one dose of lenalidomide, including 56 patients who received placebo during the DB phase of MDS-004 and then crossed over to receive lenalidomide during the OL phase. The PK-002 study has been added since, with a data cut-off data of 22 Feb 2011. The 39 patients treated with lenalidomide in PK-002 have been included in the overall analyses of the frequency of SPMs, AEs reported as SPMs, and the by-patient summary of SPMs, treatment, and outcome, but not included in the analyses of time to onset of SPMs and risk factors for SPMs . A total of 557 lenalidomide-treated patients were included in the latter 2 analyses with a data cut-off date of 22 Feb2011, as well as patients exposed to lenalidomide in the postmarketing setting (N=33,917), with a data cut-off date of 05Sep2011.

In the MDS-004 study, patients randomised to placebo could receive lenalidomide after 16 weeks if there was no evidence of at least a minor erythroid response. As a result, 56 of the 67 patients randomised to placebo subsequently received lenalidomide treatment after Week 16. Given the limited number of patients randomised to placebo who did not receive lenalidomide (11 patients) and the short duration of placebo treatment during the DB phase (median of 16 weeks), only patients randomised to lenalidomide treatment (596 patients) are included in the analyses of frequency of SPMs and AEs reported as SPMs .

Table 46. Frequency of second primary malignancies in completed studies conducted in subjects with myelodysplastic syndromes (safety population)

			Invasive SPMs					Non-invasive SPMs	
			Hematologic Malignancies						
Study	Treatment	No. of Subjects[a]	B-cell Malig n (%)	Others[b] n (%)	Total n (%)	Solid Tumors n (%)	Total Invasive SPMs[c] n (%)	Non-Melanoma Skin Cancers n (%)	Overall SPMs[d] n (%)
Overall	**Len**	**596**	**1 (0.2)**	**1 (0.2)[e]**	**2 (0.3)**	**15 (2.5)**	**17 (2.9)**	**13 (2.2)**	**29 (4.9)**
MDS-001	Len	45	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.2)	1 (2.2)	1 (2.2)	2 (4.4)
MDS-002	Len	215	0 (0.0)	0 (0.0)	0 (0.0)	3 (1.4)	3 (1.4)	3 (1.4)	6 (2.8)
MDS-003	Len	148	1 (0.7)	1 (0.7)	2 (1.4)	7 (4.7)	9 (6.1)	6 (4.1)	14 (9.5)
MDS-004	Len	138	0 (0.0)	0 (0.0)	0 (0.0)	4 (2.9)	4 (2.9)	2 (1.4)	6 (4.3)
MDS-007	Len	11	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
PK-002	Len	39	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.6)	1 (2.6)

AML = acute myeloid leukemia; Len = lenalidomide; Malig = malignancy; MDS = myelodysplastic syndromes; MM = multiple myeloma; SPMs = second primary malignancies.

[a] Includes only subjects randomized to lenalidomide treatment (MDS-004) or treated with lenalidomide (MDS-001, MDS-002, MDS-003, MDS-007, and PK-002).

[b] Progression to AML is part of the natural course of MDS and is considered to be disease progression rather than a SPM; thus progression to AML in the 6 completed MDS studies has been analyzed separately (see Section 2.1.5.9 and SCE Section 3.2.4).

[c] Total invasive SPMs is the total number of subjects with at least one hematologic malignancy or solid tumor.

[d] Overall SPMs is the total number of subjects with at least one invasive SPM or non-invasive SPM (non-melanoma skin cancer). One subject had both an invasive cancer and non-melanoma skin cancer.

[e] One case of MM was reported in the MDS-003 study, which was misclassified as an Other hematologic malignancy; MM is a B-cell malignancy.

Note: the data cutoff dates for the MDS-001, MDS-002, MDS-003, MDS-003E/MDS-009, MDS-007, and PK-002 studies in this analysis were the respective database lock dates; the data cutoff date for MDS-004 was 22 Aug 2011. An additional 2 subjects in the MDS-004 study had SPMs (invasive SPMs, solid tumors) that were reported to Celgene after the data cutoff date of 22 Aug 2011. Narratives for Subject 0174002 and Subject 0364001 are provided in Appendix 8.4.

Table 47. All adverse events of second primary malignancies by Preferred Term in completed studies conducted in patients with myelodysplastic syndromes (safety population)

	All Lenalidomide-Treated Subjects (N = 596)	
Second Malignancy / Preferred Term	**n**	**(%)**
Subjects with at least one second primary malignancy	**29**	**(4.9)**
Solid Tumors	**15**	**(2.5)**
Breast cancer	2	(0.3)
Colon cancer	2	(0.3)
Bladder cancer	1	(0.2)
Bronchioloalveolar carcinoma	1	(0.2)
Carcinoid tumor of the small bowel	1	(0.2)
Colon cancer NOS	1	(0.2)
Colorectal cancer	1	(0.2)
Endometrial cancer	1	(0.2)
Gastric neoplasm NOS	1	(0.2)
Lung cancer metastatic	1	(0.2)
Lung neoplasm	1	(0.2)
Ovarian cancer	1	(0.2)
Thymoma	1	(0.2)
Vulval cancer	1	(0.2)
Non-Melanoma Skin Cancers	**13**	**(2.2)**
Basal cell carcinoma	7	(1.2)
Squamous cell carcinoma	6	(1.0)
Squamous cell carcinoma of skin	4	(0.7)
Keratoacanthoma	1	(0.2)
Hematological Malignancies	**2**	**(0.3)**
B-cell lymphoma	1	(0.2)
Multiple myeloma	1	(0.2)

NOS = not otherwise specified.
Note: the data cutoff dates for the MDS-001, MDS-002, MDS-003, MDS-003E/MDS-009, MDS-007, and PK-002 studies in this analysis were the respective database lock dates; the data cutoff date for MDS-004 was 22 Aug 2011.

Overall, in the 6 completed MDS studies (MDS-001, MDS-002, MDS-003, MDS-004, MDS-007, and PK-002), 29 of 596 (4.9%) lenalidomide-treated patients experienced a new cancer including 17 (2.9%) patients with invasive SPMs and 13 (2.2%) patients with non-melanoma skin cancers . The incidence of SPMs was generally higher in MDS-003 (continuous regimen) compared to other MDS studies, which may be attributable to the longer mean duration of drug exposure and duration of follow-up in this study.

The MAH has submitted the following information about SPMs that occurred after the data cut-off date for the MDS-004 study. Two patients in the MDS-004 study had SPMs (invasive SPMs, solid tumours) that were reported to the MAH after the data cut-off date of 22 Aug 2011. One Patient had breast cancer (reported to the MAH in Oct 2011), and one Patient had oropharyngeal cancer stage unspecified (reported to the MAH in Sep 2011). Narratives for the 29 patients who had at least one SPM in the completed MDS clinical studies, as well as 2 patients in the MDS-004 study who had SPMs

reported to the MAH after the 22 Aug 2011 data cut-off date (up to 31 Dec 2011), have been submitted.

Since the last report submitted in the original dossier (17 Feb 2012), 2 additional SPMs (one in the PBO/5 mg group [endometrial cancer] and one in the 5 mg group [hepatocellular carcinoma]) were reported as causes of death during survival follow-up phase as causes of death, bringing the total number of patients with SPMs in Study MDS-004 to 10 of the 194 lenalidomide-treated patients. Eight patients had invasive solid tumors and 2 patients had non-melanoma skin cancers (2 patients developed 2 invasive SPMs each bringing the total number of SPMs to 12 in these 10 patients).

Updated SPM analysis (data cut-off 26 November 2012)

Pooled data from Studies MDS-003 and MDS-004 show that the incidence rates of invasive SPMs among lenalidomide-treated patients were comparable for patients treated for < 2 years (2.37/100 person-years) versus ≥2 years (1.03/100 person-years). Similarly, the incidence rates of invasive SPMs were comparable for patients treated for < 1 year (2.96/100 person-years) versus ≥ 1 year (1.14/100 person-years).

The overall incidence rate of invasive SPMs in lenalidomide-treated patients in Studies MDS-003 and MDS-004 was within the expected rate for the general elderly population (1.68/100 person-years versus approximately 2.1/100 person-years), suggesting that treatment of myelodysplastic syndrome (MDS) with single-agent lenalidomide does not have an apparent impact on the risk of developing invasive SPMs.

Progression to acute myeloid leukemia (AML) in patients with MDS represents a progression of the disease, and thus AML is not considered a second primary malignancy (SPM). However the impact of a prolonged treatment with lenalidomide on the risk of progression to AML is unknown.

Discontinuation / Dose reductions due to adverse events

Overall, the percentages of patients who had at least one dose reduction or interruption due to an AE were similar between the lenalidomide groups (59.4 % and 62.3% for the 5-mg and 10-mg groups, respectively) and higher than that of the placebo group (3.0%).

The median time to first dose reduction or interruption due to an AE was 43.0 days for the 5-mg group and 27.0 day for the 10-mg group; and occurred earlier compared with the placebo group (79.0 days).

The median duration of the first dose interruption was 7.0 days in the placebo group, and increased with increasing dose of lenalidomide (11.0 days and 14.0 days in the 5-mg and 10-mg groups, respectively).

Approximately 40% of patients in the 10-mg group received treatment for at least 52 weeks (median 50.3 weeks), compared with approximately 20% of patients in the 5-mg group (median 18.0 weeks).

At least one AE leading to dose reduction was reported in 59.4% in the 5-mg group and 60.9% in the 10-mg group.

- Neutropenia (31.9% in the 5-mg group and 37.7% in the 10-mg group);
- Thrombocytopenia (14.5% in the 5-mg group and 24.6% in the 10-mg group);
- Febrile neutropenia (2.9% in the 5-mg group and no patients in the 10-mg group)

- Rash NOS (2.9% in the 5-mg group and no patients in the 10-mg group)
- Diarrhoea NOS (2.9% in the 5-mg group and 4.3% in the 10-mg group)

The relatively high percentages of patients in both groups with dose reductions due to neutropenia and thrombocytopenia are consistent with the protocol-defined dose reduction plan for management of cytopenias.

Analysis of the long-term safety data in patients receiving lenalidomide was generally similar to that observed during the first 16 weeks, suggesting that there was no delayed or cumulative toxicity.

The dose-reduction guidance proposed for patients who receive lenalidomide and develop neutropenia or thrombocytopenia are those specified for Study MDS-004 (Table 51).

Table 48. Dose Reduction and Modification Guidelines

NCI CTCAE Toxicity Grade	Action
Neutropenia **ANC < 500/μL** **(Grade 4)**	• Interrupt lenalidomide therapy • Resume lenalidomide (decrease one dose level) when ANC recovers to ≥ 500/μL
Thrombocytopenia **Platelet count < 25,000/μL** **(Grade 4)**	• Interrupt lenalidomide therapy • Resume lenalidomide (decrease one dose level) when platelet count recovers to between ≥ 25,000/μL <50,000/ μL on at least 2 occasions for ≥ 7 days or when the platelet count recovers to ≥50,000 at any time

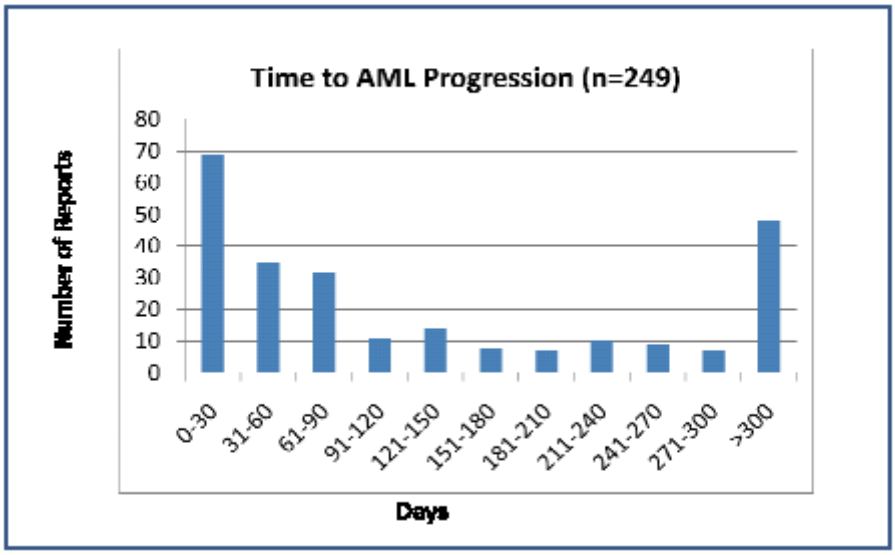
Post marketing experience

In order to explore the possible impact of lenalidomide on the time to progression to acute myeloid leukaemia (AML) in MDS del (5q) patients, Celgene implemented a specific data collection questionnaire to collect important data elements for these reports, including: date of initial MDS diagnosis; specific MDS sub-type and International Prognostic Scoring System (IPSS) category; date of lenalidomide initiation; date of progression to AML; and possible confounding factors, including previous chemotherapy, baseline bone marrow and laboratory results.

Of the 425 reports of progression to AML, 249 had sufficient data available to calculate the time from initiation of lenalidomide therapy to the diagnosis of progression to AML. Classification by the IPSS status and MDS subtype was not available for these events.

The median time to progression among patients in these 249 reports was 85 days, the mean was 179.9 days, and the range was from 2 to 1,460 days. Over half of the events (54.6%; 136/249) occurred during the first 90 days of therapy, as shown in Figure 20:

Figure 22. Time from Initiation of Lenalidomide Therapy to Progression to Acute Myeloid Leukaemia



The overall reporting rate of progression to AML is 1.3% (425/33,917). Progression to AML is considered part of the natural history of MDS and therefore a relatively small number of reports were received.

Ongoing and future studies

Study MDS-005

Study CC-5013-MDS-005 is an ongoing phase 3, multicenter, double-blind, randomised, placebo-controlled trial that compares the efficacy and safety of oral lenalidomide therapy to that of placebo in patients with transfusion-dependent (TD) anaemia due to International Prognostic Scoring System (IPSS) low- or intermediate-1 (INT 1)-risk myelodysplastic syndromes (MDS) without deletion (del) 5q[31] who are unresponsive or refractory to erythropoiesis-stimulating agents (ESAs).

2.6.1. Discussion on clinical safety

The overall safety profile of Revlimid in patients with myelodysplastic syndromes is based on data from a total of 286 patients from one Phase II study and one Phase III study. In the Phase II, all 148 patients were on lenalidomide treatment. In the Phase III study, 69 patients were on lenalidomide 5 mg, 69 patients on lenalidomide 10 mg and 67 patients were on placebo during the double-blind phase of the study.

Most adverse events tended to occur during the first 16 weeks of therapy with lenalidomide.

Serious adverse reactions included venous thromboembolism (deep vein thrombosis, pulmonary embolism), grade 3 or 4 neutropenia, febrile neutropenia and grade 3 or 4 thrombocytopenia.

The most frequently observed adverse reactions which occurred more frequently in the lenalidomide groups compared to the control arm in the Phase III study were neutropenia (76.8%), thrombocytopenia (46.4%), diarrhoea (34.8%), constipation (19.6%), nausea (19.6%), pruritus (25.4%), rash (18.1%), fatigue (18.1%) and muscle spasms (16.7%).

Adverse Drug Reactions (bacterial, viral and fungal infections, iron overload, hyperglycaemia, decreased appetite, altered mood, cardiac failure, haematoma, bronchitis, abdominal gain, toothache, dyspepsia, dry skin, pruritus, arthralgia, myalgia, back pain, pyrexia, fall, cough) were included in section 4.8 of the SmPC.

The major dose limiting toxicities of lenalidomide include neutropenia and thrombocytopenia. 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. A dose reduction may be required. In case of neutropenia, the physician should consider the use of growth factors in patient management. Patients should be advised to promptly report febrile episodes. Co-administration of lenalidomide with other myelosuppressive agents should be undertaken with caution.

An increased risk of DVT and PE is associated with the use of lenalidomide with dexamethasone in patients with multiple myeloma, and to a lesser extent in patients with myelodysplastic syndromes treated with lenalidomide monotherapy.

The potential risk of hepatic disorders was already presented in section 4.4 and 4.8 of the existing SmPC. The CHMP confirmed that other important potential risks (peripheral neuropathy, cardiac failure, cardiac arrhythmias, renal failure, ischaemic heart disease including myocardial infarction, interstitial lung disease) were already adequately reflected in the Product Information.

In clinical trials of newly diagnosed multiple myeloma, a 4-fold increased incidence of SPM has been observed in patients receiving Revlimid (7.0%) compared with controls (1.8%). The potential risk of second primary malignancies has been included in section 4.4 of the SmPC as a warning, and this adverse drug reaction is also included in section 4.8 of the SmPC. The MAH has proposed studies to understand and characterise this risk specifically for MDS (MDS PASS; US CONNECT MDS/AML Registry) as part of the Risk Management Plan.

During the double blind phase (52 weeks), 4/67 (6%) placebo patients had progression to AML versus 7/138 (6.5%) lenalidomide patients. During the entire study, 48/194 patients (24.7%) exposed to lenalidomide have progressed to AML.

The risk for progression to AML was not considered to be adequately characterised in the targeted population. Moreover, due to methodological limits, none of the updated results regarding progression to AML in Study MDS-005 or the additional sensitivity analyses from the MCR comparison to lenalidomide-treated patients in Studies MDS-003 and MDS-004 have given reassurance regarding the risk for an increased rate of progression to AML.

Baseline variables including complex cytogenetics and TP53 mutation are associated with progression to AML in patients who are transfusion dependent and have a Del (5q) abnormality (see section 4.4). The estimated 2-year cumulative risk of progression to AML were 13.8% in patients with an isolated Del (5q) abnormality compared to 17.3% for patients with Del (5q) and one additional cytogenetic abnormality and 38.6% in patients with a complex karyotype.

In a post-hoc analysis of a clinical trial of Revlimid in myelodysplastic syndromes, the estimated 2-year rate of progression to AML was 27.5 % in patients with IHC-p53 positivity and 3.6% in patients with IHC-p53 negativity (p=0.0038). In the patients with IHC-p53 positivity, a lower rate of progression to AML was observed amongst patients who achieved a transfusion independence (TI) response (11.1%) compared to a non-responder (34.8%).

Considering that (1) the risk for progression to AML has not been characterised in the targeted population, (2) the benefit of lenalidomide treatment is evidenced (achieving RBC-TI, cytogenetic response, durable response), the safer option to manage safety concern would be to reserve

lenalidomide treatment to patients with the lowest risk among transfusion dependent del 5q MDS patients, i.e.; low or int-1 MDS associated with an isolated deletion 5q.

2.6.2. Conclusions on clinical safety

To manage the safety concern of a potential increased risk of AML, the CHMP considered it necessary to restrict the indication to "patients with transfusion-dependent anaemia due to low- or intermediate-1-risk myelodysplastic syndromes associated with an isolated deletion 5q cytogenetic abnormality when other therapeutic options are insufficient or inadequate". In the restricted indication, the safety concern is mitigated.

Conditional to the approval of this indication, the CHMP considered the following measures necessary to address issues related to safety:

1. A post-authorisation non-interventional, safety study of patients with myelodysplastic syndromes (MDS) treated with lenalidomide to ascertain progression to acute myeloid leukemia (AML) and survival among patients who have been treated with at least one complete cycle of lenalidomide. The secondary objectives of the study are:

- Characterization of the safety profile of lenalidomide in terms of hematological and non-hematological adverse events, including infections, bleeding, thromboembolic events, major cardiac events and second primary malignancies (SPM) other than AML (which is considered as disease progression).
- Description of the characteristics of MDS patients treated with lenalidomide.
- Evaluation of risk factors associated with progression to acute myeloid leukemia and overall survival among enrolled MDS patients treated with lenalidomide.
- Characterization of the effectiveness profile of lenalidomide in a routine care setting, especially erythroid response, transfusion independence, cytogenetic response and related long-term outcomes.
- Monitor the off-label use of lenalidomide in MDS patients

This study should be part of the pharmacovigilance plan as Category 1 study. Patients receiving lenalidomide for treatment of MDS should be included in the PASS study. The PASS should collect: Patients demographic data, baseline characteristics including cytogenetics (del 5q status and other cytogenetic abnormalities), indication and response to ESA treatment if administered, safety outcomes including transformation to AML, occurrence of SPM and cause of death.

The PASS and enrolment of MDS patients receiving lenalidomide in it, should be considered as an imposed obligation and therefore be included as a condition of the MA (i.e. category 1 of pharmacovigilance activities according to the guideline on good pharmacovigilance practices for risk management systems). The details of such enrolment should be agreed with NCAs in the MS where lenalidomide is expected to be used in the new indication.

The final protocol is expected within 1 month after Commission Decision granting the new indication.

2. The distribution of Direct Healthcare Professional Communication informing prescribers of the granting of the extension of indication to MDS del 5q and warning about important aspects in the clinical use of Revlimid. In countries where Revlimid is already launched, the MAH should provide all potential healthcare professionals with updated educational material (HCP brochure and patient brochure including the PPP) together with the DHPC.

2.6.3. PSUR cycle

The PSUR cycle remains unchanged.

The next data lock point will be 26 December 2013.

The annex II related to the PSUR, refers to the EURD list which remains unchanged.

2.7. Risk management plan

The MAH submitted a risk management plan (version 22), which included a risk minimisation plan.

Table 49. Summary of Safety Concerns

Important Identified Risks	– Teratogenicity – Thrombocytopenia and bleeding – Neutropenia and infection – Thromboembolic events – Cutaneous reactions – Hypersensitivity and angioedema – Diarrhoea and constipation – TLS <u>Important Identified Risks Related to Indication/Target Population</u> – For NDMM[i)]: AML and B-cell malignancies[ii)] – For RRMM: NMSC[iii)]
Important Potential Risks	– Peripheral neuropathy – Cardiac failure – Cardiac arrhythmias – Renal failure – Ischaemic heart disease (including myocardial infarction) – Interstitial lung disease (interstitial pneumonitis) – Hepatic disorders – Off-label use <u>Important Potential Risks Related to Indication/Target Population</u> – For NDMM[a]: NMSC[c] – For RRMM: AML and B-cell malignancies[b] – For MDS: AML and B-cell malignancies[b]; NMSC[c] – Other SPM (i.e., those not detailed above for the NDMM, RRMM and MDS populations)
Important Missing Information	None

Table 50. Table of Ongoing and Planned Additional Pharmacovigilance Studies/Activities in the Pharmacovigilance Plan

Study/Activity Type, Title and Category (1-3)	**Objectives**	**Safety Concerns Addressed**	**Status (planned, started)**	**Date for Submission of Interim or Final Reports (planned or actual)**
MDS PASS *Non-interventional: observational Category 1*	To gather safety data on the use of lenalidomide in MDS patients and monitor off-label use.	AML and survival. Safety profile in a 'real world' setting.	Planned, study pending EU approval	Annual safety updates with PSURs

RRMM PASS *Non-interventional: Category 3*	To monitor implementation of Celgene PPP and to monitor safety in a "real world" situation.	Celgene PPP. Safety profile in a 'real world' setting.	Ongoing, protocol amendment submission to ethics committees and competent authorities is in progress.	Annual safety updates submitted during the PSUR and RMP cycles
Observational cohort study to assess VTE *Category 3*	An epidemiologic protocol of VTE occurrence, prophylaxis, and treatment in patients treated with thalidomide/dexamethasone or lenalidomide/dexamethasone is currently under review with the US FDA. This is to fulfil the postmarketing commitment of an epidemiologic study of venous thromboembolic events.	VTE	Planned, full protocol submitted to FDA on 23 Dec 2011; updated versions submitted (Most recent 25 May 2012). Finalised protocol with FDA approval is anticipated 2Q 2013.	The study report is anticipated in 1Q 2014
US CONNECT MDS/AML Registry *Non-interventional: observational Category 3*	The primary objectives of the registry will be to describe practice patterns of common first-line treatment regimens (including lenalidomide-based) in the community and academic settings. Additionally, the registry will provide insight into treatment regimens and therapy sequence in clinical practice as they relate to clinical outcomes (response, OS, PFS) in patients with symptomatic MDS. Data regarding SPM will also be collected.	SPM	Enrollment to start 3Q 2013	Annual safety updates submitted during the PSUR and RMP cycles

Table 51. Summary of Table of Risk Minimisation Measures (routine and additional) in the RMP

Safety Concern	Proposed Routine Risk Minimisation Measures	Proposed Additional Risk Minimisation Measures
Important Identified Risk		
Teratogenicity	Routine risk minimisation activities (SmPC and PL). Section 4.3: Contraindicated in pregnant women and in women of childbearing potential unless all the conditions of the Celgene PPP are met. Section 4.4: 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. Section 4.6: Fertility, pregnancy and lactation Specific pregnancy reporting form	– 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 brochure and checklists. – Therapy management o Criteria for determining women of childbearing potential, Contraceptive measures and pregnancy testing for women of childbearing potential o Advice in SmPC, Dear HCP letter and educational materials – System to ensure appropriate measures have been completed o Patient card to document childbearing status, counselling and pregnancy testing
Thrombocytopenia and Bleeding	– Section 4.2 of SmPC: dose reduction advice for thrombocytopenia. Section 4.4 of SmPC: warning of thrombocytopenia and bleeding, and advice for weekly blood tests for first 8 weeks and then monthly. – Listed as an ADR in Section 4.8 of SmPC. – Advice to patients in PL	– 'Dear HCP' letter prior to launch. – HCP Kit. – Patient Brochure.

Table 52. Summary of Table of Risk Minimisation Measures (routine and additional) in the RMP (Continued)

Safety Concern	Proposed Routine Risk Minimisation Measures	Proposed Additional Risk Minimisation Measures
Neutropenia and Infection (Continued)	– Section 4.2 of SmPC: dose reduction advice for neutropenia. – Section 4.4 of SmPC: warning of neutropenia and advice for weekly blood tests for first 8 weeks and then monthly. Advice that patients should be advised to report febrile incidences promptly. – Listed as an ADR in Section 4.8 of SmPC. – Advice to patients in PL.	– 'Dear HCP' letter prior to launch – HCP Kit - Patient Brochure
Thromboembolic Events	– Section 4.4 of SmPC: warning on the possibility of developing DVT or PE, and recommendations for the use of antithrombotic and/or anticoagulant prophylaxis – Section 4.4 of SmPC: States erythropoietic agents, or other agents that may increase the risk of thrombosis, such as hormone replacement therapy, should be used with caution in MM patients receiving lenalidomide with dexamethasone. – Listed as an ADR in Section 4.8 of SmPC. – Advice to patients in PL	– 'Dear HCP' letter prior to launch – HCP Kit – Patient Brochure
Cutaneous Reactions	– Stevens Johnson syndrome and toxic epidermal necrolysis listed in Section 4.2, 4.4 and 4.8 of SmPC and in the PL.	– HCP Kit
Hypersensitivity and Angioedema	– SmPC Section 4.3: contraindicated in patients who are hypersensitive to the active substance or any of the excipients. – Hypersensitivity listed as an ADR in Section 4.8 of SmPC and in PL. Allergic reactions listed in Section 4.4. – Angioedema listed in Sections 4.2 and 4.8 of SmPC and in the PL.	– HCP Kit
Diarrhoea and Constipation	Listed as an ADR in Section 4.8 of SmPC and in the PL.	N/A
Tumour lysis Syndrome	– SmPC Section 4.4 and 4.8.	– HCP Kit
Acute Myeloid Leukaemia and B-cell Malignancies	– Section 4.4 of SmPC warning. – Listed as an ADR in Section 4.8 of SmPC. – Advice to patients provided in PL. – Event specific questionnaire for the collection of the AE and follow-up.	– 'Dear HCP' letter prior to launch. o Dear HCP letter following European Commission Approval for MDS – HCP Kit.

Table 53. Summary of Table of Risk Minimisation Measures (routine and additional) in the RMP (Continued)

Safety Concern	Proposed Routine Risk Minimisation Measures	Proposed Additional Risk Minimisation Measures
Non-melanoma Skin Cancers	– Section 4.4 of SmPC warning. – SPM listed as an ADR in Section 4.8 of SmPC. – Advice to patients provided in PL. – Event specific questionnaire for the collection of the AE and follow-up.	– 'Dear HCP' letter prior to launch. o Dear HCP letter following European Commission Approval for MDS – HCP Kit.
Important Potential Risk		
Peripheral Neuropathy	– Section 4.4 of SmPC warning. – Listed as an ADR in Section 4.8 of SmPC.	– 'Dear HCP' letter prior to launch – HCP Kit
Cardiac Failure and Cardiac Arrhythmias	– Listed as an ADR in Section 4.8 of SmPC. – Listed in PL.	N/A
Renal Failure	– Listed as an ADR in Section 4.8 of SmPC.	N/A
Ischaemic Heart Disease (including myocardial infarction)	The association between ischaemic heart disease and lenalidomide is unknown. Close monitoring will continue. MI is included in Sections 4.4 and 4.8 of the SmPC.	N/A
Interstitial Lung Disease (interstitial pneumonitis)	– Listed as an ADR in Section 4.8 of SmPC.	N/A
Hepatic Disorders	The possible occurrence of hepatic disorders will be added to the SmPC (Section 4.4), including listing as an ADR in Section 4.8.	– Dear HCP letter after EC approval of variation EMEA/H/C/00717/058 received 19 Nov 2012.
Other SPM	– Section 4.4 of SmPC warning. – SPM listed as an ADR in Section 4.8 of SmPC. – Advice to patients provided in PL. – Event specific questionnaire for the collection of the AE and follow-up.	– 'Dear HCP' letter prior to launch. o Dear HCP letter following European Commission Approval for MDS – HCP Kit.
Off-label use	– Collection of off-label use data detailed in Section 4.4 of SmPC	– 'Dear HCP' letter prior to launch. o Dear HCP letter following European Commission Approval for MDS – HCP Kit.

In order to assist patients in avoiding foetal exposure to lenalidomide, the Applicant will provide educational material to health care professionals to reinforce the warnings about the expected teratogenicity of lenalidomide, to provide advice on contraception before therapy is started, and to provide guidance on the need for pregnancy testing.

The prescriber must inform the patient about the expected teratogenic risk and the strict pregnancy prevention measures as specified in the Pregnancy Prevention Programme and provide patients with appropriate patient educational brochure, patient card and/or equivalent tool in accordance to the national implemented patient card system.

A national controlled distribution (prescribing and dispensing control) of collecting detailed data relating to the indication in order to monitor closely the off-label use within the national territory and

the patient card system will be discussed at national level with each National Competent Authority. Pregnancy testing, issuing a prescription and dispensing should occur on the same day. Dispensing of lenalidomide to women of childbearing potential should occur within 7 days of the prescription and following a medically supervised negative pregnancy test result.

To gather safety data on the use of lenalidomide in MDS patients, a PASS including patients with MDS treated with lenalidomide was requested as a condition of the marketing authorisation. Patients with MDS treated with lenalidomide should be included in the PASS.

To inform healthcare professionals (prescribers and pharmacists) and some relevant patients' organisations on the risk factors associated with progression to acute myeloid leukaemia and the enrolment of patients into the non-interventional PASS, the DHCP letter will be distributed to each HCP expected to prescribe Revlimid. In countries were Revlimid is already launched, the educational material (HCP brochure and patient brochure including the PPP) should be distributed together with the DHPC.

2.7.1. PRAC advice

Not Applicable.

2.8. Update of the Product information

4.1 Therapeutic indications

[...]

Myelodysplastic syndromes

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

As a consequence of this new indication, sections 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC have been updated.

4.2 Posology and method of administration

R*evlimid treatment should be supervised by a physician experienced in the use of anti-cancer therapies (see section 4.4, karyotype)*

Myelodysplastic syndromes

Lenalidomide treatment must not be started if the Absolute Neutrophil Counts (ANC) < 0.5 x 10^9/l and/or platelet counts < 25 x 10^9/l.

Recommended dose
The recommended starting dose of lenalidomide is 10 mg orally once daily on days 1-21 of repeated 28-day cycles. Dosing is continued or modified based upon clinical and laboratory findings (see section 4.4).

Recommended dose adjustments during treatment and restart of treatment
Dose adjustments, as summarized below, are recommended to manage grade 3 or 4 neutropenia or thrombocytopenia, or other grade 3 or 4 toxicity judged to be related to lenalidomide.

- *Dose reduction steps*

Starting Dose	*10 mg once daily on days 1-21 every 28 days*
Dose Level -1	*5.0 mg once daily on days 1-28 every 28 days*
Dose Level -2	*2.5 mg once daily on days 1-28 every 28 days*
Dose Level -3	*2.5 mg every other day 1-28 every 28 days*

For patients who are dosed initially at 10 mg and who experience thrombocytopenia or neutropenia:

- *Thrombocytopenia*

When platelets	*Recommended Course*
Fall to < 25 x 10^9/l	*Interrupt lenalidomide treatment*
Return to ≥ 25 x 10^9/l - < 50 x 10^9/l on at least 2 occasions for ≥ 7 days or when the platelet count recovers to ≥ 50 x 10^9/l at any time	*Resume lenalidomide at next lower dose level (Dose Level -1, -2 or -3)*

- *Neutropenia*

When neutrophils	*Recommended Course*
Fall to < 0.5 x 10^9/l	*Interrupt lenalidomide treatment*
Return to ≥ 0.5 x 10^9/l	*Resume lenalidomide at next lower dose level (Dose Level -1, -2 or -3)*

For patients who experience other toxicities
For other grade 3 or 4 toxicities judged to be related to lenalidomide, stop treatment and restart at next lower dose level when toxicity has resolved to ≤ grade 2 depending on the physician's discretion.

Lenalidomide interruption or discontinuation should be considered for grade 2 or 3 skin rash. Lenalidomide must be discontinued for angioedema, grade 4 rash, exfoliative or bullous rash, or if Stevens-Johnson syndrome or toxic epidermal necrolysis is suspected, and should not be resumed following discontinuation from these reactions.

Discontinuation of lenalidomide

Patients without at least a minor erythroid response within 4 months of therapy initiation, demonstrated by at least a 50% reduction in transfusion requirements or, if not transfused, a 1g/dl rise in haemoglobin, should discontinue lenalidomide treatment.

Special populations

Paediatric population

The safety and efficacy of Revlimid in children aged 0-17 years have not yet been established. No data are available.

Elderly population

The effects of age on the pharmacokinetics of lenalidomide have not been studied. Lenalidomide has been used in clinical trials in multiple myeloma patients up to 86 years of age *and in myelodysplastic syndromes patients up to 95 years of age* (see section 5.1).

The percentage of *multiple myeloma* patients aged 65 or over was not significantly different between the lenalidomide/dexamethasone and placebo/dexamethasone groups. No overall difference in safety or efficacy was observed between these patients and younger patients, but greater pre-disposition of older individuals cannot be ruled out.

For myelodysplastic syndromes patients treated with lenalidomide, no overall difference in safety and efficacy was observed between patients aged over 65 and younger patients.

Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection and it would be prudent to monitor renal function.

Patients with renal impairment

Lenalidomide is substantially excreted by the kidney, therefore care should be taken in dose selection and monitoring of renal function is advised.

No dose adjustments are required for patients with mild renal impairment *and multiple myeloma or myelodysplastic syndromes.* The following dose adjustments are recommended at the start of therapy for patients with moderate or severe impaired renal function or end stage renal disease.

[...]

- *Myelodysplastic syndromes*

Renal Function (CLcr)	***Dose Adjustment***	
Moderate renal impairment *(30 ≤ CLcr < 50 ml/min)*	*Starting dose*	*5 mg once daily* *(days 1-21 of repeated 28-day cycles)*
	Dose level -1	*2.5 mg once daily* *(days 1-28 of repeated 28-day cycles)*
	Dose level -2	*2.5 mg once every other day* *(days 1-28 of repeated 28-day cycles)*
Severe renal impairment *(CLcr < 30 ml/min, not requiring dialysis)*	*Starting dose*	*2.5 mg once daily* *(days 1-21 of repeated 28-day cycles)*
	Dose level -1	*2.5 mg every other day* *(days 1-28 of repeated 28-day cycles)*
	Dose level -2	*2.5 mg twice a week* *(days 1-28 of repeated 28-day cycles)*
End Stage Renal Disease (ESRD)	*Starting dose*	*2.5 mg once daily*

(CLcr < 30 ml/min, requiring dialysis) *On dialysis days, the dose should be administered following dialysis.*		*(days 1-21 of repeated 28-day cycles)*
	Dose level -1	*2.5 mg every other day* *(days 1-28 of repeated 28-day cycles)*
	Dose level -2	*2.5 mg twice a week* *(days 1-28 of repeated 28-day cycles)*

Particularly, new warnings with regard to counselling, contraception, educational materials, cardiovascular disorders and myelodysplastic syndromes have been added to the product information. The Package Leaflet has been updated accordingly.

- Counselling

[…]

For male patients taking lenalidomide, pharmacokinetic data has demonstrated that lenalidomide is present in human semen at extremely low levels during treatment and is undetectable in human semen 3 days after stopping the substance in the healthy subject (see section 5.2). As a precaution, all male patients taking lenalidomide must meet the following conditions:

- Understand the expected teratogenic risk if engaged in sexual activity with a pregnant woman or a woman of childbearing potential
- Understand the need for the use of a condom if engaged in sexual activity with a pregnant woman or a woman of childbearing potential *not using effective contraception, during treatment and for 1 week after dose interruptions and/or cessation of treatment*.
- *Understand that if his female partner becomes pregnant whilst he is taking Revlimid or shortly after he has stopped taking Revlimid, he should inform his treating physician immediately and that it is recommended to refer the female partner to a physician specialised or experienced in teratology for evaluation and advice*.

- Contraception

[…]

Because of the increased risk of venous thromboembolism in patients with multiple myeloma taking lenalidomide and dexamethasone, *and to a lesser extent in patients with myelodysplastic syndromes taking lenalidomide monotherapy, c*ombined oral contraceptive pills are not recommended (see also section 4.5). If a patient is currently using combined oral contraception the patient should switch to one of the effective method listed above. The risk of venous thromboembolism continues for 4−6 weeks after discontinuing combined oral contraception. The efficacy of contraceptive steroids may be reduced during co-treatment with dexamethasone (see section 4.5).

[…]

Men

Lenalidomide is present in human semen at extremely low levels during treatment and is undetectable in human semen 3 days after stopping the substance in the healthy subject (see section 5.2). As a precaution, and taking into account special populations with prolonged elimination time such as renal impairment, all 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).*

[...]

Educational materials, *prescribing and dispensing restrictions*

In order to assist patients in avoiding foetal exposure to lenalidomide, the Marketing Authorisation Holder will provide educational material to health care professionals to reinforce the warnings about the expected teratogenicity of lenalidomide, to provide advice on contraception before therapy is started, and to provide guidance on the need for pregnancy testing. *The prescriber must inform the patient about the expected teratogenic risk and the strict pregnancy prevention measures as specified in the Pregnancy Prevention Programme and provide patients with appropriate patient educational brochure, patient card and/or equivalent tool in accordance to the national implemented patient card system. A national controlled distribution (prescribing and dispensing control) of collecting detailed data relating to the indication in order to monitor closely the off-label use within the national territory and the patient card system have been implemented in collaboration with each National Competent Authority. Ideally, pregnancy testing, issuing a prescription and dispensing should occur on the same day. Dispensing of lenalidomide to women of childbearing potential should occur within 7 days of the prescription and following a medically supervised negative pregnancy test result.*

Other special warnings and precautions for use

[...]

Venous and arterial thromboembolic events

In patients with multiple myeloma, the combination of lenalidomide with dexamethasone is associated with an increased risk of venous thromboembolism (predominantly deep vein thrombosis and pulmonary embolism) and arterial thromboembolism (predominantly myocardial infarction and cerebrovascular event) – see sections 4.5 and 4.8.

In patients with myelodysplatic syndromes, treatment with lenalidomide monotherapy was also associated with a risk of venous thromboembolism (predominantly deep vein thrombosis and pulmonary embolism), but to a lesser extent than in patients with multiple myeloma – see sections 4.5 and 4.8.

[...]

Neutropenia and thrombocytopenia

The major dose limiting toxicities of lenalidomide include neutropenia and thrombocytopenia. 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. A dose reduction may be required (see section 4.2). In case of neutropenia, the physician should consider the use of growth factors in patient management. Patients should be advised to promptly report febrile episodes. Co-administration of lenalidomide with other myelosuppressive agents should be undertaken with caution.

[...]

- Myelodysplastic syndromes

Lenalidomide treatment in myelodysplastic syndromes patients is associated with a higher incidence of grade 3 and 4 neutropenia and thrombocytopenia compared to patients on placebo (see section 4.8).

[...]

Progression to acute myeloid leukaemia in low- and intermediate-1-risk MDS

- *Karyotype*

Baseline variables including complex cytogenetics are associated with progression to AML in subjects who are transfusion dependent and have a Del (5q) abnormality. In a clinical trial of Revlimid in low- or intermediate-1-risk myelodysplastic syndromes, subjects who had a complex cytogenetics had the highest estimated 2-year cumulative risk of progression to AML (38.6%). The estimated 2-year rate of progression to AML in patients with an isolated Del (5q) abnormality was 13.8%, compared to 17.3% for patients with Del (5q) and one additional cytogenetic abnormality.

As a consequence, the benefit/risk ratio of Revlimid when MDS is associated with Del (5q) and complex cytogenetics is unknown.

- *TP53 status*

A TP53 mutation is present in 20 to 25% of lower-risk MDS Del 5q patients and is associated with a higher risk of progression to acute myeloid leukaemia (AML). In a post-hoc analysis of a clinical trial of Revlimid in low- or intermediate-1-risk myelodysplastic syndromes (MDS-004), the estimated 2-year rate of progression to AML was 27.5 % in patients with IHC-p53 positivity (1% cut-off level of strong nuclear staining, using immunohistochemical assessment of p53 protein as a surrogate for TP53 mutation status) and 3.6% in patients with IHC-p53 negativity (p=0.0038) (see section 4.8)

The results of the user consultation with target patient groups on the package leaflet submitted by the Applicant show that the package leaflet does not yet meet the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use. The applicant will address the following minor issues concerning the user consultation with target patient group population on the package leaflet:

The Applicant should commit to conduct an additional focused readability testing of the proposed Package Leaflet.

2.9. Direct Healthcare Professional Communication

The CHMP considered that a Direct Healthcare Professional Communication (DHPC) was needed to communicate on the risks associated with lenalidomide and the relevant post-authorisation safety study.

Healthcare professionals who may prescribe or dispense lenalidomide and relevant patients' organisations will be informed of the following:

- Revlimid (lenalidomide) has been approved for *"the treatment of patients with transfusion-dependent anaemia due to low- or intermediate-1-risk myelodysplastic syndromes associated with an isolated deletion 5q cytogenetic abnormality when other therapeutic options are insufficient or inadequate."*

- A clinical trial showed an increased risk of progression to AML in patients who are transfusion dependant and had complex cytogenetics at baseline compared with patients who had an isolated Del

(5q) abnormality. The estimated 2-year cumulative risk of progression to AML was 13.8% in patients with an isolated Del (5q) abnormality compared to 17.3% for patients with Del (5q) and one additional cytogenetic abnormality and 38.6% in patients with a complex karyotype. The benefit/risk ratio of Revlimid when MDS is associated with Del (5q) and complex cytogenetics is unknown. Treatment with Revlimid is therefore limited to patients with an isolated deletion 5q cytogenetic abnormality without additional cytogenetic abnormalities who are considered to be at lower risk for progression to AML.

- In agreement with the relevant National Competent Authorities, patients who are prescribed lenalidomide for the treatment of myelodysplastic syndromes should be entered into a non-interventional post-authorisation safety study (PASS) by the prescribing physician. Enrolment into the PASS is to be completed in parallel to the first prescription of lenalidomide in myelodysplastic syndromes.

The final version of this DHPC agreed by the CHMP is provided in Attachment 10 together with the communication plan (Attachment 11).

The MAH should agree the translations and local specificities of the DHPC with national competent authorities. The DHPC should be sent in accordance with its communication plan, no later than the week commencing 10 June 2013 with the revised SmPC with the changes highlighted to healthcare professionals.

3. Benefit-Risk Balance

Benefits

Beneficial effects

Apoptotic and pro-erythropoïetic properties of lenalidomide translate into clinical activity i.e., transfusion independence and erythroid response. In MDS 004 study, the overall RBC-transfusion independence response rate for the MITT population was 56.1% (23 of 41 patients) in the 10 mg lenalidomide group, 42.6% (20 of 47 patients) in the 5 mg lenalidomide group, and 5.9% (3 of 51 patients) in the placebo group. The response rates in both lenalidomide groups were statistically superior to that in the placebo group ($p < 0.001$). RBC-TI responses are associated with sustained increases in Hb levels.

The median duration of RBC-TI in Study MDS-004 has not been reached. In the Len 10 mg arm, the lower limit of 95% CI being 98.3 weeks, the shortest duration that could be observed is near 2 years. In the Len 5 mg arm, the lower limit of 95% CI is lower (46.3 wks). These updated estimations confirm that responses are maintained for a prolonged period.

Lenalidomide at 5 mg- and 10 mg doses was effective at producing cytogenetic responses with 54% and 30.2% of evaluable patients achieving a cytogenetic response (major or minor) in the 10 mg and 5 mg lenalidomide treatment groups, respectively. No cytogenetic responses were observed in the placebo group. The achievement of RBC-TI is not dependent upon complete elimination of the malignant clone since a proportion of patients achieved transfusion independence in the absence of a cytogenetic response.

The achievement of RBC-TI in lenalidomide treated patients was associated with an improvement in quality of life.

Even though lenalidomide is to be administered for a long period, the oral form (per os) is of particular interest since transfusion is an invasive and incapacitating treatment.

Uncertainty in the knowledge about the beneficial effects

With regards to the clinical development, the optimal dose (5 or 10 mg) and regimen (continuous or syncopated) had not been determined before the initiation of the comparative pivotal phase III study. Since MDS 004 was not designed to compare 5 mg 21/28d vs. 10 mg 28/28d, the optimal dose and regimen could still be further refined. However, the 10 mg dose appeared to produce better results than 5 mg.

The primary efficacy endpoint (transfusion independency) supports one single component of the benefit on a relatively short term. The updated results for Study MDS-004 confirm the expected impact of known prognostic factors in the OS analysis, in subjects with low-/INT1-risk MDS (age, baseline transfusion burden, and baseline ferritin concentration adversely affecting OS). The Cox proportional hazards model confirmed that achieving RBC TI with duration of ≥182 days was associated with a significant reduction in the relative risk of death. Eight additional months of follow up (from 31 March 2012 to 26 November 2012) inform on mid-term effect on OS. However, during the conduct of MDS 004 study 56 out of the 67 patients randomised to Pbo arm discontinued the double-blind phase of the study at week 16 due to lack of efficacy, were unblinded and crossed-over to the 5 mg lenalidomide arm. The crossover design of Study MDS-004 precludes a true estimation regarding long-term effects of lenalidomide treatment. From a methodological point of view, the statistical significance cannot be invoked. The extent of the clinical benefit of lenalidomide versus Pbo may be overestimated.

As evidenced by the percentages of MDS 004 patients who received prior ESA (around 40-50%), ESA administration is a well known off-label treatment of anaemia in MDS patients. The other half of patients, who did not receive prior ESA and were right away treated with lenalidomide, may have benefited from a first line of ESA. Other conventional anaemia treatment measures (transfusions, iron etc) are also available for such patients. Hence, the MDS indication in the Revlimid product information should be restricted as follows: “for the treatment of patients with transfusion-dependent anaemia due to low- or intermediate-1-risk myelodysplastic syndromes associated with an isolated deletion 5q cytogenetic abnormality *when other therapeutic options are insufficient or inadequate*.”

Risks

Unfavourable effects

The observed adverse reactions which occurred more frequently in the lenalidomide groups compared to the control arm in MDS 004 study were neutropenia, thrombocytopenia, diarrhoea, constipation, nausea, pruritus, rash, fatigue and muscle spasms.

Serious adverse reactions with lenalidomide treatment in MDS include, as expected, haematologic Grade 3 or 4 neutropenia, febrile neutropenia and grade 3 or 4 thrombocytopenia but the frequencies of these SAEs are much higher than in the current indication (RRMM).

Transformation to AML is likely to occur in the course of MDS pathology but, in MDS 004 study, the 2-years cumulative incidence rate of AML in lenalidomide arms (21.2 in 5 mg arm, 12.3 in 10 mg arm) is much higher than the expected rates (approximately 9%).

In previous applications for Revlimid, lenalidomide has been associated with the risk of occurrence of SPMs. According to the MAH, overall, 17 patients exhibited invasive SPMs in the 6 completed MDS

studies (9 in MDS 003, 4 in MDS 004), mainly solid tumours. One B cell malignancy is of particular concern.

Uncertainty in the knowledge about the unfavourable effects

The key uncertainty of this application, in the therapeutic indication as initially proposed by the applicant, is the assessment of risk for progression to AML in patients with MDS and treated with lenalidomide. The relationship between response and LFS/OS, or alternative ways to analyse registry data were not addressed. The methodology of the registry studies is still questioned.

Risk for progression to AML is not elucidated, preventing from appreciating benefit risk of lenalidomide in MDS del 5q patients, particularly when combined with other cytogenetic abnnormalities. However, in patients with isolated 5q deletion, this uncertainty is much smaller and it will be addressed through study MDS 005 and the MDS PASS.

Even if updated, the safety results of MDS 005 study related to transformation to AML are not yet informative since this study has been conducted on non del 5q patients (different from the population targeted for the submission, i.e.; del 5 q MDS), with a too short follow up and limited number of events constraining detailed analyses. However this trial is the only one comparing lenalidomide to placebo. So, if the comparability is maintained (i.e., no switch to lenalidomide), the upcoming results of MDS 005 study are likely to inform on a potential risk to transformation to AML in low-int 1 risk MDS patients.

Benefit-Risk Balance

Importance of favourable and unfavourable effects

Whereas transfusion is a palliative treatment, lenalidomide induces cytogenetic remissions leading to the repopulation of the BM with effective blood cell precursors and restoration of normal RBC haematopoiesis. In such, lenalidomide covers an unmet medical need.

Compared to the risks related to transfusion (haemochromatosis and its complications), lenalidomide exhibits a potential increased risks of progression to AML and death and occurrence of invasive malignancies.

Established measures exist for the treatment of anaemia, including transfusions and other supportive measures (iron, vitamins etc). From a clinical point of view, the indication claimed for Revlimid cannot be as “first line” treatment but should reflect other available treatment options prior to lenalidomide.

Benefit-risk balance

The benefit-risk balance of lenalidomide in the treatment of patients with transfusion-dependent anaemia due to low- or intermediate-1-risk myelodysplastic syndromes associated with an isolated deletion 5q cytogenetic abnormality when other therapeutic options are insufficient or inadequate is considered positive.

Discussion on the Benefit-Risk Balance

The activity of lenalidomide in correcting anaemia is undisputable in transfusion dependent MDS patients with del 5q but the extent of the clinical benefit is mitigated by the uncertainties regarding transformation to AML, occurrence of SPMs and OS.

The extensive cross over of patients from Pbo to lenalidomide arm drained the comparator arm of the "so called" comparative MDS 004 study and turned the study into a non-comparative trial. This prevents the evaluation of the impact of lenalidomide on long term outcomes (AML transformation, risk of occurrence of SPMs and OS).

Currently, there are no data from randomised controlled clinical trials that can definitively address the question of the effect of lenalidomide treatment on progression to AML or overall survival compared with standard of care (RBC transfusions). The safety concern of a potential increased risk of AML remains.

Considering that the benefit of lenalidomide treatment is evidenced (achieving RBC-TI, cytogenetic response, durable response), the safer option to manage safety concern would be to reserve lenalidomide treatment to patients with the lowest risk among transfusion dependent del 5q MDS patients i.e.; low or int-1 MDS associated with an isolated deletion 5q.

To reflect both risk of transformation to AML and prior therapies used, the CHMP proposed to restrict the use of Revlimid to "the treatment of patients with transfusion-dependent anaemia due to low- or intermediate-1-risk myelodysplastic syndromes associated with an isolated deletion 5q cytogenetic abnormality when other therapeutic options are insufficient or inadequate".

The CHMP considers the following measures necessary to address issues related to safety:

A post-authorisation non-interventional, safety study of patients with myelodysplastic syndromes (MDS) treated with lenalidomide to ascertain the progression to acute myeloid leukemia (AML) and survival among patients with MDS who have been treated with at least one complete cycle of lenalidomide.

The synopsis of this study has been agreed by the CHMP and the final protocol is expected within 1 month after Commission Decision granting the new indication.

4. Recommendations

☒ The application for an extension of indication is approvable since other concerns have all been resolved.

Final Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends, by consensus, the variation to the terms of the Marketing Authorisation, concerning the following change(s):

Variation(s) accepted		**Type**
C.1.6 a)	*Addition of a new therapeutic indication or modification of an approved one*	II

Extension of Indication to include patients with transfusion-dependent anaemia due to low- or intermediate-1-risk myelodysplastic syndromes associated with an isolated deletion 5q cytogenetic abnormality when other therapeutic options are insufficient or inadequate for Revlimid.

The requested variation proposed amendments to the SmPC, Annex II, Labelling and Package Leaflet.

Conditions and requirements of the marketing authorisation

Risk management system and PSUR cycle

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list)) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

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

- **Risk management plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

- **Additional risk minimisation measures**

1. The MAH shall agree the details of a controlled distribution system with the National Competent Authorities and must implement such programme nationally to ensure that:

    - Prior to launch, all doctors who intend to prescribe Revlimid and all pharmacists who may dispense Revlimid receive a Direct Healthcare Professional Communication as described below.

    - Prior to prescribing (and where appropriate, and in agreement with the National Competent Authority, prior to dispensing) all healthcare professionals who intend to prescribe (and dispense) Revlimid are provided with a physician information pack containing the following:
        - Educational Health Care Professional's kit
        - Educational brochures for Patients
        - Patient cards
        - Summary of Product Characteristics (SmPC) and Package Leaflet and Labelling.

2. The MAH shall implement a pregnancy prevention programme (PPP) in each Member State. Details of the PPP should be agreed with the National Competent Authorities in each Member State and put in place prior to the marketing of the product.

3. The MAH should agree the final text of the Direct Healthcare Professional Communication and the physician information pack contents with the National Competent Authority in each Member State and ensure that the materials contain the key elements as described below.

4. The MAH should agree on the implementation of the patient card system in each Member State.

5. The MAH should also agree with each Member State:
    - The details of the implementation of the MDS Post-Authorization Safety Study (MDS PASS).
    - The set-up of national measures to assess the effectiveness of and compliance with the PPP.

Key elements to be included

Direct Healthcare Professional Communications

The Direct Healthcare Professional Communication shall consist of two parts:

- A core text as agreed by the CHMP.
- National specific requirements agreed with the National Competent Authority regarding:
    - Distribution of the product
    - Assurance 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
- 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
    - Description and management of neutropenia and thrombocytopenia including incidence rates from clinical trials
    - Description and management of thromboembolic risk including incidence rates from clinical trials and post-marketing experience
    - Use in patients with hepatic and/or renal impairment
    - Disposal of unwanted medicine
    - Local country specific arrangements for a prescription for Revlimid to be dispensed
    - Description of risk of hypothyroidism
    - Explanation of unknown risk of neuropathy with long term use
    - Description of the risk of progression to AML in MDS patients including incidence rates from clinical trials
- 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 one week 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
    - 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 enroll 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 and their partners
- 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
- That Revlimid may cause neutropenia and thrombocytopenia and the need for regular blood tests
- That Revlimid may cause venous and arterial thromboembolism
- Description of the patient card and its necessity
- Disposal of unwanted medicine
- 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
- 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 drug 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

Brochure for male patients

- 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 vasectomy)
    - During Revlimid treatment
    - For one week following final dose
- That if his partner becomes pregnant he should inform his treating doctor immediately

Patient Card

The patient card shall contain the following elements:

- Verification that appropriate counselling has taken place
- Documentation of childbearing status potential
- Pregnancy test dates and results

- **Obligation to conduct post-authorisation measures**

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

Description	Due date
A post-authorisation non-interventional, safety study of patients with myelodysplastic syndromes (MDS) treated with lenalidomide to gather safety data on the use of lenalidomide in MDS patients and monitor off-label use.	Annual safety updates with PSURs

Additional data exclusivity / market protection

Furthermore, the CHMP reviewed the data submitted by the MAH, taking into account the provisions of Article 14(11) of Regulation (EC) No 726/2004 and considers, by consensus, that the new therapeutic indication brings significant clinical benefit in comparison with existing therapies (see Appendix 2).