



European Medicines Agency

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WITHDRAWAL ASSESSMENT REPORT

FOR

Lenalidomide Celgene Europe

International Nonproprietary Name: **lenalidomide**

Procedure nr EMEA/H/C/688

CHMP Assessment Report as adopted by the CHMP with
all information of a commercially confidential nature deleted.

This should be read in conjunction with the “Question and Answer” document on the withdrawal of the
application.

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1. BACKGROUND INFORMATION ON THE PROCEDURE

1.1 Submission of the dossier

The applicant, Celgene Europe Limited, submitted on 23 August 2005 an application for Marketing Authorisation to the European Medicines Agency (EMA) through the centralised procedure for Lenalidomide - Celgene Europe (lenalidomide). Lenalidomide was designated as an orphan medicinal product, EU/3/04/192, on 08 March 2004, for the following indication: Treatment of myelodysplastic syndromes. The calculated prevalence of this condition was 1 to 3 per 10,000 EU population.

The applicant applied for the following indication: 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 additional cytogenetic abnormalities.

The legal basis for this application refers to Article 8.3 of Directive 2001/83/EC, as amended - complete and independent application.

Protocol Assistance

The applicant received Protocol Assistance from the CHMP on 19 November 2004. The Protocol Assistance pertained to non-clinical and clinical aspects of the dossier.

Licensing status

Lenalidomide known as Revlimid as trade name has been given first a Marketing Authorisation for the myelodysplastic syndromes indication on 27 December 2005 in the United States of America (USA), on 17 January 2008 in Canada and 15 February 2008 in Argentina and, then, for the multiple myeloma indication on 29 June 2006 in the USA, on 14 June 2007 in the European Union (EU), on 11 July 2007 in Iceland, 13 July 2007 in Norway, on 29 August 2007 in Switzerland, on 17 September 2007 in Liechtenstein, 13 December 2007 in Australia and 15 February 2008 in Argentina.

Applications for the myelodysplastic syndromes indication were also filed in the following countries: Switzerland, Israel and Liechtenstein.

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

Rapporteur: Eric Abadie/Pierre Démolis Co-Rapporteur: Tomas Salmonson

1.2 Steps taken for the assessment of the product

- The application was received by the EMA on 23 August 2005.
- The procedure started on 28 September 2005.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 08 December 2005 The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 08 December 2005.
- During the meeting on 23-26 January 2006, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 26 January 2006.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 19 May 2006.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 30 June 2006.
- The CHMP convened an *ad hoc* expert group meeting to give input on pharmacovigilance measures and Risk Management Plan was held on 06 July 2006.
- The CHMP convened a meeting of patients and victims organisations to comment on the Risk Management Plan, the package leaflet and the labelling on 06 July 2006.
- During the CHMP meeting on 24-27 July 2006 the CHMP agreed on a 1st List of Outstanding Issues to be addressed by the applicant.

- The CHMP convened an *ad hoc* expert group meeting on revised pharmacovigilance measures and Risk Management Plan on 12 December 2006.
- The applicant submitted responses to the CHMP's 1st List of Outstanding Issues on 03 January 2007.
- The CHMP convened a 2nd meeting of patients and victims organisations to comment on the revised Risk Management Plan, the package leaflet and the labelling on 29 January 2007.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 08 February 2007.
- During the CHMP meeting on 19-22 February 2007 the CHMP adopted a 2nd List of Outstanding Issues to be addressed by the applicant.
- The applicant submitted responses to the CHMP's 2nd List of Outstanding Issues on 06 April 2007.
- The Rapporteurs circulated an updated Joint Assessment Report on the applicant's responses to the 2nd List of Outstanding Issues on 07 May 2007.
- A meeting of the Scientific Advisory Group for Oncology was held on 11 May 2007 to address questions raised by the CHMP.
- During the CHMP meeting on 21-24 May the CHMP adopted a 3rd List of Outstanding Issues to be addressed by the applicant.
- The applicant submitted responses to the CHMP's 3rd List of Outstanding Issues on 14 September 2007.
- The Rapporteurs circulated an updated Joint Assessment Report on the applicant's responses to the 3rd List of Outstanding Issues to all CHMP members on 29 September 2007.
- The applicant submitted the updated responses to the CHMP's 3rd List of Outstanding Issues on 22 October 2007.
- The Rapporteurs circulated an updated Joint Assessment Report on the updated applicant's responses to the 3rd List of Outstanding Issues to all CHMP members on 6 November 2007.
- During the CHMP meeting on 12-15 November 2007, the outstanding issues were addressed by the applicant during an oral explanation.
- Following the oral explanation, the CHMP adopted a 4th list of outstanding issues on 15 November 2007.
- The applicant submitted responses to the CHMP's 4th List of Outstanding Issues on 26 November 2007.
- The Rapporteurs circulated an updated Joint Assessment Report on the applicant's responses to the 4th List of Outstanding Issues on 3 December 2007.
- During the CHMP meeting on 10-13 December 2007, the CHMP adopted a 5th List of Outstanding Issues on 13 December 2007.
- The applicant submitted responses to the CHMP's 5th List of Outstanding Issues on 21 December 2007.
- The Rapporteurs circulated a Joint Assessment Report on the applicant's responses to the CHMP's 5th list of outstanding issues on 18 January 2008.
- During the CHMP meeting on 21-24 January 2008, the outstanding issues were addressed by the applicant during an oral explanation on 22 January 2008.
- During the meeting on 21-24 January 2008, in the light of the overall data submitted and the scientific discussion within the Committee, the CHMP was of the opinion that the application did not satisfy the criteria for authorisation and recommended the refusal of the marketing authorisation to Lenalidomide - Celgene Europe on 24 January 2008.

1.3 Steps taken for the re-examination procedure

- The applicant submitted written notice to the EMEA on 29 January 2008 to request a re-examination of the Lenalidomide - Celgene Europe CHMP opinion of 24 January 2008.
- During its meeting on 18-21 February 2008, the CHMP appointed the Rapporteur and Co-Rapporteur were:

Rapporteur: Barbara van Zwieten-Boot Co-Rapporteur: Harald Enzmann

- The detailed grounds for the re-examination request were submitted by the applicant on 31 March 2008
- The re-examination procedure started on 1 April 2008.
- During its meeting on 21-24 April 2008, the CHMP adopted the List of Questions and List of Participants to the Scientific Advisory Group for Oncology to be held on 15 May 2008.
- The Rapporteur's Assessment Report was circulated on 09 May 2008. The Co-Rapporteur's Assessment Report was circulated on 13 May 2008.
- During a meeting of the CHMP Scientific Advisory Group on Oncology on 15 May 2008, experts were convened to consider the grounds for re-examination and a list of questions from the CHMP.
- During the meeting on 27-30 May 2008, in the light of the scientific data available and the scientific discussion within the Committee, the CHMP re-examined its initial opinion and in its final opinion concluded that the application did not satisfy the criteria for authorisation and recommended the refusal of the Marketing Authorisation for Lenalidomide - Celgene Europe on 30 May 2008.

1.4 Steps taken following the final CHMP opinion

- The EMEA notified the applicant about the final CHMP opinion recommending the refusal of the marketing authorisation for Lenalidomide - Celgene Europe on 30 May 2008.
- On 30 May 2008, the applicant notified the EMEA of the applicant's decision to withdraw the application for marketing authorisation for Lenalidomide - Celgene Europe.

2 SCIENTIFIC DISCUSSION

2.1 Introduction

Myelodysplastic syndromes (MDS) are a heterogeneous group of progressive and life-threatening conditions characterised in most patients by peripheral blood cytopenia with hypercellular bone marrow and dysplasia of the cellular elements. *De novo* or idiopathic MDS accounts for 80% of new cases. Secondary MDS is associated with exposure to toxins such as benzene, chemotherapy drugs, or high doses of radiation. Idiopathic myelodysplastic syndromes occur mainly in older persons, with a median age at diagnosis of 65 to 75 years. The incidence rate in the European Community is between 1 and 3 per 10,000 persons per year in the general population, with an increase to 2 to 5 per 10,000 persons per year after 60 years of age.

Innate haematopoietic stem cell lesions, cellular/cytokine-mediated stromal defects, and immunologic derangements underlie the pathophysiology of MDS. Haematopoietic precursors in patients with myelodysplastic syndromes have an accelerated cell-cycle transition and impaired responsiveness to cytokine stimulation.

Several proposed classification systems (such French-American-British (FAB) and WHO classification based on bone marrow (BM) morphological classification and other including clinical variables) remain imprecise regarding clinical outcomes. The International Prognostic Scoring System (IPSS) -based on the percentage of marrow blasts, the cytogenetic pattern and the number and degree of cytopenias- is useful for predicting survival and the risk of leukaemia and facilitates clinical decision making in individual cases (Table 1).

Table 1 Survival and AML evolution of MDS patients within the IPSS subgroups

	Low	INT-1	INT-2	High
Median survival (yr)	5.7	3.5	1.2	0.4
Median time to AML evolution	9.4	3.3	1.1	0.2

IPSS International Prognostic Scoring System

Clonal chromosomal abnormalities are detected by routine karyotyping techniques in 40%–70% of cases of *de novo* MDS and 95% of cases of therapy-related MDS. No cytogenetic abnormality is specific for MDS or for a specific morphologic subgroup of MDS. The most common abnormality is the loss of whole or partial chromosomes by deletion or unbalanced translocations. These include loss of chromosome 5 or 7 and deletions of the long arm of 5 or 7 and deletions of 13 and 20; trisomy 8 is also common, whereas balanced or unbalanced translocations are rarely found in MDS. The incidence of chromosomal abnormalities is higher in refractory anaemia with excess blasts (RAEB), chronic myelomonocytic leukaemia (CMML) and refractory anaemia with excess blasts in transformation (RAEB-T) than in refractory anaemia (RA) or refractory anaemia with ringed sideroblasts (RARS). Chromosome abnormalities in MDS are of independent prognostic significance. An international workshop based on data from more than 900 patients found normal karyotype, isolated del 5q, del 20q and loss of Y chromosome to be factors associated with relatively favourable prognoses. Trisomy 8 marks an intermediate prognosis. Monosomy 7 or deletions of 7q portend a poor prognosis.

The natural history of these syndromes ranges from a chronic course that may span years to a rapid course of leukaemic progression. Although patients with myelodysplastic conditions may seek medical care because of symptoms of haematopoietic failure such as infection, bleeding, bruising, progressive fatigue or dyspnoea on exertion, many patients present without symptoms but with anaemia, thrombocytopenia, leucopenia or a combination of these findings on routine laboratory evaluation. The haematopoietic insufficiency and cytopenias of MDS lead to potentially serious morbidity (transfusion-dependent anaemia, bleeding manifestations) and mortality (death from infection in the setting of neutropenia), plus the additional risk of leukaemic transformation. The majority of patients with MDS develop a requirement for transfusions of red blood cells (RBC) and repeated transfusions may cause secondary haemochromatosis, resulting in congestive heart failure, diabetes mellitus, and hepatocellular carcinoma. Other cytopenias may also contribute to morbidity, such as neutropenia (~50-60%) and dysfunctional neutrophils leading to an increased incidence of infections.

Thrombocytopenia (~40-60%) and thrombocytopathy, with associated bleeding ensue in more advanced forms of MDS. In addition to having symptoms related to their cytopenias and a need for multiple transfusions, certain MDS patients have the risk of rapid evolution into acute leukaemia.

The treatment of myelodysplasia needs to be individualised, since the course of disease and response to treatment are strongly influenced by age, coexisting conditions, and the degree of haematopoietic failure. Options for treatment of MDS range from supportive care (which includes blood product transfusions and the use of growth factors) to intensive therapy with allogeneic haematopoietic stem cell transplantation.

Therapy aimed at improving cytopenias is recommended for patients with indolent disease (IPSS low and intermediate-1). Once anaemia is symptomatic, red-cell transfusions and iron chelation are the mainstays of therapy. Some investigators have reported success for transfusion dependent patients with the use of colony-stimulating factors and with thalidomide.

The goal of treatment for rapidly progressive MDS is to change the natural history of the disease (generally using high-intensity treatment, including chemotherapy and haematopoietic stem cell transplantation). At present, the only treatment that can definitely prolong survival is allogeneic haematopoietic stem-cell transplantation. Approximately one third of patients who receive an allogeneic transplant are cured, but only about 8% of all patients with a myelodysplastic syndrome are eligible for such treatment and have a donor. Moreover, the data suggest that co-administration of erythropoietin and granulocyte colony-stimulating factor (G-CSF) result in a synergistic response.

Thalidomide, a multifunctional inhibitor of angiogenesis and an immune modulator, has been reported to restore erythropoiesis and reduces transfusion dependence in approximately 18% of patients who have no response to recombinant erythropoietin.

Lenalidomide is an IMiD that counters the pro-apoptotic factors in MDS through cytokine inhibition, immune modulator effects and antiangiogenic mechanisms of action.

In summary, refractory anaemia resulting from ineffective haematopoiesis is the principal therapeutic challenge for patients with low and intermediate-1 risk MDS. Recombinant erythropoietin alone or in combination with myeloid growth factors ameliorates anaemia in some patients but is generally ineffective in patients who require two or more red-cell transfusions per month; its use rarely induces cytogenetic remissions. Thalidomide has been shown to restore erythropoiesis and to reduce transfusion dependence in approximately 18% of patients with MDS who have no response to recombinant erythropoietin. Lenalidomide shares with thalidomide the biologic effects thought to interfere with the mechanisms that contribute to the cytopenias associated with MDS. Accordingly, it is hypothesised that lenalidomide is an effective treatment for MDS with more favourable safety profile to that of thalidomide.

Celgene Europe Ltd. has applied for a marketing authorisation through the centralised procedure for the medicinal product Lenalidomide Celgene Europe 5 and 10 mg hard capsules, containing respectively 5 and 10 mg of the new chemical entity lenalidomide. Lenalidomide is an immunomodulating agent.

2.2 Quality aspects

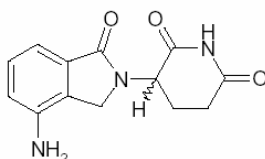
Introduction

Lenalidomide has been developed as hard capsules in 2 dosage strengths of 5 and 10 mg. Lenalidomide capsules are supplied in PVC/ACLAR (PCTFE) blisters with push through aluminium foil.

Drug Substance

- Manufacture

Lenalidomide (3-(4' aminoisoindoline-1'-one)-1-piperidine-2, 6-dione) is a new chemical entity.



It is a synthetic derivative of glutamic acid and is structurally close to thalidomide (identical backbone but differs from thalidomide by removing an oxygen from the phthalyl ring and by adding an amine group). Although it is chiral and possesses an asymmetric carbon, it has been developed as a racemic mixture since it undergoes racemisation under physiological conditions. It is obtained as an hemihydrate form and is non-hygroscopic.

Lenalidomide exhibits the phenomenon of polymorphism (8 polymorphs identified) but the commercial process leads only to the desired polymorph B (hemihydrate form).

Lenalidomide synthetic process consists of 4 steps starting from alpha-aminoglutarimide hydrochloride and methyl 2-bromomethyl-3-nitrobenzoate. The process can be summarised as follow: coupling step, reduction step (crude lenalidomide), recrystallisation (pre-micronised lenalidomide) and micronisation.

The route of synthesis has been sufficiently described including the comprehensive description of the micronisation step.

Appropriate specifications have been provided for the intermediates, starting materials (alpha-aminoglutarimide hydrochloride and methyl 2-bromomethyl-3-nitrobenzoate), reagents, solvents and auxiliary materials.

Adequate in-process controls for critical steps and intermediates have been applied during the synthesis of lenalidomide. In addition, validation of the process has been performed for the lenalidomide synthesis. Analytical methods have been sufficiently described and validated.

The structure of lenalidomide has been fully elucidated using usual methods such as elemental analysis, IR (infra-red), UV (ultra-violet), mass spectrometry, ¹H-NMR (nuclear magnetic resonance), ¹³C-NMR spectroscopy, X-ray, optical rotation, DSC (differential scanning calorimetry), TGA (thermal gravimetric analysis), and particle size analysis. Analyses were especially focused on the polymorphism of the molecule as well as the particle size.

Potential impurities, degradation products, residual solvents and metal catalysts which may be found in lenalidomide have been extensively discussed. Impurities remain below the ICH qualification limits (guideline ICH Q3A).

Batch analysis data of 20 lots of lenalidomide are within the specification. The level of impurities and residual solvents remain very low and do not exceed ICH qualification thresholds.

- Specification

Since lenalidomide is not described in any pharmacopoeia, an in-house monograph has been presented. Specifications for lenalidomide (hemihydrate) include parameters such as appearance, identification (IR and X-ray diffraction), assay (HPLC), related impurities (HPLC), residual solvents (GC), water content (Karl-Fischer), heavy metals, sulphated ash and particle size (laser diffraction).

Specification is appropriately described and justified especially for water content, residual solvents and particle size limits. Limits retained are in line with the ICH guidelines.

Analytical methods have satisfactorily described and validated.

Lenalidomide is packaged in double low-density polyethylene (LDPE) bags, placed in high-density polyethylene (HDPE) drums. The packaging materials comply with relevant EC directives and Ph. Eur. monographs.

- **Stability**

Stability studies have been conducted on 3 pilot batches of lenalidomide stored in the commercial packaging under ICH conditions (up to 24 months at 25°C/60% RH and 6 months at 40°C/75% RH). Tested parameters tested included: visual appearance, assay, related impurities, X-ray powder diffraction and water content.

All results remain well within the retained specification under long-term and accelerated conditions. Moreover, photostability stability testing indicated that lenalidomide is not light sensitive.

Based on the available data, a retest period of 2 years can be granted providing that the active substance is kept in the commercial packaging and not above 25°C. The applicant has committed to continue the studies until 36 months and to place under stability the first 3 production batches for 60 months.

Drug Product

- **Pharmaceutical development**

Active Substance: The pharmaceutical development has taken into consideration the main 2 critical aspects of the active substance: particle size and polymorphic form.

Formulation Development: A hard capsule dosage form was chosen due to its favourable performance in manufacturing studies and analytical testing. Lenalidomide capsules, 5 and 10 mg, are dose proportional and use a common blend. Formulation development is sufficiently detailed. Micronisation has been performed to ensure blend and content uniformity of the active substance present at a low level in the drug product formulation.

Overages: No overage is included in the formulation for Lenalidomide capsules 5 and 10 mg.

Physicochemical and Biological Properties: The impact of physicochemical properties (particle size and polymorphic form) of lenalidomide that could theoretically affect the performance of the product has been studied. It can be concluded that neither the particle size (when included in the distribution range of micronised particles), neither does the polymorphic form affect the dissolution of the capsules.

Manufacturing Process Development: The manufacturing process is a simple blending and filling process. The manufacturing development has been adequately described.

Container Closure System: Lenalidomide capsules, 5 and 10 mg are packaged in blisters (PVC/ACLAR) with push-through foil. Suitability of the material is demonstrated by the stability data.

Excipients: The excipients selected for the lenalidomide capsules formulation are those typically used in capsule formulations. They are all described in Ph. Eur. and comply with the corresponding monographs, and include anhydrous lactose (as diluent), microcrystalline cellulose (as diluent), croscarmellose sodium (as disintegrant) and magnesium stearate (as lubricant).

Regarding the capsule shells, adequate manufacturer's specification includes testing for appearance, colour, loss on drying, disintegration time, identity of gelatin, microbiological tests as per Ph Eur. and physical dimensions. The components of the printing inks are in compliance with Ph Eur. or USP/NF. In addition, the hard capsule colorants comply with the relevant EC Directives on colorants in foodstuffs.

Microbiological testing is performed on all excipients including the capsule shells.

Compatibility between the active substance and the excipients has been suitably demonstrated.

- **Adventitious agents**

Among the excipients used in the formulation, only lactose (ingredient of the formulation) and gelatin (component of the capsule shell) are from animal origin. However, lactose is sourced from healthy

animals under the same conditions as milk collected for human consumption (EMA 410/01 rev 1) and TSE declaration is provided in 3.2.R. TSE certificates from the gelatin suppliers are provided.

- **Manufacture of the product**

The manufacturing process is simple and consists of dry blending of the ingredients and filling the capsules. The process is considered standard as per the guideline CHMP/QWP/848/99. It has been adequately described including the equipment and the operating parameters. Appropriate in-process controls of the critical steps and intermediates have been set, such as control of the fill weight of the capsules.

Validation of the manufacturing process has been carried out satisfactorily at both manufacturing sites. However minor points remain to be resolved.

- **Product specification**

The proposed specifications at release and at the end of shelf life for Lenalidomide 5 and 10 mg capsules include appearance, identification (HPLC and UV), assay of the active substance (HPLC), related substances (HPLC), dissolution (HPLC), uniformity of dosage units (Ph Eur. 2.9.40) and microbial contamination (Ph Eur. 5.1.4 category 3A). Specification has been correctly justified.

Non-compendial analytical methods have been described and validated in accordance with ICH requirements.

Batch analyses data confirm the consistency of the manufacturing process. All the results comply with the retained specifications. Impurities levels are quite low and their limits have been justified by batch data.

Container closure system: Lenalidomide capsules, 5 and 10 mg, are packaged in blisters (PVC/ACLAR) with push-through foil. The packaging material has been adequately characterised and complies with Ph Eur. 3.1.11.

- **Stability of the product**

Stability studies have been conducted on 4 batches (pilot and commercial-scale) of each strength (5 and 10 mg) kept in the commercial packaging under ICH conditions (up to 24 months at 25°C/60% and 6 months at 40°C/75% RH). Tested parameters include appearance, assay, related impurities and dissolution.

All the results remain within the specification. Even under accelerated conditions the product is stable and no significant trend is observed except for a few out of specification results at 40°C/75%. A photostability study has showed that the finished product is not light sensitive.

The applicant has committed to continue the stability studies until 36 months and to place under stability the first three commercial batches of Lenalidomide in both strengths manufactured at both manufacturing sites.

Discussion on chemical, pharmaceutical and biological aspects

Generally, satisfactory documentation has been provided. The active substance is well characterised and the retained specification including the impurities levels. Lenalidomide is stable and stability data support the proposed re-test period providing that the active substance is kept in the commercial packaging and not above 25°C. Therefore, a shelf life of 2 years when stored below 25°C for all strengths and from both sites can be granted.

Regarding the finished product, the manufacturing process is a standard process. It is adequately described and controlled. It should ensure a consistent quality for the product. Appropriate specification has been selected for these hard-capsules. Stability studies under ICH conditions have demonstrated the good stability of the finished product. Stability data support the proposed shelf life and storage conditions.

2.3 Non-clinical aspects

Introduction

Pivotal toxicity studies have been performed in rats, monkey and rabbits (embryo-foetal toxicity). Studies on pharmacokinetics, toxicokinetics and toxicology were performed in compliance with Good Laboratory Practice (GLP).

Pharmacology

The pharmacological properties of lenalidomide were characterised in non-GLP *in vitro* and *in vivo* studies focussing on effects on erythropoiesis, haematopoietic tumours, angiogenesis, T-cell proliferation, cytokine stimulation and NK activity.

- Primary pharmacodynamics

Based on *in vitro* and *in vivo* tests, lenalidomide has been shown to:

- inhibit secretion of pro-inflammatory cytokines TNF- α , IL-1 β , IL-6 and IL-12 and increases the secretion of anti-inflammatory cytokine IL-10 by monocytes
- induce T-cell proliferation and IL-2 and IFN- γ production, and enhances NK cell activation
- inhibit the proliferation of various haematopoietic tumour cell lines, particularly the multiple myeloma
- enhance foetal haemoglobin expression upon CD34+ erythroid stem cell differentiation
- inhibit processes of angiogenesis including endothelial cell migration and tube formation
- inhibit the growth of haematopoietic tumour cells and, by inhibiting angiogenesis, reduce the growth of solid tumours *in vivo*.

The molecular target of lenalidomide is not known.

- Secondary pharmacodynamics and safety pharmacology

The complete core battery of safety pharmacology tests, following ICH guidance, was performed, to determine neuro-behavioural, cardiovascular and respiratory effects.

The effects of lenalidomide on general activity and behaviour were evaluated *in vivo*, in the rat model system. No behavioural or physiological changes were noted in lenalidomide-treated rats, when compared to control animals.

The IC₅₀ value for the inhibitory effect of lenalidomide on hERG (HEK-293 cell line) was estimated to be greater than 786.7 μ M (204 μ g/ml), a concentration that is 390 times the expected maximum plasma concentration in human (0.521 μ g/ml for an administered dose of 25 mg, clinical **Study CDC-501-001**). Lenalidomide produced no biologically important cardiovascular changes in anaesthetised beagle dogs following intravenous administration of lenalidomide up to 20 mg/kg. In addition, there were no treatment-related changes in electrocardiographic parameters after administration of lenalidomide to monkeys for 52 weeks at doses up to 6 mg/kg/day. Based on a NOAEL for cardiovascular effects of 20 mg/kg (400 mg/m²) in dogs, the margin of safety for the proposed clinical dose of 10 mg (or 6,2 mg/m²) is approximately 65-fold on a body surface area basis.

In the dog study above-mentioned, in addition to the cardiovascular parameters, respiratory components were measured. No biologically important changes were observed in any parameters measured.

Additionally, secondary pharmacodynamics performed in an experimental rabbit model of tuberculosis meningitis showed that lenalidomide when administered in conjunction with other anti-tuberculosis drugs, may halt the progression of tuberculous meningitis in rabbits.

- Pharmacodynamic drug interactions

Several *in vitro* pharmacodynamic drug interactions were performed, regarding the total effect on foetal haemoglobin, inhibition of rolipam-induced PDE4A4 foci, inhibition of cell proliferation, potentiation of NK activity and anti-tumour activity. Tested drugs were hydroxyurea, vincristine, rapamycin, paclitaxel, carboplatin, gemcitabine, cisplatin, and rituximab. Synergistic effects were observed with rapamycin in inhibition of cell growth and survival, with hydroxyurea in effects on foetal haemoglobin. One *in vivo* study was also performed in severe combined immunodeficiency mice where concurrent administration of lenalidomide and rituximab was more effective in controlling lymphoma growth and prolonging survival than rituximab therapy alone.

Pharmacokinetics

The pharmacokinetics of lenalidomide has been investigated in *in vitro* and *in vivo* studies. The significant findings of these studies are briefly presented below:

- The S and R enantiomers of lenalidomide are stable to racemisation during storage at -70°C in buffered (acidic or neutral pH) plasma from rat, monkey and man. The enantiomers undergo significant non-enzymatic racemisation in plasma at 37°C at neutral or alkaline pH
- Absolute oral bioavailability of lenalidomide is 68 %, 88 % and 50 % in rat, dog and monkey respectively
- The volume of distribution observed in all species tested indicated an extensive distribution into tissues
- The plasma protein binding is low in all species including humans (19% to 29%)
- The highest concentration of radioactivity following oral administration of [¹⁴C]-lenalidomide to rat was in the kidney. Distribution to the brain was extremely low. Distribution to the foetus was limited after oral administration to pregnant rats
- Lenalidomide is metabolically stable *in vitro*, metabolism related to hydrolysis is seen *in vivo*
- Lenalidomide does not inhibit any of the major cytochrome P450 (CYP) isozymes *in vitro*
- The elimination half-life in rats and monkeys was approximately 2 hours and 13 hours, respectively, after a single oral administration
- Lenalidomide excretion occurs mainly via the urine. The major component in the urine in humans, rats and monkeys is the parent compound.

Toxicology

- Single dose toxicity

Acute dose (40 and 2000 mg/kg) toxicology studies in mice and rats via intravenous and oral administration respectively, were conducted. No mortality was observed at either dose.

- Repeat dose toxicity (with toxicokinetics)

The potential toxicity of lenalidomide was assessed after repeated administration to rats (up to 26 weeks duration) and monkeys (up to 52 weeks duration).

Repeated oral administration of 75, 150 and 300 mg/kg/day to rats for up to 26 weeks produced a reversible treatment-related increase in kidney pelvis mineralisation in all 3 doses, most notably in females. The no observed adverse effect level (NOAEL) was considered to be less than 75 mg/kg/day, and is approximately 62-fold greater than the human daily exposure based on AUC exposure.

Repeated oral administration of 4 and 6 mg/kg/day to monkeys for up to 20 weeks produced mortality and significant toxicity (marked weight loss, reduced red and white blood cell and platelet counts, multiple organ haemorrhage, gastrointestinal tract inflammation, lymphoid organs and bone marrow atrophy). Repeated oral administration of 1 and 2 mg/kg/day to monkeys for up to 1 year produced reversible changes in bone marrow cellularity, a slight decrease in myeloid:erythroid cell ratio and thymic atrophy. The NOAEL is less than 1 mg/kg corresponding to a safety margin of 2.4. Mild suppression of white blood cell count was observed at 1 mg/kg/day corresponding to approximately the same human dose based on AUC comparison.

- Genotoxicity

An extensive battery of genotoxic studies was conducted, including the ICH guidelines for testing of genotoxic potential (a bacterial mutation test, a mouse lymphoma assay, a cultured human peripheral blood lymphocyte test, a Syrian hamster embryo transformation assay, and an *in vivo* rat micronucleus tests). There were no indications of genotoxicity in any of these assays. However, genotoxicity assays were performed without knowing the level of two impurities, namely RC3 and RC4.

- Carcinogenicity

Carcinogenicity testing was not performed because lenalidomide, although not classified as cytotoxic, is being developed for oncology in an orphan indication. Chronic rat and monkey studies revealed no potential for tumourigenicity and comprehensive genotoxicity studies indicated no mutagenic potential.

- Reproduction toxicity

A complete battery of ICH recommended reproductive/developmental toxicology studies was conducted, including studies to assess the potential adverse effects on male and female fertility and reproduction, embryo-foetal development (embryo-foetal toxicity/teratogenicity) and maternal reproductive performance and peri- and post-natal development of the offspring.

Doses of lenalidomide as high as 500 mg/kg/day did not selectively affect male or female rat reproductive performance or embryonic viability during early embryogenesis.

In the developmental toxicity study in the rats, the maternal and developmental NOAEL were 300 mg/kg/day, with threshold maternal and developmental toxicity at 500 mg/kg/day. Foetal viability was unaffected and there were no embryo-foetal alterations attributable to lenalidomide.

In rabbits, administered 3, 10 and 20 mg/kg/day orally corresponding to up to 6 times the human exposure, no limb abnormalities were attributable to lenalidomide. Developmental toxicity at the 10 and 20 mg/kg/day dose levels was characterised by slightly reduced foetal body weights, increased incidences of post implantation loss (early and late resorptions and intrauterine deaths), and gross external findings in the foetuses associated with morbidity and pharmacotoxic effects of lenalidomide (purple discoloration of the skin on the entire body). An absence of the intermediate lobe of the lung was observed at 10 and 20 mg/kg/day with dose dependence and displaced kidneys were observed at 20 mg/kg/day. Although it was observed at maternotoxic levels they may be attributable to a direct effect. The human relevance of these effects is not known. Soft tissue and skeletal variations in the foetuses were also observed at 10 and 20 mg/kg/day. These included minor variations in skull ossification (irregular nasal-frontal suture) and small delays in ossification of the metacarpals, associated with the reduced foetal body weights. In rabbits, the maternal and developmental NOAEL for lenalidomide were 3 mg/kg/day corresponding to a safety margin of 3.1 considering a 10 mg/day therapeutic dose.

In some of the rabbit studies, thalidomide was included as a positive control for teratogenicity. Thalidomide showed the expected teratogenicity and the NOAEL for developmental toxicity was estimated to be 20 mg/kg in a rabbit strain. While the observed foetal alterations in most cases affected the limbs, it should be stressed that they are distinct from the known foetal alterations occurring in humans.

The CHMP requested additional investigations to better characterise the potential embryotoxic and teratogenic effects of lenalidomide. Studies with thalidomide in monkeys have shown a relative predictive value in teratogenicity to what has been documented in humans, both in terms of doses and types of malformation. The toxicological studies with lenalidomide in cynomolgus monkeys have shown similar toxicity (at similar exposure levels) to what has been documented in patients. Therefore, cynomolgus monkeys appear to be highly relevant for the evaluation of both pharmacology and toxicology of lenalidomide. The applicant has committed to perform a study on embryo-foetal toxicity as a post-approval commitment in a sensitive species.

In the pre- and post-natal developmental toxicity study of lenalidomide in the rat, there were no adverse effects on the viability, growth or behaviour of the offspring. The NOAEL for development of the offspring was 500 mg/kg/day.

- Local tolerance

No local tolerance studies have been performed with lenalidomide.

- Other toxicity studies

No specific immunotoxicological programme has been performed with lenalidomide.

Ecotoxicity/environmental risk assessment

The Environmental Risk Assessment (ERA) for lenalidomide has been provided in compliance with the requirements of Directive 2001/83/EC as amended.

The predicted surface water concentration for lenalidomide indicates that its use in the proposed indication should pose a negligible risk to the environment. Should any lenalidomide reach the environment through disposal of unused product, the environmental risk is likely to be minimal owing to the drug's low inherent toxicity and absence of bioaccumulation potential. As with all unused medications, appropriate disposal procedures should be employed.

Discussion on non-clinical aspects

Pharmacology

Lenalidomide has shown activity in a number of model systems. The pharmacology studies suggest that the therapeutic activities of lenalidomide fall into the following categories: anti-inflammatory, immunomodulatory, anti-proliferative, anti-angiogenic and pro-erythropoietic. These partly paradoxical findings make impossible to predict the effect of lenalidomide in more complex *in vivo* models and in human disease. The molecular target of lenalidomide remains unknown for any cell type. *In vivo*, lenalidomide was shown to delay tumour growth and prolong survival in a mouse xenograft model with human lymphoma cells. Lenalidomide showed effect on solid tumour cell growth in two mouse models. Inhibition of angiogenesis was demonstrated in an *in vivo* model in the rat. The lack of molecular understanding has several consequences for the assessment of the clinical usefulness. It limits the possibility to predict unwanted pharmacological events, and it makes difficult to evaluate the relevance of different animal species for the safety assessment.

Lenalidomide has been developed based on the structure and pharmacology of thalidomide. *In vitro* data suggest that lenalidomide is much more potent. Lenalidomide was 10-1000 times more potent than thalidomide in various *in vitro* pharmacology studies of immunomodulatory, anti-proliferative, and pro-erythropoietic activities. However, the data give no evidence for a qualitative difference in pharmacology. This is a key issue, since the broad pharmacology of these compounds is most likely the basis for the safety issues which have arisen. This is particularly true for the probably most important safety concern, namely the teratogenicity of thalidomide.

Safety pharmacology studies in rat, dog and monkey gave no evidence for safety risks. However, based on the data from toxicology studies in the rat the relevance of the rat for safety assessment is questionable. The lack of hERG channel inhibition, lack of cardiovascular findings in the dog safety pharmacology study and in the monkey repeat dose toxicity study do give some reassurance that lenalidomide is devoid of cardiovascular effects.

Pharmacokinetics

Lenalidomide is rapidly absorbed after oral administration in rats and monkeys. Bioavailability varies between 50-75%. The elimination half-life in rats and monkeys is approximately 2 and 13 hours, respectively, after a single oral administration. In humans, terminal half-life is dependent on dose (3.2 hours at 5 mg and 8.7 hours at 400 mg). Lenalidomide is widely distributed with a high volume of distribution. In a whole body autoradiography study in the rat, tissues levels were comparable to the plasma values. In pregnant animals, distribution to the foetus was observed.

In vitro metabolism studies showed no evidence for metabolism of lenalidomide. *In vivo*, metabolites formed by hydrolysis were observed. However, it was apparent that such hydrolysis products were formed *ex vivo* and the presented data did not allow a clear estimate of *in vivo* hydrolysis. A comparison of data from different studies with labelled lenalidomide vs. non-labelled lenalidomide suggests that a vast majority of the administered product is present as intact lenalidomide in plasma. Lenalidomide is produced as a racemic mixture of two enantiomers. Individual enantiomers were shown to undergo significant non-enzymatic racemisation in human plasma (complete after 6 hours).

After intravenous administration in rats and monkeys, the majority of the compound was excreted in urine, while after oral administration equal amounts were found in urine and faeces. This suggests that renal elimination is the main excretion path, while after oral dosing a substantial part is not absorbed and found in the faeces. There are no data on excretion in milk or in semen. For thalidomide, excretion in semen has been demonstrated and measures have been taken to protect women from exposure during sexual intercourse with patients taking thalidomide. Data on the presence of lenalidomide in semen are required in order to take a decision whether similar measures should be introduced for lenalidomide.

Toxicology

The primary toxicities observed after repeated oral administrations of lenalidomide were associated with the haematopoietic lympho-reticular systems and the kidneys, generally reversible after a 4- to 7-week recovery period. Rats appeared to be more sensitive to the effects on the kidneys, while cynomolgus monkeys were more sensitive to the effects on the haematopoietic systems. The NOAEL for rats in the chronic 26-week toxicity study was set at < 75 mg/kg/day. Based on AUC comparison, this dose was approximately 62-fold greater than the human daily exposure. In repeated-dose toxicity studies in monkeys, NOAEL is less than 1 mg/kg; this dose was equivalent to the human daily exposure (safety margin: 2.4).

The findings in monkey are likely to be a consequence of the pharmacological effect of lenalidomide and show similarity to what has been seen in the clinic, where neutropenia and thrombocytopenia were the most common adverse effects. The findings in the rat and the monkey underline the striking species differences in pharmacology and toxicology of lenalidomide, and it is concluded that the monkey but not the rat is a relevant species for safety evaluation.

For the non-clinical safety evaluation it is not possible to reach any conclusion on safety profile of lenalidomide compared to thalidomide.

Lenalidomide showed no evidence for genotoxicity. Further *in vitro* characterisation of the genotoxicity of the active substance including impurities has to be performed.

No studies on carcinogenicity have been performed which is acceptable for the proposed indication.

The most important issue for the non-clinical assessment of lenalidomide safety is reproductive and developmental toxicity, given the structural and pharmacological similarities with thalidomide. Studies on fertility and early embryonic development and on pre-natal and post-natal have been performed in the rat. These studies showed no evidence for important toxicity but the relevance and sensitivity of the rat is questionable as the presented data on general toxicity of lenalidomide show minimal toxicity in this species.

Embryo-foetal development has been studied in rats and rabbits. The rat study showed no evidence of toxicity, but the rat species is not considered as a relevant model for thalidomide analogues as it is poorly susceptible to thalidomide teratogenicity.

In the rabbit, lenalidomide exhibited foetal toxicity with increased post-implantation loss, decreased foetal weight, and also an increased frequency of foetal alterations (absence of the intermediate lobe of the lung and displaced kidneys). Lenalidomide did not induce, in particular, any limb malformations in the rabbit.

Based on the structural and pharmacological similarity to thalidomide and the foetal alterations observed in the rabbit study, lenalidomide should be classified as a suspected human teratogen and has to be contraindicated during pregnancy and precautions should be taken for women of childbearing potential.

The embryotoxic and teratogenic potential of lenalidomide will be further characterised in a sensitive species (see also re-examination procedure).

2.4 Clinical aspects

Introduction

The clinical programme of lenalidomide, at the dose of 10 mg/day, 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 additional cytogenetic abnormalities is summarised in Table 2.

Table 2 Development programme – List of clinical studies

Protocol No.	Study design and key objective	Test product(s)	Regimen(s)	Treatment duration	Study population	No. of enrolled Subjects Demography
Clinical pharmacology studies						
1398/142 Completed	A Phase I, single-blind, placebo-controlled, ascending single oral dose, safety, tolerability and pharmacokinetic study in healthy male subjects incorporating a comparison of fed/fasted kinetics	lenalidomide	Group A: single ascending dose 5, 20, 50, 100 and 400 mg fasted Group B: 200-mg dose of lenalidomide or placebo with food	Single	Healthy male volunteers	19/0 Group A: 9/0 35 ± 7.9 years Group: B 10/0 30 ± 7.9 years
1398/180 Completed	A Phase I, single-blind, placebo-controlled, multiple oral dose, safety, tolerability, pharmacodynamic and pharmacokinetic study in healthy male subjects	lenalidomide	100 mg/day on Days 1 and 8, and 200 mg (100 mg 12 hours apart) on Days 2-7	8 days	Healthy male volunteers	8/0 Lenalidomide: 6/0 29 ± 9.3 years Placebo: 10/0 29 and 31 years
CDC-501-001 Completed	A Phase I/II, open-label, non-randomised, dose-escalation safety and pharmacokinetics study intended to find a maximum tolerated dose (MTD)	lenalidomide	5, 10, 25 and 50 mg/day	Until disease progression or until lenalidomide becomes commercially available	Patients with relapsed or refractory multiple myeloma (MM)	27 Lenalidomide: 20/7 58.1 years (40–71)
CC-5013-PK-001 Completed	The Pharmacokinetics of A Single, Oral 25 mg dose of Lenalidomide (CC-5013) in Patients with Impaired Renal Function	lenalidomide	Single 25 mg dose under fasting condition in subjects with normal renal function and in subjects with mild, moderate, and severe RI Two single 25 mg doses, separated by 7 days in subjects with ESRD (first dose administered on a non-dialysis day, second dose 3 hours prior to a start of a dialysis session)	Single 2 doses	Healthy volunteers and renal impaired subjects	19/11 Normal: 4/3, 58 years (42-70) Mild RI: 3/2, 68 years (55-76) Moderate RI: 5/1, 59 years (39-73) Severe RI: 2/4 66 years (56-74) ESRD: 5/1, 50 years (41-57)
CC-5013-PK-002 Ongoing	A Pharmacokinetic and Pharmacodynamic Study of Oral Lenalidomide (Lenalidomide) in Subjects with Low- or Intermediate-1-Risk Myelodysplastic Syndromes	lenalidomide	Monotherapy phase (7 days after single-dose): 10 mg/day lenalidomide Combined therapy phase (following non-erythroid response or erythroid relapse following response): 10 mg/day lenalidomide + rhu-EPO 40,000 U/week S.Q.	Until disease progression or until lenalidomide becomes commercially available	Patients with low- or Intermediate-1-Risk MDS	25

Protocol No.	Study design and key objective	Test product(s)	Regimen(s)	Treatment duration	Study population	No. of enrolled Subjects Demography
CC-5013-PK-003 Completed	Phase I, double-blind, placebo-controlled, randomised, two-period crossover to determine the effects of lenalidomide on the PK/PD of the S and R enantiomers of warfarin and characterize the PK of the S and R enantiomers of lenalidomide before and after warfarin	lenalidomide	- Group 1: Lenalidomide 10 mg QD x 9 days with 25 mg warfarin on Day 4 Following at least a 17-day washout placebo QD x 9 days with 25 mg warfarin on Day 4 - Group 2: the reverse order of administration in treatment (placebo then lenalidomide)	Two periods of 9 days	Healthy volunteers	18 34 years (20-41)
CC-5013-PK-004 Ongoing	Phase I, double-blind, placebo-controlled, randomised, two-period crossover to determine the effects of multiple doses of lenalidomide on the PK of digoxin and the effect of a single dose of digoxin on the steady state plasma levels of lenalidomide and safety	lenalidomide	-Group 1: Lenalidomide 10 mg qd x 7 days with 0.5 mg digoxin on Day 5. Following at least a 17 day washout placebo qd x 7 days with 0.5 mg digoxin on Day 5. -Group 2: the reverse order of administration (placebo then lenalidomide)	Two periods of 7 days	Healthy volunteers	19
Clinical efficacy and safety studies						
CC-5013-MDS-001 Ongoing	Phase 1/2, single centre, open-label, non-controlled, dose-finding study to estimate the percent of patients with MDS who experienced erythroid response and the interval to response after treatment	lenalidomide	25-mg: 25 mg qd x 28 days 10-mg cont: 10 mg qd x 28 days 10-mg sync: 10 mg qd on Days 1-21 repeated 28-day cycles	16 weeks, followed by an extension that allowed treatment until disease progression` 24 cycles (96 weeks)	Patients with IPSS low-, INT-1-, INT-2--, or high-risk MDS <u>with or without</u> a del 5q cytogenetic abnormality	45: 26/19 72 years (27-85) 25 mg: 13, 7/6 10-mg cont: 12, 9/3 10-mg sync: 20, 10/10
CC-5013-MDS-002 Ongoing	Phase 2, multicentre, open-label, single-arm, non-controlled to evaluate the efficacy and safety of lenalidomide in patients with low- or intermediate-1-risk MDS without a del 5 (q31-33) cytogenetic abnormality and RBC-transfusion-dependent anaemia	lenalidomide	10-mg cont: 10 mg qd 10-mg sync: 10 mg qd on Days 1-21 28 repeated 28-day cycles	24 cycles (96 weeks)	Patients with IPSS low- or INT-1-risk MDS <u>without</u> a del 5q cytogenetic abnormality and RBC-transfusion-dependent anaemia	215: 138/77 10-mg cont: 100, 68/32 74 years (27-94) 10-mg sync: 115, 70/45 71 years (35-92)
CC-5013-MDS-003 Ongoing	Phase 2, multicentre, open-label, single-arm, non-controlled to evaluate the efficacy and safety in patients with IPSS low- or INT-1-risk MDS associated <u>with</u> a del 5q cytogenetic abnormality and RBC-transfusion-dependent anaemia	lenalidomide	10-mg cont: 10 mg qd 10-mg sync: 10 mg qd on Days 1-21 28 repeated 28-day cycles	24 cycles (96 weeks)	Patients with IPSS low- or INT-1-risk MDS associated <u>with</u> a del 5q cytogenetic abnormality and RBC-transfusion-dependent anaemia	148: 51/97 10-mg cont: 104, 35/69 71 years (37-95) 10-mg sync: 44, 16/28 72 years (51-91)

GCP

According to the applicant, all studies were conducted following appropriate Good Clinical Practice guidelines and considerations for the ethical treatment of human subjects. 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.

A routine GCP inspection of the pivotal study was requested by the CHMP and was conducted at one investigational site in Germany in May 2006. The main findings were:

- incomplete reporting of transfusion and non-compliance to transfusion rules which could have led to an overestimation of efficacy, but a sensitivity analysis taken into account all unexplained increases in haemoglobin as non-reported transfusions did not show major difference in overall response rate for transfusion independence.
- an unexpected incidence reporting of deaths and/or AML occurrence which could have led to an underestimation of safety. The applicant provided updated data on deaths and AML occurrence which are further detailed and discussed in the safety section.
- substantially higher incidence of Grade 3 and 4 thrombocytopenia and neutropenia than initially reported. The applicant provided additional data on Grade 3 and 4 thrombocytopenia and neutropenia summarised in the safety section.
- systematic deficiencies in the conduct of the clinical trial and the quality control procedures in the sponsor responsibility.

Pharmacokinetics

The pharmacokinetics is based on 3 completed studies (**Studies 1398/142, 1398/180 and CC-5013-PK-003**) in healthy volunteers, with doses ranging from 5 to 400 mg, one 10-mg dose study performed in myeloma patients (**Study CDC-501-001**) and one study in subjects with renal impairment (**Study CDC-5013-PK-001**). No PK data from MDS patients were available. However, one pharmacokinetic study in MDS patients and one in healthy volunteers investigating drug-drug interaction with digoxin were ongoing at the time of the application evaluation.

The commercial formulation is identical to that used for clinical trials. The analytical method used for the detection of lenalidomide in blood and urine samples is a liquid chromatography method with tandem mass spectrometric detection (LC-MS/MS). These methods were properly validated and associated with satisfactory lower limits of quantitation.

A comparison of main pharmacokinetic parameters between single oral 100-mg doses from single- and multiple-dose Studies 1398/142 and 1398/180 in healthy volunteers and from a multiple-dose study in multiple myeloma patients are provided in Table 3.

Table 3 Comparison between single oral 100-mg doses from single- and multiple-dose studies in healthy volunteers and from a multiple-dose study in multiple myeloma patients

Pharmacokinetic Parameter	CC-5013-1398/142 n = 6	CC-5013-1398/180 n = 6	CDC-501-001 n = 27
Age (years)	29	29	58
AUC(0-∞) [ng h/ml]	5997 (± 18%)	6006 (± 20%)	9400 (± 42%)
Cmax (ng/ml)	1735 (± 46%)	1618 (± 33%)	1982 (± 17%)
Median T _{max} [h] (range)	1.5 (1-1.5)	1.0 (0.5-2)	1.0 (0.5-1.5)
t _{1/2} [h ⁻¹]	4.7 (± 33%)	3.5 (± 4.9%)	4.0 (± 33%)
Cl/F (ml/min)	278 (± 18%)	277 (± 20%)	177 (± 42%)

• Absorption

Absolute bioavailability has not been determined in humans. However, results from animal studies and clinical pharmacokinetics show that absorption is linear and rapid. Lenalidomide can be taken either

before or after food, taking into consideration that co-administration with food delays absorption of the active substance.

- **Distribution**

The binding of radiolabelled “semi-racemic” lenalidomide to human plasma proteins was investigated *in vitro* by ultrafiltration at concentrations of 30-10000 ng/ml. The mean binding was 23 and 29% in plasma from myeloma patients and healthy volunteers, respectively. No concentration dependency was observed. The apparent oral volume of distribution was different between doses and studies but may be in the order 50-200 l.

- **Elimination**

Lenalidomide is not metabolised via cytochrome P450 in humans and further enzymatic systems have not been studied. The excretion of lenalidomide via the renal pathway is high, with the overall urinary recovery of unchanged drug being approximately 85% of the administered single oral dose. Urinary excretion of lenalidomide is approximately 27% lower when lenalidomide is administered in the fed condition compared to fast condition. Renal clearance was at least 190 ml/min, suggesting that active renal secretion occurs.

In vitro studies investigating which transporters are involved in the active renal secretion of lenalidomide are ongoing.

- **Dose proportionality and time dependencies**

The pharmacokinetic disposition of lenalidomide is linear in healthy volunteers and patients. The maximum concentration (C_{max}) and area-under-the-curve (AUC) increased in a dose-proportional manner over the dose range studied (5 to 400 mg).

There is no clinically important time- or dose-dependency in the pharmacokinetics of lenalidomide when administered to healthy volunteers or patients with relapsed multiple myeloma.

- **Special populations**

No formal studies have been conducted to assess the effects of age, gender, race or hepatic impairment on the pharmacokinetics of lenalidomide.

Study CC-5013-PK-001 studied the pharmacokinetics of lenalidomide after a single 25 mg oral dose under fasting conditions in subjects of different degrees of renal function and in patients with end stage renal disease (ESRD) receiving haemodialysis as follows:

Renal Function Groups			
Group	N	Description	Measured creatinine clearance (CLcr)
1	7	Normal renal function	> 80 ml/min
2	5	Mild renal impairment (RI)	$50 \leq \text{CLcr} \leq 80$ ml/min
3	6	Moderate RI	$30 \leq \text{CLcr} < 50$ ml/min
4	6	Severe RI	< 30 ml/min but not on dialysis
5	6	End Stage Renal Disease (ESRD)	Requiring dialysis

Subjects with ESRD received 2 single 25 mg doses at least 7 days apart: 1 dose was on a non-dialysis day and one 3 hours before a 4-hour haemodialysis period

Table 4 presents the pharmacokinetic parameters.

Table 4 Study CC-5013-PK-001 - Pharmacokinetic parameters

Mean (SD)	Normal	Mild RI	Renal function group		ESRD (off dialysis)	ESRD (on dialysis)
			Moderate RI	Severe RI		
	(n = 7)	(n = 5)	(n = 6)	(n = 6)	(n = 6)	(n = 6)
C _{max} (ng/ml)	605 (246)	691 (110)	592 (177)	765 (81.3)	552 (140)	385 (112)
t _{max} (h) median	1.00	1.00	1.00	1.50	1.25	2.00
(min-max)	(0.500, 2.00)	(1.00, 1.00)	(0.500, 1.50)	(0.500, 2.00)	(1.00, 2.00)	(0.500, 6.00)
AUC _t (ng.h/ml)	2065 (673)	2659 (1084)	5713 (744)	7872 (1312)	10501 (2048)	6310 (1018)
AUC _∞ (ng.h/ml)	2181 (703)	2767 (1094)	6021 (847)	8191 (1317)	11121 (2133)	6830 (919)
CL/F (ml/min)	207 (59)	166 (49)	71 (12)	52 (101)	39 (7)	62 (9)
Vz/F (l)	58 (15)	51 (13)	62 (15)	41 (8)	52 (8)	86 (14)
t _{1/2,z} (h)	3.34 (0.878)	3.67 (0.703)	10.6 (3.33)	9.22 (2.44)	15.6 (1.14)	16.1 (1.73)

A decrease in renal function resulted in an increase in total exposure (mean AUC_t and AUC_∞). C_{max} and t_{max} were not markedly affected by renal impairment. The exposure of the R and S-enantiomers were similarly affected by renal impairment. Subjects with normal renal function had higher mean % dose excreted unchanged in urine (85%), followed by subjects with mild RI (69%), subjects with moderate RI (42%) and subjects with severe RI (44%).

- Pharmacokinetic interaction studies

The potential for lenalidomide to cause drug-drug interactions was investigated *in vitro* and *in vivo*. A study to investigate the inhibitory effects of lenalidomide on the activities of selected P-450 cytochromes has been carried out *in vitro* to show that it is unlikely that lenalidomide causes metabolic drug interactions by inhibiting CYP activities. A study on the potential interaction of lenalidomide with p-glycoprotein is currently being completed.

Results from a chronic study in monkeys showed that lenalidomide at the dose of up to 2 mg/kg/day causes no notable effects on hepatic, microsomal protein or cytochrome P450 concentrations or on the activities of CYP1A, CYP2B, CYP2C, CYP3A, or CYP4A. Regarding the potential interaction with drugs having a high plasma-protein binding potential, the weak plasma-protein binding rate of lenalidomide (19%-29%) in all species including humans, makes the risk of drug-drug interactions related to displacement from plasmatic proteins, unlikely. However, formal clinical interaction studies have only been conducted for warfarin and digoxin, two frequently used drugs in the target population of patients. While no effect of lenalidomide on either enantiomer of warfarin was detected, there may be a possible drug interaction between lenalidomide and digoxin, although it may not be clinically relevant.

Warfarin

Co-administration of multiple doses of 10 mg of lenalidomide had no effect on the single dose pharmacokinetics of R- and S-warfarin. Co-administration of a single 25 mg dose of warfarin had no effect on the pharmacokinetics of lenalidomide. However, it is not known whether there is an interaction during clinical use (concomitant treatment with dexamethasone). Dexamethasone is a weak to moderate enzyme inducer and its effect on warfarin is unknown. Close monitoring of warfarin concentration is advised during the treatment.

Digoxin

Concomitant administration with lenalidomide 10 mg/day increased the plasma exposure of digoxin (0.5 mg, single dose) by 14% with a 90% CI (confidence interval) [0.52%-28.2%]. It is not known whether the effect will be different in the therapeutic situation (higher lenalidomide doses and concomitant treatment with dexamethasone). Therefore, monitoring of the digoxin concentration is advised during lenalidomide treatment.

- Pharmacokinetics using human biomaterials

No pharmacokinetic studies using human biomaterials have been conducted other than those already conducted to study pharmacokinetic interactions, namely: to determine extent of *in vitro* binding of (14C)-lenalidomide to plasma proteins, to determine the effect of lenalidomide on selected cytochrome P450 activities in human liver microsomes; to identify human P450 isoenzymes involved

in the metabolism of lenalidomide and to investigate the *in vitro* metabolism of (14C)-lenalidomide in human hepatocytes.

Pharmacodynamics

- Primary and secondary pharmacology

The pharmacological profile of lenalidomide was investigated in a series of studies designed to characterize the effects of the compound on the modulation of cytokine production, on stem cell differentiation, on innate immunity and on haematopoietic tumour cell proliferation:

- Cytokine modulation: In several *in vitro* assays, lenalidomide inhibited the production of pro-inflammatory mediators by monocytes, including tumour necrosis factor alpha (TNF- α), interleukin (IL)-1 β , IL-6, and IL-12, increased the secretion of anti-inflammatory cytokine IL-10 from peripheral blood mononuclear cells (PBMC) and inhibited expression of cyclooxygenase-2 (COX-2) and release of prostaglandin E₂ (PGE₂). In lipopolysaccharide (LPS)-stimulated PBMC, a dose-dependent inhibition for the following cytokines: TNF- α , IL-1 β , IL-6, IL-12, MCP-1 and MIP-1 α and a dose-dependent stimulatory effect on IL-10 were observed.
- Induction of T-cell proliferation: In various *in vitro* and *in vivo* studies, lenalidomide increased the proliferation and production of IL-2 and interferon gamma (IFN- γ) by T-cells and enhanced T-cell and NK-cell-mediated killing of tumours. In anti-CD3 stimulated CD4⁺ T-cells, stimulation of IFN- γ , IL-2 and RANTES was observed. NK cell-mediated killing of tumour cells was more than doubled at 1 mg/ml.
- Anti-proliferative effects: the proliferation of various haematopoietic tumour cell lines, including multiple myeloma (MM), Burkitt's lymphoma, MDS, acute myeloid leukaemia, non-Hodgkin's lymphoma and in particular those with cytogenetic defects of chromosome 5, e.g., the Namalwa cell line were inhibited by lenalidomide *in vitro*. In *in vivo* tumour growth models have demonstrated that lenalidomide inhibits growth of MM cells.
- Inhibition of angiogenesis: lenalidomide inhibits angiogenesis by blocking the formation of microvessels and endothelial cell tubes as well as the migration and adhesion of endothelial cells in *in vitro* angiogenesis models. In a human tissue culture model of angiogenesis, lenalidomide inhibited the microvessel formation emanating from an arterial explant in a dose-dependent manner. In *in vivo* tumour growth models have demonstrated that the inhibition of angiogenesis by lenalidomide has resulted in reduced growth of solid tumours.
- Induction of foetal haemoglobin: In a model of human haematopoietic progenitor differentiation, lenalidomide enhanced expression upon CD34⁺ haematopoietic stem cell differentiation in a model of erythroid progenitor differentiation. When CD34⁺ cells were cultured in the presence or absence of lenalidomide and hydroxyurea, alone or in combination, the induction of foetal haemoglobin production with lenalidomide was similar to that of hydroxyurea and there was a major synergistic effect when lenalidomide (10 μ M) was combined with hydroxyurea, resulting in a striking reactivation of foetal haemoglobin.
- In addition, lenalidomide suppressed oedema, mechanical and thermal hyperalgesia in a model of inflammatory pain.

Secondary pharmacology studies were conducted in two healthy volunteer PK-PD studies (**Studies 1398/142 and 1398/180**) and suggest that lenalidomide could have an effect on immune response.

Study 1398/142: lenalidomide appeared to have a possible effect on the immune response. An apparent dose-related decrease in CD4 count was observed at the higher dose levels of 200 mg lenalidomide (fasted and fed) and 400 mg lenalidomide (fasted) with the most pronounced effect occurring at 48-hour post-dose. In contrast, the CD8 count showed no treatment-related changes over time.

Study 1398/180: Multiple dosing with lenalidomide appeared to have an effect upon the immune response. An apparent dose-related decrease in both CD4 and CD8 blood counts was observed from Day 4 onwards. For CD4 counts, the magnitude of the decreases was relatively constant (approximately 300/mm³) on Days 4, 6 and 8, with values approaching baseline levels by the

post-study assessment. By contrast, decreases in mean CD8 counts were most pronounced on Day 8 (242 /mm³), with levels still considerably lower than the baseline value at the post-study assessment.

- Discussion on clinical pharmacology

The effects of age on the pharmacokinetics of lenalidomide have not been studied. 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.

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

The following dose adjustments are recommended at the start of therapy for patients with impaired renal function.

Renal function	Drug dose adjustment
Mild renal impairment (80 > CLcr ≥ 50 ml/min)	10 mg (Full Dose) Every 24 hours
Moderate renal impairment (30 ≤ CLcr < 50 ml/min)	5 mg Every 24 hours
Severe renal impairment (CLcr < 30 ml/min, not requiring dialysis)	5 mg Every 48 hours
End Stage Renal Disease (CLcr < 30 ml/min, requiring dialysis)	5 mg 3 times a week following each dialysis

The mechanism of action of lenalidomide in MDS is not known. However, the effect of lenalidomide on myelodysplastic haematopoiesis appears to be dual, at least initially 1) increasing red-cell production and 2) decreasing neutrophil and platelet production. This observation cannot be explained by a direct effect on clonal stem cells alone, which should cause parallel changes in peripheral-blood cells. More likely, lenalidomide is likely to modify the marrow microenvironment and thus to favour efficiency of erythropoiesis while inhibiting granulocytopoiesis and megakaryocytopoiesis. These effects are consistent with an anti-cytokine activity of lenalidomide and with the enhancement of the anti-apoptotic activity of erythropoietin on erythroid progenitors and the diminution of the anti-apoptotic activity of inflammatory cytokines on myeloid and megakaryocytic progenitors. Apart from these effects, the complete cytogenetic remissions seen in patients with the 5q- syndrome makes difficult to rule out a direct effect of the drug on myelodysplastic clones with the 5q deletion (Cazzola M., 2005).

No pharmacodynamic data from MDS trial are available and therefore no relationship between plasma concentration and effect has been investigated in MDS patients.

Secondary pharmacology: haematotoxicity (neutropenia and thrombocytopenia) is the dose limiting toxicity. Furthermore, a neurotoxicity of lenalidomide may be suspected.

Since lenalidomide is mainly renally excreted unchanged, lenalidomide has not formally been studied in patients with impaired hepatic function and there are no specific dose recommendations.

No studies on the effects on the ability to drive and use machines have been performed. Lenalidomide may have minor or moderate influence on the ability to drive and use machines. Fatigue, dizziness, somnolence and blurred vision have been reported with the use of lenalidomide. Therefore, caution is recommended when driving or operating machines.

Clinical efficacy

The clinical efficacy and safety of lenalidomide has been investigated in 3 non-controlled studies involving a total of 408 patients treated with at least 1 dose of lenalidomide (Table 2):

- Study CC-5013-MDS-001, a Phase I/II pilot, dose-finding study in patients with MDS

- **Study CC-5013-MDS-002**, an ongoing, Phase II, multicentre, open-label, single-arm study in patients with an IPSS diagnosis of low- or intermediate-1-risk MDS without an associated del 5q cytogenetic abnormality and with RBC-transfusion-dependent anaemia.
- **Study CC-5013-MDS-003**, an ongoing, Phase II, multicentre, open-label, single-arm study in patients with an IPSS diagnosis of low- or intermediate-1-risk MDS associated with a del 5q cytogenetic abnormality and with RBC-transfusion dependent anaemia.

The efficacy of lenalidomide for the claimed indication is based on the ongoing **Study MDS-003**. **Studies MDS-001** and **MDS-002** was considered as supportive data.

- Dose-response study(ies)

No dose response study was conducted in MDS patients and no MTD has been determined in this target population. The first dose that has been used in MDS population was 25 mg orally once daily of a 28-day cycle in **Study MDS-001**.

However, a high incidence of neutropenia and thrombocytopenia developed within 4 to 8 weeks of starting therapy. Thus, after 13 patients were enrolled and after a protocol amendment the dose was decreased up to 10 mg and patients were randomised into two treatment groups:

- a 10-mg continuous regimen (patients received 10 mg of lenalidomide orally once daily)
- a 10-mg syncopated regimen (patients received 10 mg orally once daily on Days 1 to 21 every 28 days)

No statistical comparison between both continuous and syncopated regimen was foreseen in the protocol.

Erythroid response was observed with each of the 3 lenalidomide dosing regimens. Based on the **Study MDS-001** results, **Studies MDS-002** and **MDS-003** were initiated to confirm the efficacy and safety of lenalidomide at a dose of 10 mg/day in patients with low- or intermediate-1-risk MDS (with or without a del 5q).

- Main studies

Study CC-5013-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

METHODS

Study participants

This was a multicentre study conducted at 32 centres in USA and 1 centre in Germany.

Main inclusion criteria were:

- IPSS diagnosis of low- or intermediate-1-risk MDS associated with an abnormality of chromosome 5 that involves a deletion between bands q31 and q33, with the del 5q cytogenetic abnormality either representing an isolated cytogenetic finding (the 5q- syndrome) or being associated with other cytogenetic abnormalities
- RBC-transfusion-dependent anaemia, defined as receiving 2 or more units of RBC within 8 weeks of the first day of study treatment
- ECOG 0, 1 or 2

Main exclusion criteria were:

- ANC < 500 cells/mm³ and platelet count < 50,000/mm³
- No proliferative CMML
- No clinically significant anaemia due to other factors (e.g., iron, vitamin B₁₂, or folate deficiencies...)
- Compromised renal/hepatic function
- Prior grade 3 or 4 hypersensitivity reaction to thalidomide
- Use of growth factors within 7 days

Treatments

Patients were initially treated using a “syncopated” regimen of lenalidomide 10 mg once daily for 3 weeks followed by 1 week rest (cycle duration 28 days). By the protocol amendment #1, dated 27 August 2003, continuous regimen was instituted administration of lenalidomide 10 mg daily. Forty-five patients were already enrolled when the amended was implemented.

Patients who began therapy on the “syncopated” regimen and who did not experience dose-limiting adverse events (AE) were allowed to switch to the continuous regimen. Treatment continued until unacceptable AE, bone marrow disease progression, progression or relapse following erythroid improvement is documented or for a maximum of 24 cycles, whichever occurred first. Myeloid growth factors for the management of an exacerbation of neutropenia were the only cytokines permitted.

Temporary treatment discontinuations and dose reductions were based on the severity and type of the AE that occurred:

- First reduction: from 10 to 5 mg per day
- Second reduction: from 5 mg per day to 5 mg every other day

Various rules for restarting treatment are summarised below:

- the ANC is $\geq 500/\mu\text{l}$
- the platelet count is $\geq 30,000/\mu\text{l}$, and if no evidence of haemostatic failure (i.e., bleeding or petechiae) is present
- any drug-related allergic or hypersensitivity reaction, sinus bradycardia, or other cardiac arrhythmia has resolved to grade 0 or 1
- any other drug-related AE has resolved to Grade ≤ 2

Dose escalation above 10 mg daily was not allowed.

Objectives

The objective of this study was to determine the efficacy and the safety of lenalidomide.

Outcomes/endpoints

The primary efficacy endpoint was “transfusion independency” defined as no need for RBC transfusion for any consecutive 56 days and an increase in haemoglobin of at least 1 g/dl during the transfusion-free period (excluding 30 days after last transfusion) from the minimum value during the 8-week period prior to inclusion.

The secondary efficacy endpoints were:

Erythroid	$a \geq 50\%$ decrease in 8-week RBC-transfusion requirements compared with baseline
Cytogenetic	Major: restoration of a normal karyotype in patients with a pre-existing clonal chromosome abnormality Minor: $\geq 50\%$ reduction in the percentage of bone marrow metaphases with any clonal abnormality (number of abnormal metaphases/number of metaphases assessed)
Time to response	Time-to-transfusion independence
Neutrophil and platelet responses	MDS IWG criteria (major and minor)
Bone marrow response	MDS IWG criteria (complete, partial, progression and AML transformation)

Sample size

Based on a one-stage hypothesis-testing model, the largest proportion suggesting that the drug not be studied further was set to be 30% and the smallest proportion suggesting that the drug is worthy of further study was set to be 60%. A sample of 30 patients who completed 6 cycles or dropped out early was adequate to test response rates of 30% versus 60%.

For 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%.

Randomisation

The study was a single-arm study.

Blinding (masking)

The study was open-label.

Statistical methods

In this hypothesis-testing setting, this CI approach is equivalent to reject the null hypothesis (the response rate $\leq 30\%$) in favour of the alternative hypothesis (response rate is $\geq 60\%$) if at least 15 responses occurred in the first 30 patients. This criterion requires that the 2-sided 95% CI for the percentage of patients who became RBC-transfusion independent based on the normal approximation lies entirely above 30%. This test has an error probability of < 0.025 of incorrectly rejecting the null hypothesis when the true response rate is $\leq 30\%$ and a probability of < 0.20 of incorrectly rejecting alternative hypothesis when the true response rate is $\geq 60\%$.

Three populations were defined for the efficacy analysis:

- Intent-to-treat (ITT) Population: all patients who received at least 1 dose of study medication.
- Modified intent-to-treat (mITT) Population: all patients who 1) received ≥ 2 units of packed RBC in each of the 8-week periods (56 days) during the 16 weeks prior to administration of study drug and who did not have a 56-day, RBC-transfusion-free period during the 16 weeks prior to administration of study drug, 2) have a diagnosis of low- or int-1-risk MDS confirmed by central review, 3) have a confirmed 5q- based on central cytogenetic review and 4) took at least 1 dose of study drug.
- Per-protocol (PP) population: all patients who 1) received ≥ 2 units of packed RBC during the immediate 56 days prior to administration of study drug, 2) have a diagnosis of low- or int-1-risk MDS confirmed by central review, 3) have a confirmed del 5q based on central cytogenetic review and 4) took at least 1 dose of study drug.

The data were displayed by the initial lenalidomide dosing regimen (i.e., continuous or syncopated) and for the overall population of lenalidomide-treated patients. However, the study was not designed or powered to prospectively compare the efficacy and safety of the 2 regimens.

RESULTS

Participant flow

A total of 148 patients were enrolled into the study. The cut-off date for clinical data of the original application was 15 September 2004. Table 5 displays the patient disposition.

Table 5 Study MDS-003 - Patient disposition at the cut-off of 15 September 2004

Disposition	10 mg continuous		10 mg syncopated		Overall	
	n	%	n	%	n	%
Entered	103	100.0	45	100.0	148	100.0
Ongoing	77	74.8	29	64.4	103	69.6
Did not complete Week 24	3	2.9	0	0.0	3	2.0
Discontinued prior Week 24	20	19.4	14	31.1	34	23.0
Overall discontinuations	26	25.2	16	35.6	42	28.4
Adverse event	7	6.8	9	20.0	16	10.8
Lack of therapeutic effect	9	8.7	4	8.9	13	8.8
Patient withdrew consent	1	1.0	1	2.2	2	1.4
Patient lost to follow-up	0	0.0	0	0.0	0	0.0
Death	6	5.8	2	4.4	8	5.4
Protocol violation	0	0.0	0	0.0	0	0.0
Other	3	2.9	0	0.0	3	2.0

Recruitment

The enrolment period was from 01 July 2003. At 15 September 2004 cut-off date, the median duration of follow-up was 33 weeks ranging of 1.3 to 59.1 weeks.

Conduct of the study

The protocol for this study, originally dated 02 May 2003, was amended 3 times. The 3 amendments are summarised below:

Amendment #1, dated 27 August 2003

- modified the statistical analysis plan and statistical methods to increase the sample size from 36 to 90 and to change the definition of the MITT population
- changed the dosing regimen from a syncopated regimen to a continuous regimen
- increased the duration of treatment from 6 cycles to until bone marrow disease progression or progression/relapse following erythroid haematologic improvement or for a total of 24 cycles, whichever occurred first
- clarified the dose modifications for thrombocytopenia, hyperthyroidism, and other toxicities
- added an exclusion criterion: patients with dry tap at screening/baseline and proliferative CMML
- clarified that local laboratory results (including haematologic and cytogenetic data) are used to determine eligibility and dose modifications

Amendment #2, dated 12 September 2003

- clarified the dose reduction schedule in patients who remained on the syncopated regimen
- clarified that local laboratory results for haemoglobin could be used in the analysis of the secondary efficacy endpoints if central values were missing or invalid

Amendment #3, dated 13 January 2004

- required a weekly CBC during the first 8 weeks of therapy, to monitor for early haematologic AE
- added guidance on management of dose modification for neutropenia and thrombocytopenia that occurs during the first 4 weeks of therapy
- clarified the procedures for the central cytogenetic reviewer

Table 6 summarises protocol deviations for the entire study population.

Table 6 Study MDS-003 - Patient disposition at the cut-off of 15 September 2004

	Number of occurrences	Number of patients n = 148
Deviation from inclusion criteria	16	15 (10.1)
Deviation from exclusion criteria	9	9 (6.1)
Investigational drug non compliance	120	63 (42.6)
Concomitant medication non compliance	13	10 (6.8)

The most common protocol deviations were errors in the study medication regimens (e.g., missed dose).

Baseline data

Patient population baseline demographic and disease characteristics are displayed in Table 7.

Table 7 Studies MDS-003 - Demographic and disease characteristics

	ITT/safety n = 148	Per protocol n = 115	mITT n = 94
Age			
Median (years)	71.0	71.0	71.5
Range (years)	37.0-95.0	37.0-95.0	41.0-95.0
Patients > 65 years (n, %)	100 (67.5)	77 (67.0)	63 (67.0)
Gender (n, %)			
Male	51 (34.5)	37 (32.2)	32 (34.0)
Female	97 (65.5)	78 (67.8)	62 (66.0)
Ethnic origin (n, %)			
Caucasian	143 (96.6)	111 (96.5)	91 (96.8)
ECOG performance (n, %)			
0	59 (39.9)	46 (40.0)	38 (40.4)
1	75 (50.7)	57 (49.6)	47 (50.0)
2	14 (9.5)	12 (10.4)	9 (9.6)
FAB classification (based on central review) (n, %)			
RA	77 (52.0)	75 (65.2)	58 (61.7)
RARS	16 (10.8)	15 (13.0)	14 (14.9)
RA/RARS	2 (1.4)	1 (0.9)	1 (1.1)
RAEB	30 (20.3)	21 (18.3)	18 (19.1)
CMML	3 (2.0)	3 (2.6)	0
RAEB-T	0	0	3 (3.2)
Acute leukaemia	1 (0.7)	0	0
Not diagnostic of MDS	2 (1.4)	0	0
Unable to classify	17 (11.5)	0	0
IPSS risk category (based on central review) (n, %)			
Low	55 (37.2)	53 (46.1)	42 (44.7)
Int-1	65 (43.9)	62 (53.9)	52 (55.3)
Int-2	6 (4.1)	0	0
High	2 (1.4)	0	0
Missing	20 (13.5)	0	0
Transfusion dependent at baseline (n, %)			
Yes	-	-	94 (100)
Duration of MDS (years)			
Median	2.5	2.1	3.1
Range	0.1-20.7	0.3-14.4	0.2-20.7
5q (-) chromosomal abnormality (n, %)			
Yes	147 (99.3)	115 (100)	94 (100)
Isolated del 5q	110 (74.8)	-	-
Isolated del 5q and other cytogenetic abnormalities	37 (25.2)	-	-

In each patient population, there was no significant difference between patients who received syncopated or continuous treatment in terms of baseline demographic and disease characteristics.

Numbers analysed

A total 54 patients were excluded from the mITT population. The reasons for exclusion from the mITT population included:

- For 19 patients, inability to prove that the patient received ≥ 2 units of RBC in the 8- to 16-week period prior lenalidomide (generally, these were patients who had been transfused elsewhere, prior to referral to a centre participating in this study)
- For 28 patients, the diagnosis of low- or int-1-risk was not documented by baseline central review (20 unable to classify; 6 intermediate 2-risk MDS and 2 high-risk MDS)
- And 7 patients were found to have been RBC-transfusion-free for ≥ 56 days during the immediate 16 weeks prior study treatment.

Efficacy data were also analysed for the ITT and PP populations, which include 148 and 115 patients, respectively (Table 8).

Table 8 Studies MDS-003 – Patient population

	10 mg continuous		10 mg syncopated		Overall	
	n	%	n	%	n	%
Intent-to –treat (ITT)	130	100	45	100	148	100
Safety	103	100	45	100	148	100
Per protocol (PP)	78	75.7	37	82.2	115	77.7
Modified intent-to-treat	63	61.2	31	68.9	94	63.5

*Outcomes and estimation***Primary and secondary endpoint analyses**

At the cut-off date of 15 September 2004, Table 9 presents the results of the primary and secondary endpoints for the mITT population.

Table 9 Studies MDS-003 – Summary of the efficacy results (mITT)

	10 mg continuous n = 63	10 mg syncopated n = 31	Overall n = 94
<i>RBC-transfusion independence (number, % and 95% CI)</i>			
Overall	41 (65.1) [52.0, 76.7]	16 (51.6) [33.1, 69.8]	57 (60.6) [50.0, 70.6]
IPSS low risk	n = 33 20 (60.6) [42.1, 77.1]	n = 9 7 (77.8) [40.0, 97.2]	n = 42 27 (64.3) [48.0, 78.4]
IPSS int-1 risk	n = 30 21 (70.0) [50.6, 85.3]	n = 22 9 (40.97) [20.7, 63.6]	n = 52 30 (57.7) [43.2, 71.3]
<i>Time to RBC-transfusion independence response (median and range)</i>			
	5.3 weeks [0.3-19.1]	3.8 weeks [0.3-16.3]	4.7 weeks [0.3-19.1]
<i>Duration of RBC-transfusion independence (median and range)</i>			
	28.0 weeks [8.1-44.0+]	41.1 weeks [8.1-46.1+]	30.1 weeks [8.1-46.1+]
<i>Increase in haemoglobin level (median and range)</i>			
	5.6 g/dl [2.2-11.4]	5.4 g/dl [1.1-9.1]	5.5 g/dl [1.1-11.4]
<i>At least 50% decrease in their pre-treatment RBC-transfusion requirements (number and %)</i>			
	46 (73.0)	22 (71.0)	68 (72.3)
<i>Cytogenetic responses (number and %)</i>			
	n = 45	n = 23	n = 68
Major	12 (26.7)	10 (43.5)	22 (32.4)
Minor	17 (37.8)	5 (21.7)	22 (32.4)
Major complete resolution of all cytogenetic abnormalities compared with baseline			
Minor ≥ 50% reduction in the proportion of haematopoietic cells with cytogenetic abnormalities compared with baseline			

As of data cut-off date, the Kaplan-Meier estimate of median duration of response had not yet been reached: 82.5% (47) of the 57 responders remained RBC-transfusion independent and 17.5% (10) had relapsed and duration of response of at least 24 weeks was noted in 39 of 57 (68.4%) patients.

Achievement of transfusion independence was not affected by age, gender, race, baseline ECOG, FAB classification or IPSS classification. There was no noticeable clinical relevant difference between patients who received a syncopated or continuous treatment.

Table 10 presents the summary results of the primary and secondary endpoints for the ITT population, at cut-off date of 15 September 2004.

Table 10 Studies MDS-003 –Summary of the efficacy results (ITT)

	10 mg continuous n = 103	10 mg syncopated n = 45	Overall n = 148
<i>RBC-transfusion independence (number, % and 95% CI)</i>			
Overall	70 (68.0) [58.0, 76.8]	25 (55.6) [40.0, 70.4]	95 (64.2) [55.9, 71.9]
IPSS low risk	n = 42 28 (66.7) [50.5, 80.4]	n = 13 11 (84.6) [54.6, 98.1]	n = 55 39 (70.9) [57.1, 82.4]
IPSS int-1 risk	n = 40 29 (72.5) [56.1, 85.4]	n = 25 12 (48.0) [27.8, 68.7]	n = 65 41 (63.1) [50.2, 74.7]
IPSS int-2 risk	n = 4 2 (50.0) [6.8, 93.2]	n = 2 0 (0.0) [0.0, 84.2]	n = 6 2 (33.3) [4.3, 77.7]
IPSS high risk	n = 1 1 (100.0) [2.5, 100.0]	n = 1 0 (0.0) [0.0, 97.5]	n = 2 1 (50.0) [1.3, 98.7]
<i>Time to RBC-transfusion independence response (median and range)</i>			
	4.5 weeks [0.3-19.1]	3.6 weeks [0.3-18.9]	4.1 weeks [0.3-19.1]
<i>Duration of RBC-transfusion independence (median and range)</i>			
	27.5 weeks [8.1, 44.0+]	40.7 weeks [8.1, 48.1+]	30.0 weeks [8.1, 48.1+]
<i>Increase in haemoglobin level (median and range)</i>			
	5.1 g/dl [2.2-11.4]	5.3 g/dl [1.1-9.1]	5.2 g/dl [1.1-11.4]
<i>At least 50% decrease in their pre-treatment RBC-transfusion requirements (number and %)</i>			
	79 (76.7)	31 (68.9)	110 (74.3)
<i>Cytogenetic responses (number and %)</i>			
	n = 78	n = 33	n = 111
Major	32 (41.0)	14 (42.4)	46 (41.4)
Minor	21 (26.9)	8 (24.2)	29 (26.1)
Major complete resolution of all cytogenetic abnormalities compared with baseline			
Minor ≥ 50% reduction in the proportion of haematopoietic cells with cytogenetic abnormalities compared with baseline			

Seventy-four (67.3%) of the 110 patients with an isolated del 5q abnormality and 21 (56.8%) of the 37 patients with a del 5q abnormality and an additional cytogenetic abnormality achieved RBC-transfusion independence.

The study results for the PP population were similar to those observed in the mITT and ITT populations.

On request of the CHMP, the applicant provides updated efficacy data with a cut-off date 01 September 2005, the median duration of treatment was 52.5 weeks, with a range of 0.4 to 105.1 weeks in the mITT population. There were no significant difference in the response rates in the mITT or ITT populations as well as in subgroups of patients with del 5q with or without additional cytogenetic aberrations.

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

No analysis was performed across trials or on pooled data.

- Clinical studies in special populations

No studies in special populations e.g. in children, in the elderly and in patients with hepatic impairment was performed.

- Supportive study(ies)

Study MDS-001 was single-arm, single centre (US) study for which the first patient enrolled 20 February 2002. At the cut off date of 05 February 2004, a total of 45 patients with MDS, all FAB subtypes (RA to RAEB-T) were enrolled.

Initially 13 patients were treated with 25 mg daily. The study protocol was then amended to explore, sequentially 10 mg daily continuously in 12 patients and 10 mg “syncopated” (3 weeks on, 1 week off) in 20 patients.

The 43 patients were considered evaluable for efficacy. All erythroid responses were observed in patients with IPSS low and int-1 (22/38) vs. none in 5 patients with IPSS int-2 and high risk. With respect to initial dosing, responses were seen as follows 6/13 (25 mg), 6/12 (10 mg continuous) and 10/18 (10 mg syncopated).

The response rate in terms of transfusion independency in transfusion-dependent patients with del 5q with or without other abnormalities was found to be 7/10 vs. 10/25 in patients without del 5q.

The 25-mg regimen was found to be more toxic (mainly neutropenia) than the other tested regimens without apparent benefits in terms of improved activity.

Study MDS-002 had similar designed as **Study MDS-003** except the patient population. The targeted patient population was patient without del 5q and cytogenetic abnormality.

The main inclusion criteria were:

- Low- or intermediate-1-risk MDS
- RBC transfusion dependent (at least 2 units within 8 weeks prior to inclusion)
- ECOG 0, 1 or 2

The main exclusion criteria were:

- Deletion 5 (q31-33)
- ANC < 500 cells/mm³ and platelet count < 50,000/mm³
- Compromised renal/hepatic function
- Prior grade 3 or 4 hypersensitivity reaction to thalidomide
- Use of growth factors within 7 days

The treatment was initially “syncopated” lenalidomide 10 mg once daily for 3 weeks followed by 1 week of rest (cycle duration 28 days) and then continuous administration of lenalidomide 10 mg daily following the protocol amendment #1 dated on 12 September 2003.

The primary endpoint was “transfusion independency” defined as no need for RBC transfusion for any consecutive 56 days and increase in haemoglobin of at least 1 g/dl during the transfusion-free period (excluding 30 days after last transfusion) from the minimum value during the 8-week period prior to inclusion.

The primary efficacy population was the mITT defined as that patients for whom documented transfusion dependency (≥ 2 units) for at least 2 consecutive 8-week periods prior to inclusion and without a 56-day transfusion-free period during these 16 weeks, centrally confirmed low- or int-1-risk MDS and lack of del 5q and at least 1 dose of study drug.

The first patient enrolled 30 June 2003. At the data cut-off date of 15 June 2004, 215 patients (136 planned) were enrolled and treated with lenalidomide between. The median duration of follow-up for this analysis is 21.0 weeks, with a range of 1.9 to 42.1 weeks.

Table 11 displays the patient disposition.

Table 11 Study MDS-002 - Patient disposition at 15 June 2004 cut-off date

Disposition	10 mg continuous		10 mg syncopated		Overall	
	n	%	n	%	n	%
Entered	100	100.0	115	100.0	215	100.0
Ongoing	52	52.0	47	40.9	99	46.0
Did not complete Week 24	30	30.0	8	7.0	38	17.7
Discontinued prior Week 24	44	44.0	48	41.7	92	42.8
Overall discontinuations	48	48.0	68	59.1	116	54.0
Adverse event	20	20.0	29	25.2	49	22.8
Lack of therapeutic effect	14	14.0	24	20.9	38	17.7
Patient withdrew consent	9	9.0	6	5.2	15	7.0
Patient lost to follow-up	0	0.0	1	0.9	1	0.5
Death	3	3.0	3	2.6	6	2.8
Protocol violation	0	0.0	1	0.9	1	0.5
Other	2	2.0	4	3.5	6	2.8

Patient population baseline demographic and disease characteristics are presented in Table 12.

Table 12 Studies MDS-002 - Demographic and disease characteristics

	ITT/safety n = 215	Per protocol n = 166	mITT n = 118
Age			
Median (years)	71.2	72.0	72.0
Range (years)	27.0-94.0	27.0-94.0	27.0-87.0
Patients > 65 years (n, %)	164 (76.3)	126 (75.9)	90 (76.3)
Gender (n, %)			
Male	138 (64.2)	107 (64.5)	73 (61.9)
Female	77 (35.8)	59 (35.5)	45 (38.1)
Ethnic origin (n, %)			
Caucasian	202 (94.0)	156 (94.0)	113 (95.8)
ECOG performance (n, %)			
0	88 (40.9)	68 (41.0)	45 (38.1)
1	118 (54.9)	92 (55.4)	70 (59.3)
2	5 (2.3)	3 (1.8)	0
Missing	3 (1.4)	2 (1.2)	2 (1.7)
FAB classification (based on central review) (n, %)			
RA	40 (18.60)	39 (23.5)	26 (22.0)
RARS	86 (40.0)	83 (50.0)	64 (54.2)
RA/RARS	7 (3.3)	5 (3.0)	3 (2.5)
RAEB	24 (11.2)	19 (11.4)	14 (11.9)
CMML	20 (9.3)	16 (9.6)	10 (8.5)
RA/CMML	1 (0.5)	1 (0.6)	0
RARS/CMML	1 (0.5)	1 (0.6)	1 (0.6)
RAEB-T	5 (2.3)	2 (1.2)	0
Acute leukaemia	1 (0.5)	0	0
Not diagnostic of MDS	3 (1.4)	0	0
Unable to classify	20 (9.3)	0	0
Missing	7 (3.3)	0	0
IPSS risk category (based on central review) (n, %)			
Low	93 (43.3)	91 (54.8)	65 (55.1)
Int-1	76 (35.3)	75 (45.2)	53 (44.9)
Int-2	6 (2.8)	0	0
High	2 (0.9)	0	0
Missing	38 (17.7)	0	0
Duration of MDS (years)			
Median	2.2	2.2	2.4
Range	0.0-12.9	0.0-12.9	0.1-12.9
5q (-) chromosomal abnormality (n, %)			
Yes	2 (0.9)	0	0
No	204 (94.9)	166 (100)	118 (100)
Missing	9 (4.2)	0	0

A total 97 patients were excluded from the mITT population. The reasons for exclusion from the mITT population included:

- For 43 patients, inability to prove that the patient received ≥ 2 units of RBC in the 8- to 16-week period prior lenalidomide (generally, these were patients who had been transfused elsewhere, prior to referral to a centre participating in this study)
- For 46 patients, the diagnosis of low- or int-1-risk was not documented by baseline central review (20 unable to classify; 6 intermediate 2-risk MDS and 2 high-risk MDS)
- Seven patients were found to have been RBC-transfusion-free for ≥ 56 days during the immediate 16 weeks prior study treatment
- And 1 patient had a deletion 5(q31 q33)

The efficacy results for the mITT population were:

- 21.2% (25/118) of the patients achieved RBC-transfusion independence
- The median response duration is not achieved, the duration of response of at least 16 weeks was noted in 18/25 patients
- The median time-to-response for the 25 responders was 4.1 weeks (range, 0.3-26.1 weeks)
- As of data cut-off date, 18 (72.0%) of the 25 responders remained RBC-transfusion independent and 7 (28%) relapsed
- The median increase in blood haemoglobin level from baseline to the maximum haemoglobin level achieved to date during RBC-transfusion independence was 3.0 g/dl (range 1.0-7.2 g/dl) in the 25 responders
- Overall, 38.1% (45/118) of the patients achieved a $\geq 50\%$ decrease in their pre-treatment RBC-transfusion requirements) during lenalidomide therapy
- No major or minor neutrophil or platelet responses were observed in the small number of patients who had neutropenia or thrombocytopenia at baseline

As for **Study MDS-003**, the applicant provided updated efficacy information for **Study MDS-002** with a cut-off date of 01 September 2005. There were no significant difference in the response rates in the ITT population for patients with low- or int-1 risk without del 5q.

- Discussion on clinical efficacy

The pharmacodynamic documentation of lenalidomide, submitted for the present application, is rather limited.

No dose response study has been undertaken and no MTD has been established in MDS patients. The only ascending multiple dose study was performed in healthy subjects. The choice of the 25 mg initial dose used in the Phase I/II **Study MDS-001** was based on the MTD determined in multiple myeloma. After including 13 patients in **Study MDS-001**, due to neutropenia and thrombopenia, the dose was decreased up to 10 mg. This study showed activity of lenalidomide in terms of erythroid response in MDS patients with low or int-1 grades only and particularly in MDS patients with a 5q deletion for any dosing regimen (25 mg and both the 10 mg [syncopated and continuous]) associated with a high rate of neutropenia and thrombopenia. There is an ongoing study, **Study MDS-004** which investigates the efficacy and safety of 2 doses (5 and 10 mg/day) of lenalidomide vs. placebo in patients with IPSS low- or int-1-risk MDS associated with a del 5q and RBC-transfusion-dependent anaemia and might bring some answer to absence of a proper dose-response study.

The mechanism of action is unknown.

In Phase II studies, lenalidomide showed activity in terms of erythroid responses in patients with low- or intermediate-1-risk MDS and an associated del 5q with or without additional cytogenetic abnormalities. The response criteria were stringent and transfusion independence was to be associated to a significant increase of mean haemoglobin blood level. The targeted population of **Study MDS-003** was adequately documented (except for EPO responder status). Results based on both ITT and mITT analyses are comparable. Histological and cytogenetic analyses showed that responses were

achieved in a minority of patients, suggesting that lenalidomide might not modify the course of the disease.

The effect of lenalidomide in maintaining a response has never been investigated, consequently it is not possible to recommend whether lenalidomide has to be a continuous treatment (assuming it is well tolerated) or could be interrupted without rebound effect and how will be the treatment effect if lenalidomide has be re-administered. This information would be of special interest given the toxicity of lenalidomide in such population.

Clinical safety

The assessment of the tolerance and safety profile of lenalidomide in the claimed indication was based on MDS studies (Table 2).

- Patient exposure

The pooled safety database as of 15 September 2004 includes 408 patients of which 395 received treatment with the recommended starting dose of 10 mg/day. Table 13 displays the exposure by starting dose.

Table 13 Studies MDS-001, -002 and -003 – Patient exposure

	All MDS Studies			
	25 mg n = 13	10 mg continuous n = 215	10 mg syncopated n = 180	10 mg overall n = 395
Duration (weeks)				
Mean	35.0	22.5	23.1	22.7
SD	32.54	13.96	14.26	14.09
Median	20.6	21.7	23.0	22.4
Min-Max	1.3-87.0	0.4-71.1	0.7-59.1	0.4-71.1
Distribution of treatment duration				
At least one dose	13 (100)	215 (100)	180 (100)	395 (100)
At least 4 weeks	10 (76.9)	199 (92.6)	158 (87.8)	357 (90.4)
At least 8 weeks	9 (69.2)	175 (81.4)	143 (79.4)	318 (80.5)
At least 16 weeks	8 (61.5)	142 (66.0)	121 (67.2)	263 (66.6)
At least 24 weeks	6 (46.2)	102 (47.4)	87 (48.3)	189 (47.8)
At least 32 weeks	6 (46.2)	50 (23.3)	47 (26.1)	97 (24.6)
At least 48 weeks	4 (30.8)	7 (3.3)	11 (6.1)	18 (4.6)

The majority of patients in the MDS studies were aged older than 65 years of age (72%, mean age 70 years and age range 27-95 years) and white (94.7%) and half of the patients were male. A total of 158 patients (40%) had a deletion 5q whereas 226 of exposed patients did not have the deletion 5q.

- Adverse events

Table 14 presents pooled results of all adverse events that were reported by the patients or observed by the investigators and recorded in the case report form (CRF) for **Studies MDS-001, -002 and -003**. The severity of adverse events and laboratory abnormalities was graded according to National Cancer Institute (NCI) Common Toxicity Criteria (CTC) (Version 2.0).

Table 14 Studies MDS-001, -002 and -003 – Adverse events reported in 5% or more of patients

	All MDS Studies			
	25 mg n = 13	10 mg continuous n = 215	10 mg syncopated n = 180	10 mg overall n = 395
Patients with at least one AE	13 (100.0)	215 (100.0)	179 (99.4)	394 (99.7)
Gastrointestinal disorders				
Diarrhoea NOS	6 (46.2)	81 (37.7)	61 (33.9)	142 (35.9)
Constipation	3 (23.1)	53 (24.7)	42 (23.3)	95 (24.1)
Nausea	4 (30.8)	41 (19.1)	34 (18.9)	75 (19.0)
Vomiting NOS	1 (7.7)	17 (7.9)	18 (10.0)	35 (8.9)
Abdominal pain NOS	3 (23.1)	20 (9.3)	11 (6.1)	31 (7.8)
Dry mouth	0 (0.0)	14 (6.5)	15 (8.3)	29 (7.3)
Abdominal pain upper	1 (7.7)	16 (7.4)	9 (5.0)	25 (6.3)
Skin and subcutaneous tissue disorders				
Pruritis	8 (61.5)	71 (33.0)	53 (29.4)	124 (31.4)
Rash NOS	5 (38.5)	69 (32.1)	48 (26.7)	117 (29.6)
Dry skin	1 (7.7)	21 (9.8)	15 (8.3)	36 (9.1)
Night sweats	1 (7.7)	12 (5.6)	14 (7.8)	26 (6.6)
Rash pruritic	0 (0.0)	10 (4.7)	10 (5.6)	20 (5.1)
General disorders and administration site conditions				
Fatigue	9 (69.2)	64 (29.8)	67 (37.2)	131 (33.2)
Oedema peripheral	4 (30.8)	29 (13.5)	45 (25.0)	74 (18.7)
Pyrexia	3 (23.1)	37 (17.2)	24 (13.3)	61 (15.4)
Asthenia	3 (23.1)	23 (10.7)	11 (6.1)	34 (8.6)
Oedema NO	0 (0.0)	12 (5.6)	16 (8.9)	28 (7.1)
Pain NOS	2 (15.4)	13 (6.0)	12 (6.7)	25 (6.3)
Chest pain	1 (7.7)	14 (6.5)	6 (3.3)	20 (5.1)
Blood and lymphatic system disorders				
Neutropenia	9 (69.2)	112 (52.1)	52 (28.9)	164 (41.5)
Thrombocytopenia	7 (53.8)	101 (47.0)	63 (35.0)	164 (41.5)
Anaemia NOS	1 (7.7)	20 (9.3)	15 (8.3)	35 (8.9)
Respiratory thoracic and mediastinal disorders				
Cough	6 (46.2)	31 (14.4)	37 (20.6)	68 (17.2)
Dyspnoea NOS	5 (38.5)	32 (14.9)	32 (17.8)	64 (16.2)
Nasopharyngitis	1 (7.7)	31 (14.4)	17 (9.4)	48 (12.2)
Epistaxis	1 (7.7)	20 (9.3)	22 (12.2)	42 (10.6)
Pharyngitis	0 (0.0)	24 (11.2)	18 (10.0)	42 (10.6)
Musculoskeletal and connective tissue disorders				
Muscle cramp	1 (7.7)	39 (18.1)	33 (18.3)	72 (18.2)
Arthralgia	3 (23.1)	41 (19.1)	29 (16.1)	70 (17.7)
Back pain	1 (7.7)	32 (14.9)	29 (16.1)	61 (15.4)
Pain in limb	2 (15.4)	19 (8.8)	21 (11.7)	40 (10.1)
Myalgia	2 (15.4)	12 (5.6)	13 (7.2)	25 (6.3)
Peripheral swelling	0 (0.0)	11 (5.1)	9 (5.0)	20 (5.1)
Nervous system disorders				
Headache	3 (23.1)	35 (16.3)	33 (18.3)	68 (17.2)
Dizziness	1 (7.7)	32 (14.9)	32 (17.8)	64 (16.2)
Dysgeusia	0 (0.0)	15 (7.0)	7 (3.9)	22 (5.6)
Infections and infestations				
Upper respiratory tract infection NOS	4 (30.8)	24 (11.2)	20 (11.1)	44 (11.1)
Urinary tract infection NOS	3 (23.1)	18 (8.4)	19 (10.6)	37 (9.4)
Pneumonia NOS	2 (15.4)	19 (8.8)	12 (6.7)	31 (7.8)
Sinusitis NOS	1 (7.7)	12 (5.6)	10 (5.6)	22 (5.6)
Metabolism and nutrition disorders				
Anorexia	1 (7.7)	23 (10.7)	14 (7.8)	37 (9.4)
Appetite decreased NOS	1 (7.7)	12 (5.6)	13 (7.2)	25 (6.3)
Eye disorders				
Vision blurred	0 (0.0)	6 (2.8)	17 (9.4)	23 (5.8)
Psychiatric disorders				
Insomnia	0 (0.0)	14 (6.5)	17 (9.4)	31 (7.8)

NOS, not otherwise specified

Almost 100% of patients, who were treated with the 10-mg/day starting dose, experienced an AE, 89.1% a drug-related AE, 79.5% Grade 3 or 4 AE and 38.2% a serious AE. The main drug-related AE are the following:

Haematological toxicity is the dose limiting toxicity: Grade 3 or 4 thrombocytopenia in 30.4% of the patients, febrile and non febrile neutropenia in 34.2% and serious in 1.8 and 3.6% respectively (with 2.3% neutropenia and 1.3% febrile neutropenia).

The most frequently reported adverse events leading to treatment discontinuation were neutropenia and thrombocytopenia (respectively 6.1 and 3.5%) and dose reductions.

The NADIR for ANC was generally observed within approximately 2 to 3 weeks after the start of dosing. These effects are dose-related and could be managed with dose reductions or interruptions of the treatment. Growth factor has been administered in 14.6% of patients and red blood cells transfusions in 10.6% of patients. There was no correlation between baseline neutrophil and platelet count and neutropenia or thrombocytopenia.

Furthermore, Grade 3 or 4 bleedings were reported in 34.4% patients during the treatment, however, none of them was reported as serious and drug-related.

Infections: among the 15 serious infections, pneumonia was the principal infection reported (7 cases).

Skin reactions: Grade 3 or 4 rash occurred in 4.8% of patients and all were considered to be related to lenalidomide. There were 3 serious reports of rash and one serious report of acute febrile neutrophilic dermatosis. There was no report of toxic epidermal necrolysis or Stevens-Johnson syndrome.

Gastrointestinal disorders: Grade 3 or 4 diarrhoea were reported in 2.5% of the patients including one reported as serious with hypokalaemia and no Grade 3 or 4 constipation.

Grade 3 or 4 **fatigue** (6%) and **somnolence** (including 3 serious reports) were reported.

Nervous system: 10 reports of somnolence (2.5%), 9 reports of peripheral neuropathy (2.3%) 6 cases of neuropathy (1.5%) and 3 cases of neuropathic pain.

A total of 17% events (67 patients) were reported which could potentially be indicative of a peripheral neuropathy. Of these 67 events, 35 (more than a half) were considered to be related to lenalidomide as follows: 7 hypoaesthesia, 10 paresthesia, 8 peripheral neuropathy NOS, 4 neuropathy NOS, 2 peripheral sensory neuropathy, 2 burning sensation, 2 peripheral neuropathy aggravated. Only 4 events were grade 3 or 4, and no serious AE were reported.

Thrombosis: there were 4 reports of thrombosis i.e. 2 pulmonary embolisms, 1 transient ischaemic attack and 1 cerebrovascular accident. All were considered as SAE and each patient had a significant past medical history predisposing to a risk of deep vein thrombosis or pulmonary embolism.

Cardiac events: there were 3 reports of congestive cardiac failure, 1 of cardiac failure and 1 reports of pulmonary oedema. There were 5 reports of bradycardia and 7 of syncope and 3 of each Grade 3 or 4. A total of 31 tachyarrhythmia were reported, some of them have been considered as a serious AE but none drug-related.

Hypersensitivity: there were 5 reports of hypersensitivity of which 2 were associated with a positive rechallenge.

Endocrine disorders: There were a total of 10 reports of acquired hypothyroidism. In **Study MDS-003**, acquired hypothyroidism was reported in 5.4% of the patients and 14.2% had laboratory thyroid function changes. Overall, thyroid abnormalities were of Grade 2 in severity.

Pregnancy: No cases were reported during studies. Women of childbearing potential were required to have a negative pregnancy test within 7 days of starting lenalidomide and men and women were required to use adequate methods of contraception whilst on lenalidomide.

The applicant has not provided an update on the pooled safety database during the application evaluation but the updated safety information from Studies MDS-002 and -003 did not raised any additional or new concerns.

- Serious adverse event/deaths/other significant events

Table 15 summarises the serious adverse events that were reported in $\geq 1\%$ of the patients.

Table 15 Studies MDS-001, -002 and -003 – Serious adverse events reported in 1% or more of patients

	All MDS Studies			
	25 mg n = 13	10 mg continuous n = 215	10 mg syncopated n = 180	10 mg overall n = 395
Patients with at least one AE	5 (38.5)	83 (38.6)	68 (37.8)	151 (38.2)
Blood and lymphatic system disorders				
Anaemia NOS	0 (0.0)	8 (3.7)	8 (4.4)	16 (4.1)
Neutropenia	0 (0.0)	9 (4.2)	3 (1.7)	12 (3.0)
Thrombocytopenia	0 (0.0)	4 (1.9)	5 (2.8)	9 (2.3)
Febrile neutropenia	1 (7.7)	4 (1.9)	4 (2.2)	8 (2.0)
Pancytopenia	0 (0.0)	4 (1.9)	1 (0.6)	5 (1.3)
Infections and infestations				
Pneumonia NOS	2 (15.4)	14 (6.5)	8 (4.4)	22 (5.6)
Urinary tract infection NOS	0 (0.0)	3 (1.4)	2 (1.1)	5 (1.3)
Sepsis NOS	0 (0.0)	2 (0.9)	2 (1.1)	4 (1.0)
General disorders and administration site conditions				
Pyrexia	2 (15.4)	6 (2.8)	5 (2.8)	11 (2.8)
Asthenia	0 (0.0)	2 (0.9)	2 (1.1)	4 (1.0)
Respiratory thoracic and mediastinal disorders				
Pleural effusion	0 (0.0)	4 (1.9)	2 (1.1)	6 (1.5)
Dyspnoea NOS	0 (0.0)	3 (1.4)	1 (0.6)	4 (1.0)
Pulmonary embolism	0 (0.0)	1 (0.5)	2 (1.1)	3 (0.8)
Gastrointestinal disorders				
Diarrhoea NOS	0 (0.0)	4 (1.9)	2 (1.1)	6 (1.5)
Cardiac disorders				
Cardiac failure congestive	0 (0.0)	3 (1.4)	4 (2.2)	7 (1.8)
Atrial fibrillation	0 (0.0)	3 (1.4)	3 (1.7)	6 (1.5)
Metabolism and nutrition disorders				
Dehydration	0 (0.0)	5 (2.3)	1 (0.6)	6 (1.5)

NOS, not otherwise specified

The number of on-study deaths (i.e. deaths occurring within 30 days of last dose) in the 3 MDS studies was 32 of which 5 were considered as related to lenalidomide. The causes of death were:

- pancytopenias associated with sepsis
- 1 respiratory failure
- 2 neutropenias associated with infection

Of the other reports, the causes of death were disease progression (8 deaths), cardiac events (5 deaths), respiratory infection (6 deaths), multi-organ failure (3 deaths) and other reasons.

Other significant AE: AML transformation

In **Study MDS-003**, Table 16 gives updated information on AML transformation in October 2007 as cut-off date.

Table 16 Studies MDS-003 – Long-term data on survival and AML transformation

	Overall study population n = 148	Confirmed low/int-1	
		All confirmed n = 120	Isolated del 5q n = 95
Survival follow-up information	137 (92.6)	114 (95.0)	91 (95.8)
Died	73 (49.3)	60 (50.0)	42 (44.2)
Alive	64 (43.2)	54 (45.0)	49 (51.6)
AML transformation follow-up information	128 (86.5)	106 (88.3)	86 (90.5)
No AML	96 (64.9)	81 (67.5)	70 (73.7)
AML	32 (21.6)	25 (20.8)	16 (16.8)
No AML at last observation prior to death	9 (6.1)	8 (6.7)	5 (5.3)
Lost to follow-up	2 (1.4)	2 (1.7)	2 (2.1)
Refused consent	3 (2.0)	2 (1.7)	1 (1.1)
Other/not obtained	6 (4.1)	2 (1.7)	1 (1.1)

- Laboratory findings

No clinically significant changes were noted for vital signs measurements or clinical laboratory values. This included thyroid-stimulating hormone, the thyroid function test.

No clinically important effects of lenalidomide/dexamethasone relative to placebo/dexamethasone were observed on ECG. A small number of patients in each treatment group (2 in the lenalidomide/dexamethasone group and 3 in the placebo/dexamethasone group) had a worsening (e.g., a normal finding at baseline and a clinically significant finding at the end of treatment) in their ECG from baseline to the end of treatment; the follow-up ECG abnormalities were generally not suspected by the investigators to be related to treatment with the study medications.

Little variation in body weight was observed in either treatment group during the study. Mean body weight decreased in both treatment groups during the first 6 cycles of therapy and then tended to increase after Cycle 6.

- Safety in special populations

No formal studies have been conducted to assess the effects of age, gender, race or hepatic impairment on the pharmacokinetics of lenalidomide. The available clinical data do not indicate that adjustments in the dose of lenalidomide are needed for safety-related reasons in these subpopulations. However, significantly more patients above 65 years of age withdrew from therapy due to thrombocytopenia and neutropenia and asthenia was also more frequently reported as a serious AE. Despite, no gender-related differences were found as regards withdrawal from therapy, thromboses, neutropenia and nausea were more frequently reported in women.

No data regarding overdosage are available.

- Safety related to drug-drug interactions and other interactions

Safety related to drug-drug interactions was investigated in 2 interaction studies and assessed by adverse events, clinical laboratory findings, physical examinations, vital signs, and ECG.

Warfarin interaction study

There were no clinically meaningful changes in clinical laboratory findings, physical examinations, vital signs, or ECG. The adverse events were all mild in severity and evenly divided between lenalidomide and placebo. The most frequent adverse events were dermatological and were also evenly reported by lenalidomide (35% of subjects) and placebo (41% of subjects), beginning after the warfarin dose on Day 4. As expected during warfarin therapy, elevations in prothrombin time (PT) and international normalised ratio (INR) were observed during the study. However, based on a comparison of the PT and INR values that were observed during co-administration of placebo and warfarin and those that were observed during co-administration of lenalidomide and warfarin, co-administration of lenalidomide had no effect on PT or INR. Moreover, the results of this study show no pharmacokinetic or pharmacodynamic interactions between lenalidomide and warfarin; therefore, lenalidomide and warfarin may be co-administered.

Digoxin interaction study

Only 3 mild adverse events (headache, sinus headache, somnolence) were reported by 3 (16%) of the 19 subjects dosed in this study. The adverse events occurred in the placebo group prior to digoxin administration. There were neither serious adverse events reported, nor subjects were discontinued from the study due to adverse events and all adverse events resolved without therapy.

- Discontinuation due to adverse events

A total of 23.5% of the patients discontinued treatment due to one of more adverse events and 61.3% had a dose reduction or treatment interruption, mainly due to haematotoxicity.

- Post-marketing experience

Lenalidomide was approved for the MDS indication in the United States of America on 27 December 2005, for Multiple Myeloma indication on 29 June 2006 and more recently in EU for Multiple Myeloma indication on 14 June 2007.

Safety update for lenalidomide is covering the period from 27 December 2005 to June 2007, Table 17 summarises the number of patients treated and the main indications for treatment by decreasing frequency.

Table 17 Post-marketing experience in the US – Demographic and indication

	PSUR 1 Dec 05 to Jun 06	PSUR 2 Jun 06 to Dec 06	PSUR 3 Dec 06 to Jun 07
Total number of patients	4848	10,445	13,976
Total number of women	2,070 (42.7)	4,691 (44.9)	6,305 (45.1)
Number of women of childbearing potential	80 (3.9)	245 (5.2)	355 (5.6)
Indication:			
Multiple myeloma	1,417 (29.2)	6,663 (63.8)	9,890 (70.8)
MDS	3,086 (63.7)	3,160 (30.3)	3,048 (21.8)
Malignant neoplasm prostate	73 (1.5)	105 (1.0)	127 (0.9)
Myelofibrosis	68 (1.4)	117 (1.1)	120 (0.9)
Chronic lymphoid leukaemia	12 (0.3)	31 (0.3)	111 (0.8)
Amyloidosis	18 (0.4)	52 (0.5)	89 (0.6)
Uncertain behaviour neoplasm NEC/NOS	10 (0.2)	20 (0.2)	72 (0.5)
Monoclonal gammopathy	10 (0.2)	33 (0.3)	68 (0.5)
Lymphomas NEC/Lymphomas NEC mult	10 (0.2)	27 (0.3)	67 (0.5)
Others	144 (3.0)	237 (2.3)	384 (2.8)

A total of 21,965 ADR were received by the applicant during the 3 PSUR periods regardless the source post-marketing or clinical trial reporting of which 6,898 and 5,307 were serious ADR and unlisted ADR, respectively (the remaining ADR correspond to non-serious ADR listed and unlisted).

From the post-marketing experience in the US, of a total of 1,392 reports with fatal outcome, the primary cause of death was the progression of the disease, unknown or unreported. Table 18 presents the main ADR reported over the 3 PSUR periods.

Table 18 Post-marketing experience in the US – Adverse drug experiences/reactions

	PSUR 1 Dec 05 to Jun 06	PSUR 2 Jun 06 to Dec 06	PSUR 3 Dec 06 to Jun 07
Total number of patients	4,848	10,445	13,976
Total number of ADR	4,282	9,779	9,240
Serious ADR unlisted	807 (16.6)	2,361 (24.1)	1,483 (10.6)
Non serious ADR unlisted	1,820 (37.5)	4,453 (45.5)	4,155 (29.7)
Serious ADR listed	505 (10.4)	893 (9.1)	946 (6.8)
Non serious ADR listed	1,150 (23.7)	2,072 (21.2)	2,676 (19.1)
Most frequent serious unlisted ADR			
Thrombocytopenia	219 (4.5)	545 (5.2)	512 (3.7)
Rashes	203 (4.2)	459 (4.4)	487 (3.5)
Infections	88 (1.8)	291 (2.8)	478 (3.4)
Peripheral neuropathy	64 (1.3)	268 (2.6)	335 (2.4)
Neutropenia	87 (1.8)	240 (2.3)	293 (2.1)
Thromboembolic	29 (0.6)	157 (1.5)	223 (1.6)
Renal failure	17 (0.4)	56 (0.5)	93 (0.7)
Cardiac arrhythmia	31 (0.6)	66 (0.6)	74 (0.5)
Serious haemorrhage	37 (0.8)	68 (0.7)	73 (0.5)
Hypersensitivity	23 (0.5)	66 (0.6)	72 (0.5)
Acute myeloid leukaemia	4 (0.1)	9 (0.1)	3 (< 0.1)

- Discussion on clinical safety

Since lenalidomide is a structural analogue of thalidomide, the expected safety profile could include:

- dose-related haematotoxicity, essentially neutropenia
- late peripheral neuropathies (after 6-month treatment) occurring in 1 to 70% of treated patients, more or less irreversible, and related to the total cumulated dose (beyond 50 g)
- dose-related constipation
- thromboembolic adverse events
- dose-related rash, some Steven Johnson syndromes and Lyell syndromes (exceptionally), hypersensitivity reactions, hypothyroidism and bradycardia
- major teratogenicity.

The potential teratogenicity induced by lenalidomide in human is still the main safety issue that needs further investigation. For lenalidomide no clinical data on exposed pregnancies are available. Therefore, lenalidomide is contraindicated during pregnancy. Women of childbearing potential should use effective method of contraception. If pregnancy occurs in a woman treated with lenalidomide, treatment must be stopped and the patient should be referred to a physician specialised or experienced in teratology for evaluation and advice. For male patients taking lenalidomide, there is no clinical data available on the presence of lenalidomide in human semen. Therefore male patients taking lenalidomide should use condoms if their partner is of childbearing potential and has no contraception.

Pooled safety data, including adverse events, laboratory findings, vital signs and electrocardiogram (ECG) data, Phase I/II, multicentre, open-label studies of lenalidomide were provided as evidence of the safety of the lenalidomide in treatment of MDS patients (**Studies MDS-001, -002 and -003**), 395 patients were treated with the 10-mg lenalidomide as starting dose.

The most serious reactions were:

- Grade 4 neutropenia
- Venous thromboembolism (deep vein thrombosis and pulmonary embolism).

The most frequently observed drug-related adverse events were neutropenia (60.8%), thrombocytopenia (58.8%), pruritus (33.1%), rash (28.4%), diarrhoea (25.0%), fatigue (12.8%) and constipation (12.2%). Grade 3 and 4 neutropenia occurred in 19.6 and 39.2% of patients respectively. Grade 3 and 4 thrombocytopenia occurred in 40.5 and 9.5%, respectively.

Transformation to AML has been observed in **Study MDS-003**, the estimate ranges between 16.8 to 26.3% in the population of the claimed indication. From individual case reports for all cases of AML, it appears there is no increased risk for acute leukaemia through clonal selection. Comparisons to existing registries are of limited validity; therefore, the absence of additional risk due to lenalidomide treatment is not clearly quantified.

Overall, the single arm design of the pivotal trial and possible underreporting of severe adverse events, AML transformation makes difficult to properly assess the overall safety of lenalidomide in the claimed indication. A SAG-oncology has been consulted concerning clinical safety concerns about initial leucopenia and thrombocytopenia and the potential increase in mortality and/or AML transformation:

- Initial leucopenia and thrombocytopenia: Based on a conservative estimate of the efficacy (at least approximately 50% of patients achieving transfusion independence), the acute haematological toxicity (in particular neutropenia and thrombocytopenia) is considered manageable and acceptable for patients included in the claimed indication provided adequate mention in the SPC.
- Potential increase in mortality and/or AML transformation: Given the treatment effect of lenalidomide in terms of transfusion independence and cytogenetic response one would indeed expect a lower rate of AML transformation. In view of the observed AML transformation rate in **Study MDS-003** and the absence of reliable data for comparison it is difficult to confirm or rule out a causal relationship between treatment with lenalidomide and AML transformation and it might be necessary to address this issue formally and exclude or quantify any excess risk of transformation before an informed judgement.

No formal studies have been conducted to assess the effects of age, gender, race or hepatic impairment on the pharmacokinetics of lenalidomide. However, the available clinical data do not indicate that adjustments in the dose of lenalidomide are needed for safety-related reasons in these subpopulations. Dose adjustment is recommended in case of renal impairment.

It is not known whether lenalidomide is excreted in human milk. Therefore breast-feeding should be discontinued during therapy with lenalidomide.

2.5 Pharmacovigilance

Detailed description of the Pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

Risk Management Plan

The MAA submitted a risk management plan, which included a risk minimisation plan.

The CHMP, having considered the data submitted in the MA application is of the opinion that the following risk minimisation activities are necessary for the safe and effective use of the medicinal product.

2.6 Overall conclusions, risk/benefit assessment and recommendation

Myelodysplastic syndromes are a relatively rare condition. In the less severe forms of MDS (e.g., IPSS low- and intermediate-1-risk), the goal of a treatment is to achieve symptoms alleviation through supportive care. Anaemia is treated with EPO and transfusion. Treatment with EPO is not always successful and transfusions are associated with risk of iron overload and infectious complications.

Quality

The quality of this medicinal product is considered satisfactory. The documentation provided for the active substance lenalidomide is comprehensive and adequately detailed. The pharmaceutical development is adequate for this oral formulation and took into consideration properties such as particle size and polymorphism and the stability of the active substance. The excipients are those typically used for capsule formulations. Similarly, the packaging material is well documented and no incompatibility has been noticed. The validation of the manufacturing process ensures consistency and reproducibility of the finished product. The finished product has been satisfactorily controlled and stability studies conducted under ICH conditions showed that the product is stable throughout the proposed shelf life.

Non-clinical pharmacology and toxicology

Lenalidomide has been developed based on the structure and pharmacology of thalidomide. *In vitro* data suggest that lenalidomide is much more potent. Lenalidomide was 10-1000 times more potent than thalidomide in various *in vitro* pharmacology studies of immunomodulatory, anti-proliferative, and pro-erythropoietic activities. The molecular target of lenalidomide remains unknown. *In vivo*, lenalidomide was shown to delay tumour growth and prolong survival in a mouse xenograft model with human lymphoma cells. Lenalidomide showed effect on solid tumour cell growth in two mouse models. Inhibition of angiogenesis was demonstrated in an *in vivo* model in the rat.

The primary toxicities observed after repeated oral administrations of lenalidomide were associated with the haematopoietic lympho-reticular systems and the kidneys, generally reversible after a 4- to 7-week recovery period. Rats appeared to be more sensitive to the effects on the kidneys, while cynomolgus monkeys were more sensitive to the effects on the haematopoietic systems. The NOAEL for rats in the chronic 26-week toxicity study was set at < 75 mg/kg/day. Based on AUC comparison, this dose was approximately 62-fold greater than the human daily exposure. In repeated-dose toxicity studies in monkeys, NOAEL is less than 1 mg/kg; this dose was equivalent to the human daily exposure (safety margin: 2.4).

Lenalidomide showed no evidence for genotoxicity. Further *in vitro* characterisation of the genotoxicity of the drug substance including impurities has to be performed.

Carcinogenicity studies with lenalidomide have not been conducted.

A fertility and early embryonic development study in male and female rats, with administration of lenalidomide up to 500 mg/kg/day, produced no parental toxicity and no adverse effects on fertility or early embryonic development.

Developmental toxicity studies were conducted in rats and rabbits. In rats, lenalidomide was not teratogenic at oral doses of up to 500 mg/kg/day. Nevertheless, rat species is not considered as a relevant model for thalidomide analogues.

In the rabbit, lenalidomide exhibited foetal toxicity with increased post-implantation loss, decreased foetal weight, and also an increased frequency of foetal malformations (absence of the intermediate lobe of the lung and displaced kidneys).

Based on the structural and pharmacological similarity to thalidomide and the malformations observed in the rabbit study, lenalidomide is contraindicated during pregnancy and precautions should be taken for women of childbearing potential.

The embryotoxic and teratogenic potential of lenalidomide should be further characterised in the cynomolgus monkey which is considered to be the most relevant species (see also re-examination procedure).

Efficacy

The application targets a sub-population characterised by some factors related to a better prognosis (low- and intermediate-1 IPSS classification and 5q deletion) and by other factors that could indicate an increased risk (transfusion dependency and no response to EPO).

In a single-arm, open-label study (**Study MDS-003**), transfusion independence (in 64.3% low-risk and in 57.7% int-1-risk patients) and an increase in blood haemoglobin level from baseline to the maximum haemoglobin level (median 5.5 g/dl; range, 1.1-11.4 g/dl in the 57 responders) were observed after lenalidomide treatment.

The size of this benefit is difficult to assess due to the non-comparative design of the study and some methodological problems highlighted during the GCP inspection. Non-compliance to transfusion rules predefined by the protocol has been observed in roughly 40% of patients. In addition, in these patients who were not completely followed by the investigators, additional transfusions prescribed outside the study might have impacted on efficacy results. Post-hoc sensitivity analysis performed taking into account all unexplained increases in haemoglobin did not show major difference in overall response rate for transfusion independence.

Safety

Due to the non-comparative design of the study, safety of lenalidomide was difficult to assess since the main adverse effects could also occur in MDS patients in absence of treatment with lenalidomide (disease feature).

Leucopenia and thrombocytopenia occurred relatively early in the treatment and were manageable with dose reductions. A multivariate analysis of cytopenias and response to treatment showed that patients with greater early myelosuppression were to be more likely to respond to lenalidomide treatment. Clinically-significant cytopenias in responding patients were seen early in treatment (before onset of response) or after treatment failure (loss of transfusion independence response or other evidence of MDS progression).

The incidence of AML transformations observed in the **Study MDS-003** ranged from 16.8 to 32.5% depending on the patients population considered and handling of missing data for patients who had no follow-up information. A historical comparison was not possible due to the fact that the patient population of published data does not mirror the **Study MDS-003** population. Moreover, the ongoing, placebo-controlled **Study MDS-004** will not be able to provide an answer to AML transformation incidence since a crossover to lenalidomide after 4 months is allowed by the study protocol, making the detection of a difference in overall survival or AML occurrence difficult to obtain.

User consultation

The Patient Information Leaflet (PIL) for Lenalidomide Celgene Europe (lenalidomide) has been tested in English in accordance with Articles 59(3) and 61(1) of Directive 2001/83/EC, as amended by Directive 2004/27/EC. The PIL for Lenalidomide Celgene Europe (lenalidomide) was found to contain all the necessary information in a way that is accessible and understandable to those who participated in this test.

It is considered that the tested PIL meets the requirements set for User Testing.

Risk-benefit assessment

Lenalidomide Celgene Europe provided transfusion independence in approximately two thirds of the patients with transfusion-dependent anaemia due to low- and intermediate-1 (IPSS classification) myelodysplastic syndromes associated with 5q deletion and with or without additional cytogenetic abnormalities.

The high incidence of leucopenia and thrombocytopenia -including Grade 3 or 4 toxicities in the majority of the patients- were considered as manageable with dose reduction and temporary treatment discontinuation.

However, major findings were highlighted during the GCP inspection of one investigational site indicating that there may have been an overestimation of the treatment effect (and underestimation of the toxicity). Importantly, the incidence estimate of the AML transformation in the targeted patient population is considered high in absence of reliable comparative information. Furthermore, there are uncertainties about the optimal dose and treatment duration.

The CHMP requested the SAG-oncology to answer to following 4 questions:

1. In the treatment of MDS what are the acceptable toxicities for a treatment aiming to RBC transfusions reduction and, are the reported cytopenic episodes acceptable for all patients included in the claimed indication?
2. What is the relationship between response to therapy (according to the study protocol) and duration and severity of cytopenias, and does this have an impact on the acceptability of toxicity?
3. Cases of AML constitute a concern. Based on currently available information, is there a possible/probable causal relation between lenalidomide therapy and evolution of AML, e.g., is it conceivable that suppression of the 5q- clone would allow the emergence of an AML clone (similar to emergence of “normal” haematopoiesis in responding patients)?
4. In the treatment of MDS what is the clinical importance of this risk of evolution to AML possibly related to lenalidomide treatment?

In response to questions #1 and 2, the SAG-oncology considered that following the findings of the GCP inspection, it was established that the observed effect in terms of transfusion reduction might be slightly overestimated because of occasional underreporting of transfusions outside the study centres. However, it is reasonable to assume that based on these findings a conservative estimate is that at least approximately 50% of patients will achieve transfusion independence, even outside protocol treatment. Given this effect, the acute haematological toxicity (in particular neutropenia and thrombocytopenia) is considered manageable and acceptable for patients included in the claimed indication. However, adequate mention should be given in the SPC, in particular as regards thrombocytopenia. In addition, due to the frequent need for dose reductions due to toxicity observed it is possible that the recommended dose is too high. It is essential that further studies explore lower starting doses, treatment duration (also for non-responders), aiming to improve the benefit-risk balance of the drug. Until such data are available, adequate information reflecting the existing uncertainties about optimal dose and duration of treatment should be provided in the SPC.

In response to questions #3 and 4, the SAG-oncology stated that given the effect of lenalidomide in terms of transfusion independence and cytogenetic response one would indeed expect a lower rate of AML transformation. Based on the GCP inspection findings, the available data were very sparse (both in terms of AML transformation and overall deaths) and it is difficult to conclude from the historical data from the Düsseldorf registry unless important bias in the patient selection and treatment comparison can be ruled out. However, the high rate of AML transformation observed is a concern and the risk of progression to AML is clinically important. There is at least a possible relation between lenalidomide therapy and progression to AML although there are no data to confirm or rule out a causal relationship between treatment with lenalidomide and AML transformation. Given the high rate of AML transformation observed, it will be necessary to address this issue formally and exclude or quantify any excess risk of transformation before an informed judgement on the benefit risk balance can be made.

The applicant presented a number of arguments and additional analyses to address the outstanding issues raised by the CHMP. The applicant argued that differences in baseline characteristics and in particular in terms of cytogenetic complexity and baseline transfusion burden explain, at least for an important part, the differences observed between centres in terms of AML transformation. The applicant argued that there was no clear difference between sites in terms of follow-up but that the patients recruited into the German site might have been at higher risk for AML transformation since

this centre is a MDS referral centre and therefore might have a higher proportion of patients with longer duration of disease at study entry and higher transfusion burden. Lastly, the applicant argued that long-term inspected data have been obtained mainly at the German site but that long-term data are available for most patients in the study.

The CHMP considered the arguments presented by the applicant. However, the CHMP maintained the view that due to the quality of the data presented, there remain important concerns about a high observed rate of AML transformation. Therefore, the data provided were insufficient to demonstrate a favourable 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 a 5q deletion with or without additional cytogenetic abnormalities, or an isolated deletion 5q cytogenetic abnormality, only, due to the following grounds:

1. The high incidence of transformation to AML observed in a single-arm trial is of concern since it could indicate an increased risk associated with lenalidomide. Given the non-comparative nature of the data, it is unknown if the claimed benefits outweigh the risks.
2. Major findings were highlighted during the GCP inspection of one investigational site and these observations could affect the reliability of the collected safety data, in particular the rate of AML transformation.

Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by majority decision that the risk-benefit balance of Lenalidomide Celgene Europe 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 was not favourable and therefore did not recommend granting of the marketing authorisation.

2.7 Re-examination of the CHMP opinion of 24 January 2008

Following the CHMP conclusion in January 2008 saying that the risk-benefit 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, the applicant submitted detailed grounds for the re-examination of the grounds for refusal. The applicant presented a number of arguments regarding the grounds for refusal.

Ground #1 (high incidence of transformation to AML). The Applicant:

- acknowledged the limitations inherent to the non comparative design of **Study MDS-003** and the scarce historical data available for comparisons
- stated that potential effects of lenalidomide on the risk of AML transformation have been carefully scrutinised using a number of analyses, including the most appropriate analyses currently possible, which have uniformly shown a lack of a signal of an increased risk

The patient characteristics between the German site and the US sites were similar with 2 exceptions:

- the median duration of MDS prior to inclusion in **Study MDS-003**: 3.5 years at the German site compared with 2.2 years at the US sites
- the median transfusion burden: 6 pRBC units per 8 weeks at the German site compared with 4 pRBC units per 8 weeks at the US sites, suggesting more advanced bone marrow failure in the German patients.

There was also no difference in the extent of exposure to lenalidomide or in median duration of follow-up for patients treated at the German study site versus those treated at the US study sites.

Table 19 provides 4-year cumulative incidence of AML among all centrally confirmed low/intermediate-1 risk IPSS patients.

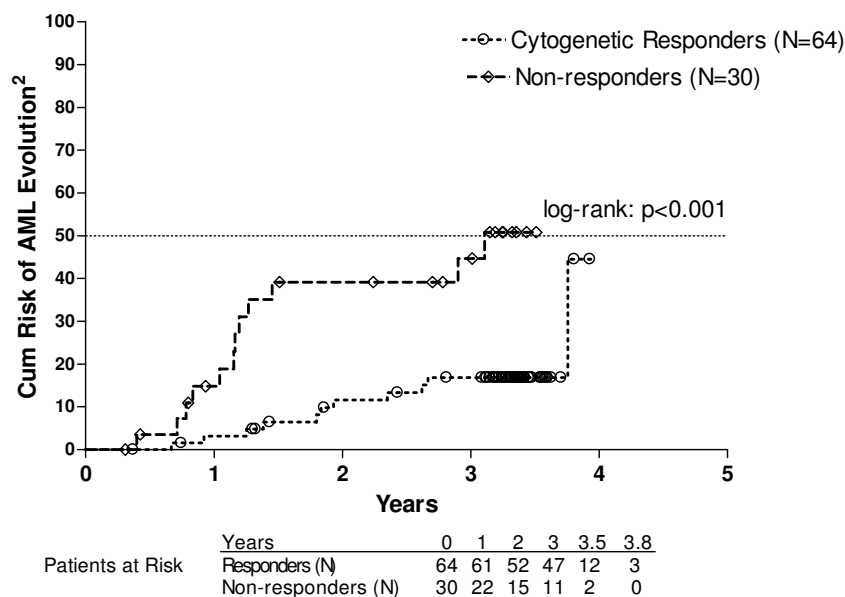
Table 19 Studies MDS-003 – 4-year cumulative incidence of AML transformations for patients with centrally confirmed low/int-1 del 5q MDS

	All n = 120	US sites n = 90	German site n = 30
AML transformation	25 (21%)	16 (18%)	9 (30%)
95%CI	14.5–29.0	11.1–27.1	16.5–48.0
IPSS			
Low (n = 55)	10 (18%)	7/41 (17%)	3/14 (21%)
Intermediate-1 (n = 65)	15 (23%)	9/49 (18%)	6/16 (38%)
Patients with <u>isolated</u> del 5q MDS	n = 95	n = 70	n = 25
AML transformation	16 (17%)	9 (13%)	7 (28%)

Results of multivariate analyses consistently indicated that AML transformation risk for **Study MDS-003** patients was associated with 2 risk factors also identified as important predicting risk factors for AML transformation in other MDS populations (Malcovati, J Clin Oncol 2005 and 2007): baseline transfusion burden and cytogenetic complexity. These analyses have further determined that the nominally higher cumulative rate of AML transformation observed at the German site in **Study MDS-003** is at least substantially explained by the higher baseline transfusion burden.

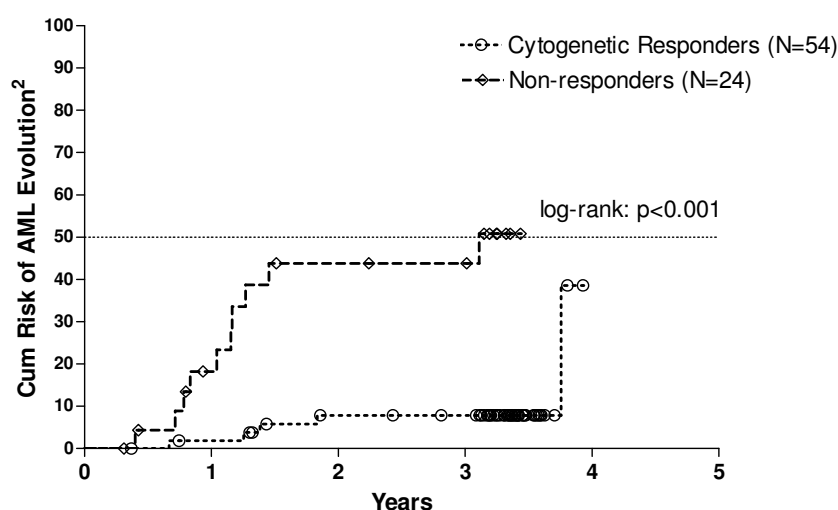
Figures 1 and 2 show the patterns of AML transformation over time in the cytogenetic responders and non responders for all 94 patients eligible for assessment of cytogenetic responses and 78 of those who had an isolated deletion 5q, respectively.

Figure 1 Studies MDS-003 – AML evolution cytogenetic response in all patients with centrally confirmed low/int-1 del 5q MDS



[1] Includes deletion 5q, transfusion-dependent MDS-003 patients who had Low/Intermediate-1 IPSS risk MDS confirmed by independent central review.
 [2] Kaplan-meier method.

Figure 2 Studies MDS-003 – AML evolution cytogenetic response patients with centrally confirmed low/int-1 isolated del 5q MDS



	Years	0	1	2	3	3.5	3.8
Patients at Risk	Responders (N)	54	52	45	43	12	3
	Non-responders (N)	24	17	11	10	1	0

[1] Includes transfusion-dependent MDS-003 patients who had an Isolated deletion 5q abnormality and Low/Intermediate-1 IPSS risk MDS confirmed by independent central review.

[2] Kaplan-meier method.

The relationship between lenalidomide exposure and AML transformation risk was investigated. Table 20 summarises the findings.

Table 20 Studies MDS-003 - Incidence rates, cumulative incidence and hazard ratios for cumulative dose of lenalidomide

Cumulative dose (mg)	Number of patients at risk	AML	Person-days	Rate/10 ⁵ person-days	Hazard ratio ^b	95% CI
Patients with centrally confirmed low/int-1 del 5q MDS						
1- 540	31	5	12,415	40.27		
541 - 1670	29	7	19,409	36.07	0.896	0.28 - 3.09
1671 - 4015	30	10	31,034	32.22	0.800	0.28 - 2.59
4016 - 12530	30	3	35,603	8.43	0.21	0.04 - 0.91
TOTAL	120	25	98,461	25.39		
Patients with centrally confirmed low/int-1 isolated del 5q MDS						
1- 540	23	5	8,609	58.08		
541 - 1670	24	6	15,046	39.88	0.69	0.20 – 2.44
1671 - 4015	24	5	26,339	18.98	0.33	0.09 – 1.22
4016 - 12530	24	0	29,146	0	0	0.00 – 0.24
TOTAL	95	16	79,140	20.22		

^b Each quartile is compared to the first quartile (lowest exposure group, i.e., 1-540 mg)

The overall rate of AML transformation is slightly higher in the patient population of IPSS low/intermediate-1 MDS patients (25.39 per 100,000 person-days) than those with isolated del 5q (20.22 per 100,000 person-days). Hazard ratios are consistent with decreasing AML transformation rates associated with higher cumulative doses of lenalidomide and the comparisons of the highest with the lowest quartiles of cumulative dose in both study populations attain statistical significance. These findings are not consistent with the hypothesis that higher cumulative doses of lenalidomide might be associated with an increase in the AML transformation rate.

The baseline prognostic factors including IPSS permitted analyses of the risk for AML transformation and mortality between data of 120 **Study MDS-003** patients with transfusion-dependent low/intermediate-1 risk MDS and data obtained from 59 patients with similar characteristics of the Düsseldorf Registry.

The overall 4-year cumulative incidence of AML was similar: 20% for **Study MDS-003** and 19% for the Registry (RR = 1.07; 95% CI 0.56–2.04; p = 0.8433) and as well within IPSS categories (IPSS low 16% versus 10%, p = 0.42; IPSS intermediate-1 23% vs. 29%, p = 0.58). Similar conclusions were reached when 4-year mortality risk (IPSS low 42% vs. 35%, p = 0.57; IPSS intermediate-1 55% vs. 54%, p = 0.87).

A finalised Cox proportional hazards model identified IPSS risk group (HR = 2.29; p = 0.021) and baseline neutrophil count (HR = 1.14; p = 0.104) as risk factors that significantly affected the rate of AML transformation. The final model demonstrated that there was no significant difference in the rate of AML transformation between **Study MDS-003** and Registry patients (HR = 1.07, p = 0.863).

With regard to mortality, a Cox proportional hazards model identified age (HR = 1.04; p ≤ 0.001), cytogenetic complexity (HR = 1.76; p = 0.020) and FAB classification (HR = 1.58; p = 0.096) as risk factors that significantly affect the mortality rate. The final model demonstrated that there was no significant difference in the mortality rate between **Study MDS-003** and Registry patients (HR = 0.862; p = 0.576).

Clonal evolution (i.e., development of additional changes in the del 5q clone itself) likely represents the most common mechanism leading to AML transformation in patients with del 5q MDS, however an acceleration of clonal evolution in lenalidomide-treated del 5q MDS patients is unlikely since:

1. lenalidomide suppresses the del 5q clone in the substantial majority of patients, based on findings in patients with repeated cytogenetic analyses
2. lenalidomide suppresses the growth of certain malignant cell lines in preclinical studies, and has not been found to be a growth factor for any malignant cell lines
3. lenalidomide is not genotoxic, mutagenic, or clastogenic in non-clinical models
4. AML transformation has been more commonly observed in patients who have not evidenced a cytogenetic response to lenalidomide treatment and who have frequently had limited exposure to this drug
5. the observed rate of clonal evolution was as expected based on literature reports, including findings in a cohort of del 5q MDS patients at the Mayo Clinic.

Overall evaluations of the observed pattern of AML transformation events in **Study MDS-003** and other clinical and non-clinical data provide a significant weight of evidence that substantially mitigates the likelihood of any clinically meaningful risk that would outweigh the clear benefit of lenalidomide to induce durable transfusion independence in the targeted population of isolated del 5q transfusion-dependent, low/int-1 IPSS risk MDS.

Ground #2 (GCP inspection findings). The Applicant:

- acknowledged the GCP deficiencies identified by the EMEA inspection of the German study site within **Study MDS-003**, has implemented corrective actions and is of the opinion that the issues raised have been acceptably resolved in particular the 4 critical findings related to safety, aside from the question of a possible increased risk of AML transformation and completeness of reporting
- stated that crucial safety information has been reported accurately

- has not identified any discrepancies suggesting any under-reporting of events of AML transformation or death which supported by conclusion reached by the US FDA following inspection of 4 sites of **Study MDS-003**, including the German site.

Therefore, the deviations noted at the GCP inspection have not adversely affected the reporting of AML cases and do not indicate any lack of reliability of the information available for review regarding AML transformation events occurring in **Study MDS-003** patients.

Concerning teratogenicity, on 19th March 2008, the Applicant informed of the preliminary results of teratogenicity study in monkeys.

The CHMP requested the SAG-Oncology to answer to following questions:

- A. In the context of this re-examination, the experts are invited to provide their views on the following CHMP grounds for refusal, taking into account applicant's responses:
1. The high incidence of transformation to AML observed in a single-arm trial is of concern since it could indicate an increased risk associated with lenalidomide. Given the non-comparative nature of the data, it is unknown if the claimed benefits outweigh the risks.
 2. Major findings were highlighted during the GCP inspection of one investigational site and these observations could affect the reliability of the collected safety data, in particular the rate of AML transformation.

The SAG-Oncology has no comment on the grounds for refusal which reflects the conclusion of the SAG-Oncology meeting held in May 2007. Having considered the applicants grounds for re-examination, there was no fundamental disagreement CHMP grounds for refusal.

- B. Given the applicant's claims and argumentations, the experts are invited to also comment on the following specific issues regarding the possible benefit of lenalidomide in treatment of patients transfusion dependent anaemia due to low- or intermediate-1 –risk MDS associated with an isolated deletion 5q cytogenetic abnormality:
1. The applicant now applies for an indication of a subgroup within the study population. While these results in a subgroup, which has not been prospectively defined in this small, open-label, uncontrolled study, raise interest which would warrant further investigations, the SAG-Oncology is asked to discuss whether these results can already be considered confirmatory evidence for patient benefit.

The pitfalls of the design, conduct and analysis of the trial have been highlighted on numerous occasions. Although due to these deficiencies the data cannot be considered as “confirmatory”, they are nevertheless convincing in terms of establishing an effect in terms of transfusion independence for the subgroup. However, the magnitude of the effect is more uncertain due to these deficiencies. Assuming that the need for transfusions does not change dramatically as opposed to baseline, one could expect that about 10 to 20 transfusions would be avoided for at least 50% of the patients, over a period of at least two years. There remain also a number of open questions related for example to the optimal dose and the treatment duration for both responders and non-responders.

2. Although based on currently available information, the causal relation between lenalidomide therapy in patients with isolated del 5q syndrome and evolution of AML is unlikely, such a risk cannot be excluded, as Study MDS-003 was not designed to address long-term efficacy and safety of lenalidomide. Please discuss potential mechanisms (other than clonal evolution) how lenalidomide could contribute to such a risk.

It is difficult to speculate what are the potential mechanisms that could contribute to development of AML in patients with isolated del 5q syndrome. The mechanism of action of lenalidomide in MDS is not known. One can hypothesise that clonal evolution would play a

greater role in complex abnormalities but less so in the isolated subgroup but there are no data (neither non-clinical nor clinical) to confirm this hypothesis.

3. AML transformation has been more commonly observed in patients who have not evidenced a cytogenetic response to lenalidomide treatment and who have frequently had a limited exposure to this drug. Does this observation have implications for the target indication isolated del 5q, e.g., restriction to the '5q- syndrome' (with less than 5% BM blasts)?

Although the numerical differences are noted, it is difficult to agree on the significance of this finding because of the number of different datasets and analyses and the small size of the subsets. In any case, even if true, it is difficult to conclude how this would have important implications for the target indication.

4. Considering the possible increased risk of transformation into AML, does the SAG-Oncology consider the chosen endpoint "RBC transfusion independence" (defined as an interval without red blood cell transfusions of at least 8 weeks) to be sufficient for establishing a positive benefit-risk relationship for lenalidomide on the basis of a single uncontrolled study?

As stated in the answer to question #1, the SAG agreed that the endpoint chosen is adequate and allows concluding that lenalidomide is associated with a clear benefit due to durable avoidance of transfusions for at least half of the patients. However, this benefit must be balanced against the risk of AML transformation. In the context of a relatively indolent disease any excess risk of AML transformation is not acceptable, particularly if there is no established benefit in terms of leukaemia-free survival and overall survival.

A prevalent view was that the incidence of AML transformation in patients treated with lenalidomide was high and cannot be clearly explained by patient, prior treatment, disease characteristics or centre differences. Thus, the observed cases of AML transformation are of concern and the risk of AML transformation for lenalidomide in the target population seemed unacceptably high. According to the prevalent view it was impossible to establish positive benefit-risk balance due to the risk of transformation to AML.

According to one opposing view, the data do not establish a significant risk of AML and the apparent excess risk is probably due to a number of factors such as the play of chance and the inclusion bias of more advanced patients in one of the centres. According to this view the observed cases of AML do not constitute a major concern although they warrant to be monitored and to be further investigated. According to this view based on the data available it is already possible to conclude on a positive benefit-risk balance due to the large benefit in terms of transfusion independence.

5. If a marketing authorisation for the indication isolated del 5q MDS would be recommended by the CHMP, should the company be committed to perform studies to address risk of transformation to AML, e.g., by requirement of regular cytogenetic and molecular studies.

The SAG-Oncology was unanimously of the opinion that additional data are needed to rule out or at least to re-assure about the risk of AML transformation. There were discussions on which type of data could be required for providing reassurance.

The ongoing trial, Study MDS-004, with results expected in August-September 2008 and additional molecular and cytogenetic studies might provide some reassurance in this respect, although it is possible that this study will not in itself bring conclusive information about the risk of AML transformation. It was acknowledged that it might be difficult to conduct very large, randomised trials to rule out small differences in AML transformation in this indication due to the large sample size needed in a rare condition and the window of opportunity for conducting such trials. Unfortunately, it would also be probably impossible to extrapolate from the results observed in other indications (e.g., myeloma).

6. Alternatively, would the SAG-Oncology agree that even in the absence of a plausible mechanism of AML induction for safety reasons it would be prudent for the company to fully investigate any possible increased risk of AML transformation prior to marketing in a study using time-to-AML as more appropriate endpoint to establish a positive benefit-risk relationship?

With one exception, the SAG-Oncology agreed for the need to rule out a higher risk of AML transformation. In the absence of reassurance about that risk, it is impossible to conclude on a positive benefit-risk balance.

Overall conclusion on grounds for re-examination

Study MDS-003 was planned as an uncontrolled, Phase 2 study initially for 36 patients based on very limited information from an earlier study that included 10 patients with MDS del 5q with encouraging cytogenetic results. Study objectives were the evaluation of the efficacy of lenalidomide to achieve haematopoietic improvement and safety in patients with low- or intermediate-1 risk IPSS MDS associated with a del (5q31-33) cytogenetic abnormality. The study was designed with an inclusion criterion for documentation of transfusion dependence (2 or more packs of RBC within 8 weeks prior to first dose of lenalidomide) and follow-up of patients was restricted to 30 days after study. Time related endpoints were not included in the study protocol.

Reported efficacy results after lenalidomide treatment were transfusion independence for at least 56 days 60.6% (57/94, 94 out of 148 treated) in the mITT population, an increase in blood haemoglobin level from baseline to the maximum haemoglobin level of 5.5 g/dl (range 1.1-11.4 g/dl) in the 57 responders and major cytogenetic responses in 32.4% (22/68) evaluable mITT patients.

As for the initial opinion, despite post-hoc sensitivity analyses, the size of this benefit is difficult to evaluate due to the study design and conduct highlighted during the GCP inspection.

Similarly, due to the design of the study (non-comparative, absence of long-term prospectively planned safety data collection) and GCP observations (restrictive rules for AE reporting, under-reporting of SAE and death and expedited actions related to AML transformations) the safety of lenalidomide is difficult to assess.

In **Study MDS-003**, the observed incidence of AML transformations ranged from 16.8 to 32.5% depending on the patients population considered and handling of missing data for patients who had no follow-up information. A historical comparison was not possible due to the fact that the patient population of published data does not mirror the **Study MDS-003** population.

Thus, concerning the grounds for negative opinion, having considered the arguments presented by the applicant and the answers from the SAG, the CHMP maintained the view that due to the quality of the data presented, there remain important concerns about a high observed rate of AML transformation. Therefore, the data provided were insufficient to demonstrate a favourable 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 a 5q deletion with or without additional cytogenetic abnormalities, or an isolated deletion 5q cytogenetic abnormality, only, due to the following grounds:

1. The high incidence of transformation to AML observed in the single-arm trial is of concern since it could indicate an increased risk associated with lenalidomide. Given the non-comparative nature of the data, there is insufficient evidence to establish that the benefits outweigh the risks.
2. Major findings were highlighted during the GCP inspection of one investigational site and these observations could affect the reliability of the collected safety data, in particular the rate of AML transformation.

Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus that the risk-benefit balance of Lenalidomide Celgene Europe 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 was not favourable and therefore did not recommend granting of the marketing authorisation.