30 May 2013
EMA/CHMP/427059/2013
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Pomalidomide Celgene

International non-proprietary name: **pomalidomide**

Procedure No. EMEA/H/C/002682

Note

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

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7523 7455
E-mail info@ema.europa.eu **Website** www.ema.europa.eu

Product information

Name of the medicinal product:	Pomalidomide Celgene
Applicant:	Celgene Europe Limited 1 Longwalk Road, Stockley Park, Uxbridge, UB11 1DB, United Kingdom
Active substance:	pomalidomide
International Nonproprietary Name/Common Name:	pomalidomide
Pharmaco-therapeutic group (ATC Code):	Immunomodulating agent L04AX06
Therapeutic indication:	Pomalidomide Celgene in combination with dexamethasone is indicated in the treatment of adult patients with relapsed and refractory multiple myeloma who have received at least two prior treatment regimens, including both lenalidomide and bortezomib, and have demonstrated disease progression on the last therapy.
Pharmaceutical form:	Capsule, hard
Strengths:	1 mg, 2 mg, 3 mg and 4 mg
Route of administration:	Oral use
Packaging:	blister (PVC/PCTFE)
Package size(s):	21 capsules

Table of contents

List of abbreviations

AE	Adverse event
ASCT	Autologous Stem Cell Transplant
ATE	Arterial thrombotic events
BCP-ALL	Human B cell precursor acute lymphoblastic leukaemia
BM	Bone marrow
CEP	Certificate of suitability European Pharmacopoeia
CI	Confidence interval
CR	Complete response
CRBN	Protein cereblon
DMSO	Dimethyl sulfoxide
DOR	Duration of response
DVT	Deep vein thrombosis
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EU	European Union
FTIR	Fourier transform infrared spectroscopy
GC	Gas chromatography
HD-Dex	High-dose dexamethasone
HPLC	High Performance Liquid Chromatography
ICH	International conference on harmonization
ICP-MS	Inductively coupled plasma mass spectrometry
IFM	Intergroupe Francophone du Myélome
IMWG	International Myeloma Working Group
IR	Infrared spectroscopy
IRAC	Independent Review Adjudication Committee
KF	Karl Fischer

MM	Multiple myeloma
MR	Minor response
MTD	Maximum tolerated dose
NMR	Nuclear magnetic resonance
OS	Overall survival
PD	Progressive disease
Ph.Eur.	Pharmacopoeia Europea
PFS	Progression free survival
PR	Partial response
PCTFE	polychlorotrifluoroethylene
PVC	polyvinyl chloride
QbD	Quality by Design
QD	Once daily
QOD	Every other day
RH	Relative humidity
RMP	Risk Management Plan
RRMM	Relapsed/refractory multiple myeloma
SAE	Serious adverse event
SCT	Stem Cell Transplant
SD	Stable disease/Standard deviation
SmPC	Summary of Product Characteristics
SOC	System organ class
SPM	Second primary malignancy
TEAE	Treatment-emergent adverse event
TSE	Transmissible spongiform encephalopathy
TTP	Time to progression
VGPR	Very good partial response
VTE	Venous thromboembolism

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Celgene Europe Limited submitted on 29 May 2012 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Pomalidomide Celgene, through the centralised procedure falling within the Article 3(1) and point 4 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 15 December 2011.

Pomalidomide Celgene, was designated as an orphan medicinal product EU/3/09/672 on 8 October 2009. Pomalidomide Celgene was designated as an orphan medicinal product in the following indication: treatment of multiple myeloma.

Following the CHMP positive opinion on this marketing authorisation, the Committee for Orphan Medicinal Products (COMP) reviewed the designation of Pomalidomide Celgene as an orphan medicinal product in the approved indication. The outcome of the COMP review can be found on the Agency's website ema.europa.eu/Find medicine/Rare disease designations.

The applicant applied for the following indication:

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

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain tests or studies.

Information on Paediatric requirements

Pursuant to Article 7of Regulation (EC) No 1901/2006, the application included an EMA Decision CW/1/2011 on the granting of a class waiver.

Information relating to orphan market exclusivity

Similarity

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

Applicant's request(s) for consideration

New active Substance status

The applicant requested the active substance pomalidomide contained in the above medicinal product to be considered as a new active substance in itself, as the applicant claims that it is not a constituent of a product previously authorised within the Union.

Protocol Assistance

The applicant did not seek Protocol Assistance at the CHMP.

Licensing status

The product was not licensed in any country at the time of submission of the application.

Pomalidomide has been given a Marketing Authorisation in the USA on 8 February 2013 .

A new application was filed in the following country: Switzerland.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Robert James Hemmings Co-Rapporteur: Arantxa Sancho-Lopez

CHMP Peer reviewer: Jens Ersbøll

The application was received by the EMA on 29 May 2012.

- The procedure started on 20 June 2012.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 7 September 2012. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 12 September 2012.
- A consultation meeting of Patients' and Thalidomide stakeholders' organisations took place at the EMA on 9 October 2012 to comment on the Risk Management Plan, the package leaflet and the labelling.
- During the meeting on 18 October 2012, 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 18 October 2012.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 18 January 2013.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 18 February 2013.
- In March 2013, a second, written consultation of Patients' and Victims' organisations was

held to comment on the revised Risk Management Plan, the package leaflet and the labelling.

- During the PRAC meeting on 7 March 2013, the PRAC adopted an RMP Advice and assessment overview.
- The Rapporteurs circulated the updated Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 18 March 2013.
- During the CHMP meeting on 21 March 2013, the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 26 April 2013
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the list of outstanding issues to all CHMP members on 7 May 2013.
- The Rapporteurs circulated the updated Joint Assessment Report on the applicant's responses to the list of outstanding issues to all CHMP members on 13 May and 24 May 2013.
- During the PRAC meeting on 16 May 2013, the PRAC adopted an RMP Advice and assessment overview.
- During the meeting on 30 May 2013, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Pomalidomide Celgene.
- The CHMP adopted a report on similarity of Pomalidomide Celgene with Revlimid and Thalidomide Celgene on 30 May 2013.

2. Scientific discussion

2.1. Introduction

Multiple myeloma (MM) is a rare and incurable disease that is characterised by the accumulation of clonal plasma cells in the bone marrow (BM) and accounts for 10% of all haematological malignancies. In Europe, there are approximately 27,800 new cases each year. The median age of patients at diagnosis is 65 years and the disease has a typical course characterised by a chronic phase lasting several years, and an aggressive terminal phase. Due to the availability of new agents in recent years including thalidomide, bortezomib and lenalidomide, and autologous stem cell transplant (ASCT), the 5-year survival rate has improved to 40% - 50%.

The clinical features of MM are varied but the most common criteria used in diagnosis of symptomatic MM are the presence of neoplastic plasma cells comprising greater than 10% of BM cells or presence of a plasmacytoma; paraprotein (M protein) in the serum and/or urine; and evidence of related organ or tissue impairment due to plasma cell disorder. Symptomatic MM, signalling the necessity for treatment, is typically manifested by hypercalcaemia, renal

insufficiency, anaemia, and bone lesions (CRAB). This deterioration leads to progressive morbidity and eventual mortality by infection and causes significant skeletal destruction, and less commonly, neurological complications and hyperviscosity. The prognosis depends on a variety of factors including age and stage of MM at time of diagnosis.

Therapies for MM currently consist of the following 6 classes of agents: proteasome inhibitors (bortezomib), immunomodulatory medicinal products (thalidomide, lenalidomide), corticosteroids, alkylators, anthracyclines, nitrosoureas (to a lesser extent), plus high-dose chemotherapy and transplantation for those who are eligible. There is currently no generally accepted standard treatment. First line treatment options should contain at least one of the novel therapies followed by ASCT if indicated.

However, the disease remains fatal, as patients inevitably progress and will relapse. Although patients with relapsed disease can achieve responses to subsequent anti-myeloma regimens, the duration of response typically decreases with successive relapses until resistant disease develops.

The following are definitions of relapsed and refractory disease by the International Myeloma Working Group (IMWG):

Relapsed Disease: Previously treated myeloma patients who, after a period of being off-therapy, require salvage therapy but do not meet criteria for "primary refractory" or "relapsed-and-refractory" categories, as outlined below.

Refractory Disease: MM that is non-responsive while on therapy or progresses within 60 days of last therapy. Relapsed-and-refractory myeloma is defined as relapse of disease in patients who achieve minor response (MR) or better, and then either become non-responsive while on salvage therapy, or progress within 60 days of last therapy. Primary refractory myeloma refers to patients who have never achieved an MR with any therapy.

The main considerations for choosing the optimal treatment for a patient with relapsed refractory MM (RRMM) include prior therapy, age, physical condition and presence of aggressive features like extramedullary disease, pancytopenia or rapid increase in tumour load/bone lesions, and cytogenetic profile. The goal is to control the disease for as long as possible, since no treatment is curative.

Bortezomib and lenalidomide-based regimens are the most commonly used agents in the treatment of relapsed or refractory MM in combination with corticosteroids, and sometimes an alkylator or with an anthracycline. Corticosteroids (pulsed or weekly dexamethasone) are recommended for use in combinations with most products.

Refractory disease can sometimes be treated with a particular agent to which resistance has developed if the agent is used in conjunction with other compounds that produce synergistic anti-MM effect or at a different posology. At second or subsequent relapses, usually after the patient has been treated with bortezomib and at least one immunomodulatory agent, there are limited options, and once patients have become refractory to both of them (double refractory), the outcome is very poor.

Pomalidomide belongs to the pharmacotherapeutic group of immunomodulating agents which also includes thalidomide and lenalidomide with apparent limited cross resistance within the class and with the potential to improve patient outcome in a relapsed/refractory setting.

The exact mechanism of action of pomalidomide is unknown but results in tumouricidal, immunomodulatory, anti-angiogenic, and anti-inflammatory properties seen also with other drugs of the same class. When used in combination with dexamethasone a synergy in anti-proliferative activity is shown. In addition, pomalidomide inhibits proliferation of lenalidomide resistant MM cells.

Celgene Europe Ltd has applied for Pomalidomide Celgene in combination with dexamethasone to be indicated in the *treatment of adult patients with relapsed and refractory multiple myeloma who have received at least two prior treatment regimens, including both lenalidomide and bortezomib, and have demonstrated disease progression on the last therapy.*

2.2. Quality aspects

2.2.1. Introduction

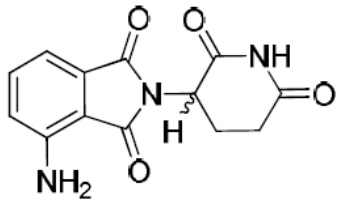
The finished product is presented as hard gelatin capsules containing 1mg, 2 mg, 3 mg or 4mg of pomalidomide as active substance.

Other ingredients are: mannitol, pregelatinised starch and sodium stearyl fumarate. The capsule shells are made of gelatin and contain different colorants depending on the strength, as described in section 6.1 of the Summary of Product Characteristics (SmPC).

The product is available in polyvinyl chloride (PVC)/ polychlorotrifluoroethylene (PCTFE) blisters with push through aluminium foil.

2.2.2. Active Substance

The chemical name of pomalidomide is (RS)4-Amino-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione and has the following structure:



The structure of pomalidomide has been confirmed by elemental analysis, mass spectrometry (electrospray ionization), nuclear magnetic resonance (1H-NMR and 13C-NMR) spectroscopy, UV spectrophotometry, and infrared spectrophotometry (FTIR-KBr).

The active substance is a crystalline non-hygroscopic yellow powder, which is slightly soluble in acetone, acetonitrile, methylene chloride, methyl ethyl ketone and tetrahydrofuran; very

slightly soluble in absolute ethanol, ethyl acetate, heptane, methanol, 2-propanol and toluene; and practically insoluble in water.

Pomalidomide has one stereochemical centre. The active substance is obtained as a racemic mixture, no optical rotation is observed. X-Ray Powder Diffraction (XRPD), Differential Scanning Calorimetry (DSC), thermogravimetry (TGA) studies conducted have identified one single polymorphic form of pomalidomide, designated as Form A.

In relation to the new active substance claim, although pomalidomide is a structural analogue of lenalidomide and thalidomide, it cannot be derived from any of these compounds in a simple synthetic modification or *in vivo*. Therefore, pomalidomide is not considered to be a derivative of lenalidomide or thalidomide. Pomalidomide is not a salt, ester, ether, isomer, mixture of isomers, complex or derivative of a chemical substance previously authorised as a medicinal product in the European Union and is considered to be a new active substance in itself.

Manufacture

The active substance is supplied by two manufacturers. Pomalidomide is synthesized in two main steps using commercially available well defined starting materials with acceptable specifications. The first step consists of a coupling reaction in which the starting materials react to form crude pomalidomide. The second step is a purification process consisting on filtration, crystallization and drying to obtain the final drug substance.

As stated above, pomalidomide molecule has one stereochemical centre, which is introduced during the coupling step (step 1). The synthetic process yields a racemic mixture of pomalidomide (1:1 R:S) and a single polymorphic form, form A, is obtained.

The manufacturing process has been developed using a combination of conventional univariate studies and elements of QbD such as risk assessment and design of experiment (DOE) studies to gain process understanding and knowledge. No design space has been applied for.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances. Potential and actual impurities have been well discussed with regards to their origin and characterised.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented.

Specification

The active substance specification includes tests for: appearance (visual examination), identification (IR), assay (HPLC), related impurities (HPLC), residual solvents (GC), water content (KF), sulphated ash (Ph.Eur.), heavy metals (ICP-MS), and particle size (Ph. Eur.).

The absence of a test to control chirality has been adequately justified. The enantiomeric purity of the racemic starting material is controlled by its own specification, and there are no asymmetric reagents, solvents, chromatography, or resolution used in the synthesis of pomalidomide that would enrich the stereochemistry. In addition, the racemic content of pomalidomide was confirmed using chiral HPLC on the 24 month stability time point samples.

The analytical methods used have been adequately described and(non-compendial methods appropriately validated in accordance with the ICH guidelines.

Batch analysis data on 3 commercial scale batches of the active substance manufactured at each of the proposed manufactured sites are provided. The results are within the specifications and consistent from batch to batch.

Stability

Stability data on two commercial scale batches of active substance from one of the proposed manufacturers and three commercial scale batches from the other proposed manufacturer stored in the intended commercial package for 12 months under long term conditions at 25 ºC / 60% RH and for up to 6 months under accelerated conditions at 40 ºC / 75% RH according to the ICH guidelines were provided.

Supportive stability data on two pilot scale batches stored for up to 60 months at long term conditions(25 ºC / 60% RH) and 6 months at accelerated conditions (40 ºC / 75% RH) from an additional manufacturer (not proposed as commercial manufacturing site, but using the proposed commercial manufacturing process) have been submitted.

Additional supportive stability data (24 months under long term-conditions and 6 months at accelerated conditions) on three commercial scale batches manufactured by one of the registered manufacturers have been presented. These batches were prepared using a similar manufacturing process as the one proposed for commercialization, with the exception of the recrystallization solvents used in the final step (ethanol/DMSO instead of water/DMSO).

Photostability testing following the ICH guideline Q1B was performed on one batch, showing that pomalidomide is photo-stable.

Results on stress conditions under acid and base heated stress conditions, thermal, and oxidation stress conditions were also provided on one laboratory scale batch manufactured by the synthetic route proposed for commercial use with the exception of the final recrystallization solvents.

The following parameters were tested*:* description, related substances and assay. The analytical methods used in the stability studies were the same as those used for release testing of commercial products.

No significant changes where observed in any of the primary, or supportive pomalidomide stability study results during the evaluated periods.

The stability results indicate that the drug substance manufactured by the proposed supplier(s) is sufficiently stable, and indicate that Form A is maintained during the re-test period. The stability results justify the proposed retest period in the proposed container.

2.2.3. Finished Medicinal Product

Pharmaceutical Development

The aim of the pharmaceutical development was to formulate hard capsules containing 1 mg, 2 mg, 3 mg and 4mg pomalidomide per capsule, respectively.

Several formulations were evaluated during development. The first formulation developed contained anhydrous lactose, microcrystalline cellulose, croscarmellose sodium, and magnesium stearate. In an effort to improve processing, anhydrous lactose was replaced with anhydrous dibasic calcium phosphate, and other excipients were changed accordingly. The revised formulation contained pomalidomide, anhydrous dibasic calcium phosphate, pregelatinized starch, croscarmellose sodium, and sodium stearyl fumarate. All the batches met the specification. However some instability was detected at accelerated and room temperature conditions. To overcome the instability of this formulation, additional formulations were studied.

Based on the development study results, the proposed formulation was selected. The proposed capsule strengths use two common blends comprised of the same excipients, varying in the proportion of drug substance and two excipients, mannitol and sodium stearyl fumarate. Pomalidomide capsules, 1 mg and 2 mg, are dose proportional and utilize a common blend. Pomalidomide capsules, 3 mg and 4 mg, are dose proportional and utilize another common blend.

A simple blending and encapsulation process has been selected. The effect of the active substance particle size distribution on dissolution and content uniformity is controlled by setting appropriate specification limits.

The commercial formulation is identical to the clinical formulation; the only difference between them is the capsule shell dye components. The clinical reddish-brown capsule shells contain iron oxide and the commercial capsule shells contain various iron oxides and FD&C dyes.

All excipients are well known pharmaceutical ingredients typically used in capsule formulations and their quality is compliant with Ph. Eur standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC.

Compatibility of the excipients with the drug substance on the proposed capsule formulations has been demonstrated.

The primary packaging is polyvinyl chloride (PVC)/ polychlorotrifluoroethylene (PCTFE) blisters with push through aluminium foil. The material complies with Ph.Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Adventitious agents

Gelatine obtained from bovine sources is used in the product. Valid TSE CEP from the suppliers of the gelatine used for the manufacture of the capsule shells is provided.

No other excipients derived from animal or human origin are used.

Manufacture of the product

The manufacturing process consists of four main steps. In brief, pomalidomide is blended with mannitol and a portion of pregelatinised starch (Blend 1), further blended with the remainder of the pregelatinised starch (Blend 2) and mixed with sodium stearyl fumarate (Blend 3) which is then filled into the hard gelatin capsule shells and packed into blisters.

Adequate in-process controls have been set up and a detailed description along with a process flow scheme have been provided.

Since the active substance content per unit dose product is below 2% of the composition in all cases, according to the Guideline on Process Validation (EMA/CHMP/CVMP/QWP/70278/2012-Rev1) the manufacturing process is considered a non-standard process, and therefore validation data for all proposed manufacturing sites have been submitted. These data demonstrate that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this manufacturing process.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form, namely: appearance (visual examination), identification (UV-Vis, HPLC), assay (HPLC), related impurities (HPLC), uniformity of dosage units (Ph. Eur.), dissolution (HPLC) and microbial limits (Ph. Eur).

Batch analysis results are provided for three commercial scale batches of each strength manufactured at the two proposed manufacturing sites batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Analytical methods have been fully validated in accordance with the EU/ICH Validation Guidelines, and have proven to be stability indicating.

Stability of the product

Stability data of three batches of finished product per strength manufactured by one of the proposed manufacturers stored under long term conditions for 18 months at 25 ºC /60% RH and for up to 6 months under accelerated conditions at 40 ºC/75% RH according to the ICH guidelines were provided. The batches of pomalidomide capsules are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Registration stability batches represent the selected colour combinations for the commercial capsules shells, except for the 1 mg capsule which has a medium blue body instead of the yellow body proposed for the commercial formulation. The 3 mg and 4 mg proposed commercial capsules are the same colour as the registration stability batches however the dye composition used in the capsule shells were modified to reduce the likelihood of fading.

In addition, supportive stability studies for pomalidomide clinical capsules in reddish-brown coloured (iron oxide) capsule shells have been carried out for up to 36 months storage for 1 mg and 2 mg and up to 18 months for 3 mg pomalidomide capsules stored under long-term (25 ºC/60% RH) and 6 months under accelerated (40 ºC/75% RH) conditions. Samples were tested

for appearance, assay, related impurities, and dissolution. The analytical procedures used are stability indicating.

For all batches of all strengths in the proposed container closure there were no significant changes or trends in any of the parameters monitored under long term or accelerated conditions.

All data were well within the proposed specification and no significant changes were observed.

In addition, one batch of each strength was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. These studies showed that pomalidomide capsules are photostable when stored in the proposed container.

Based on available stability data, the shelf-life stated in the SmPC with no storage conditions is acceptable.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

The applicant has applied QbD principles in the development of the active substance. However, no design spaces were claimed for the manufacturing process of the active substance.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.2.6. Recommendation(s) for future quality development

Not applicable.

2.3. Non-clinical aspects

2.3.1. Introduction

The goal of the nonclinical studies was to support the registration of pomalidomide for the treatment of multiple myeloma.

All pivotal toxicology and safety pharmacology studies were conducted in accordance with the GLP regulations of the country where the study was performed.

2.3.2. Pharmacology

Primary pharmacodynamic studies

Primary pharmacodynamics were evaluated both in vitro and in vivo. The molecular mechanism of action of pomalidomide was evaluated in vitro. Pomalidomide appeared to have a dual mechanism of action, being both directly tumouricidal for MM cells and also having immunomodulatory activity with direct effects on T and NK-mediated immunity.

In vitro studies have identified a molecular mechanism for the pleiotropic effects of pomalidomide in MM and in T cells. Specifically, pomalidomide bound to the protein cereblon (CRBN), part of an E3 ligase complex, and the expression levels of CRBN in myeloma cells was linked to both the efficacy of pomalidomide and to the acquisition of resistance to lenalidomide.

Pomalidomide was claimed to have direct antiproliferative activity against B cell lines derived from MM and Burkitt's lymphoma patients. Pomalidomide in combination with dexamethasone increased this effect in a dose dependent manner.

In lenalidomide-resistant MM cell lines, pomalidomide treatment inhibited cell proliferation. However, data from some in vitro studies indicated that although pomalidomide displayed inhibitory activities against several MM cell lines, pomalidomide did not display activity against samples obtained from MM patients. This finding suggested that the product might not show efficacy in patients that display the same type of MM cells. The Applicant provided data which demonstrated that pomalidomide has in vitro tumouricidal activity against MM cells.

Cell proliferation and gene expression studies were performed in MM cell lines to identify molecular differences in the mechanisms of action between pomalidomide and lenalidomide. A comparison of the effect on gene expression levels of key genes in several signalling pathways revealed that both compounds may commonly modulate expression levels of many genes however 4 genes may be modulated only by pomalidomide.

Pomalidomide inhibited the proliferation of 6 human B cell precursor acute lymphoblastic leukaemia (BCP-ALL) cell lines. Pomalidomide inhibited proliferation and induced apoptosis in fresh BCP-ALL cells from paediatric subjects. Pomalidomide also had antiproliferative effects in 6 breast cancer cell lines.

Pomalidomide increased T cell stimulation by augmenting T cell proliferation, increasing IFN-γ, IL-2, and RANTES production and decreasing IL-10 production by CD4 T cell co-stimulated with the anti-CD-3 monoclonal antibody.

The effect of pomalidomide on cytokine signalling triggered by the interaction of immune effector cells with either MM cells or BM stromal cells was also studied. Pomalidomide induced in vitro proliferation of CD4, CD8 T cells, NK and NKT cells from patients with MM. Additionally, pomalidomide induced expression of costimulatory molecules CD28, inducible costimulator (ICOS), and inducible costimulator ligand (ICOSL) in $CD3^+$ gated effector cells within MM-PBMCs. Pomalidomide stimulated intracytoplasmic IFN-γ and IL-2 expression in CD4 T cells, CD8T cells, and NK T cells from peripheral blood of MM patients. There was also significantly increased secretion of IFN-γ and IL-2 as well as decreased secretion of IL-6 in MM-BMMCs cultured with pomalidomide. In addition, pomalidomide also reduced inhibitory T cell

populations. Pomalidomide significantly reduced suppressor of cytokine signalling 1 (SOCS1) expression in CD4 T, CD8 T, NK cells, and NK T cells from healthy donors and MM patients. Pomalidomide inhibited the production of many pro-inflammatory cytokines and chemokines from LPS-stimulated human PBMC, including TNF-α, IL-1β, IL-6, IL-12, MCP-1, and MIP-1αand increased production of the anti-inflammatory cytokines, IL-10 and RANTES. Pomalidomide also significantly reduced the expression of SOCS1 protein in all effector cells co-cultured either with MM cell lines alone or with MM cell lines and MM-BMSC.

A study of the inhibition of angiogenesis in human umbilical artery explants revealed that pomalidomide caused a significant dose-dependent inhibition of microvessel formation. Pomalidomide inhibited the VEGF-induced endothelial cord formation in a dose dependent manner. Pomalidomide inhibited angiogenesis by blocking the migration and adhesion of endothelial cells.

In vivo, anti-tumour efficacy was investigated in tumour models. Pomalidomide reduced tumour volumes and demonstrated anti-angiogenic activity. In beige-nude-xid mice injected with the Hs Sultan (Burkitt's lymphoma) tumour cells the pomalidomide-treated animals showed significant inhibition of tumour growth after 18 days of treatment. Also, mice receiving pomalidomide treatment showed an almost complete suppression of tumour growth until they were euthanized on Day 35 post-inoculation. In a SCID-hu model of human MM pomalidomide had no significant efficacy at any of the tested doses in the LAGλ-1 and the non-secretory LAGκ-1B tumour-bearing mice. However, pomalidomide reduced tumour volume growth and IgG levels in mice bearing the LAGκ-1A tumours but these results were not significant.

The effect of pomalidomide on therapy resistant acute lymphoblastic leukaemia was examined in NOD/SCID mice injected s.c with leukaemic blast cells from patients. Pomalidomide significantly inhibited tumour growth and in tumours from treated animals MVD was lower. In another NOD/SCID model in which mice were inoculated i.v. with tumour cells from relapsed BCR/ABL positive BCP-ALL subjects dissemination of leukaemic cells into spleen was significantly reduced by pomalidomide treatment.

In a human Burkitt's lymphoma tumour model in SCID mice, the concurrent administration of pomalidomide with rituximab was more effective in controlling tumour growth and prolonging survival than rituximab alone. Lymphoma-bearing SCID mice treated with pomalidomide showed greater recruitment of NK cells into the tumour bed, in particular more centralised infiltration into tumours than the peripheral pattern in DMSO treated controls. Pomalidomide showed an anti-angiogenic effect evidenced by a reduction in MVD of the tumours. In the MMPA pomalidomide inhibited microvessel formation.

Secondary pharmacodynamic studies

Non-neoplastic hematologic disorders (e.g., SCD), autoimmune inflammatory disorders such as SSc and effects on endothelial progenitor cell differentiation were considered to be secondary pharmacodynamics.

Pomalidomide had anti-fibrotic properties. In an in vivo mouse model of systemic sclerosis (SSc) utilizing bleomycin as an inducer of skin fibrosis, pomalidomide reduced dermal thickness and alpha-smooth muscle actin (α-SMA) staining of myofibroblasts, which is a direct measure of

dermal fibrosis. Most notably, pomalidomide was efficacious in this SSc mouse model with either prophylactic or therapeutic dosing.

Pomalidomide also affected the regulation of fetal haemoglobin (HbF) making it a potential therapeutic agent for the treatment of non-malignant hematologic disorders such as sickle cell disease (SCD) and β-thalassemia. In vitro pomalidomide was a more potent inducer of HbF than HU, the only treatment currently approved for SCD. Pomalidomide increased the expression of genes directing the production of HbF as well as γ- and ε-globin gene transcription and expression during erythroid differentiation. In an in vivo knockout transgenic mouse model of SCD, pomalidomide (10 mg/kg; 5 QD/week x 8) stimulated erythropoiesis as indicated by bone marrow hyperplasia and increased extramedullary hematopoiesis, a trend toward higher reticulocytes and significantly higher red blood cell (RBC) levels. Pomalidomide significantly increased HbF expression with a trend toward higher gamma-globin chain A (Aγ) levels. The pomalidomide responder rate, defined as the percentage of animals that exceeded the maximum HbF and Aγ levels in the vehicle group, reached 67% and 78% respectively. Among responders, pomalidomide induced a nearly 2-fold increase in HbF and the increase in Aγ levels was significant and was similar to the approved HbF-inducing agent HU.

Safety pharmacology programme

In oral dose CNS and respiratory function studies in the rat, there were no treatment related effects up to the highest dose tested. In vitro, pomalidomide had no significant effect on hERG current at up to 87.5 µm. In anaesthetised dogs, pomalidomide had no effects on QTc following i.v. administration of up to 25mg/kg although there was an effect on respiration and b.p. in 1/4 dogs. In a conscious telemetered monkey study oral doses of pomalidomide of up to 10mg/kg had no adverse effects on CVS, electrocardiogram (ECG) and haemodynamic parameters, or respiration.

Pharmacodynamic drug interactions

Pomalidomide was examined alone and in combination with dexamethasone and bortezomib for the inhibition of MM.1S tumour growth in a xenograft mouse model of multiple myeloma. As a single agents, pomalidomide and dexamethasone inhibited tumour growth approximately 43% and 38% (Day 8) - 87% and 65% (Day 25), respectively compared with the control. The combination of pomalidomide with bortezomib, dexamethasone, or dexamethasone and bortezomib further increased the tumour suppression to approximately 93%, 93%, and 96%, respectively on Day 25.

Another in vivo study was also conducted where concurrent administration of pomalidomide and rituximab was more effective in prolonging survival than rituximab therapy alone.

In vivo, synergistic effects were observed with hydroxyrurea in increasing Foetal Haemoglobin expression during erythroid differentiation and with the histone deacetylase (HDAC) inhibitors in the expansion of CD34+ and CD133+ cells.

2.3.3. Pharmacokinetics

In vitro and in vivo studies were conducted to characterize the absorption, distribution, metabolism, and excretion of pomalidomide (racemate). Analytical methods for the determination of concentrations of pomalidomide and its enantiomers in pharmacokinetic and toxicokinetic studies were developed

In vitro and in vivo studies demonstrated that pomalidomide enantiomers readily undergo racemisation. Following repeated doses of pomalidomide, the exposure (AUC) ratio of S-enantiomer/R-enantiomer ranged from 0.43 to 0.57 in rats and 0.73 to 1.07 in monkeys. In human and monkey plasma, the S-enantiomer had a higher per cent protein bound than the R-enantiomer suggesting a possible stereoselectivity of the product in plasma protein binding maybe as a consequence of chiral discriminative properties of the binding sites of the protein fractions. Additional data suggested that the distribution of pomalidomide into tissues is not extensive and that differences in enantiomer distribution would be minor.

In rats and monkeys, systemic clearance of pomalidomide was low (<1/6th liver blood flow), the volume of distribution was 2- to 4-fold body water volume, suggesting good tissue distribution of the compound), and the terminal half-lives of pomalidomide in animals ranged from mean values of 4 to 7 hours following an IV dose. In rats and monkeys, the oral bioavailability of pomalidomide (racemate) was low (mean values of 13% to 15%) following a 100 mg/kg dose. However, the bioavailability in monkeys was high (approximately 100%) at a dose of 2 mg/kg, indicating the extent of absorption is solubility limited. In rats, there was slight gender difference in systemic exposure (up to 2.5-fold higher in females), but this was not observed in monkeys. Following repeated dosing in rats, systemic exposure (AUC) increased in a less than dose-proportional manner and the extent of pomalidomide accumulation was minimal in males and moderate (<2.0-fold) in females. Following repeated dosing to monkeys, systemic exposure (AUC) increased in approximately a dose-proportional manner and accumulation of pomalidomide generally did not occur at doses less 1 mg/kg, but was observed at higher doses (up to 3-fold accumulation).

Following oral administration of ^{14}C-pomalidomide to pigmented rats, drug related radioactivity was widely distributed into tissues, with most tissue concentrations peaking at 3 hours and decreasing to below quantifiable levels by 12 hours post-dose. The highest measured tissue concentrations occurred in the kidney, the gastrointestinal tract, urinary bladder, and bile, with lesser levels observed in most other tissues including liver, endocrine glands, secretory glands, and pigmented skin. Additional studies investigating the penetration of pomalidomide into the CNS of rats and mice indicated moderate distribution into the brain, with brain to plasma/blood ratios ranging from 0.39 to 0.49.

Pomalidomide plasma protein binding ranged from approximately 12% to 59% at concentrations between 30 and 1000 ng/mL in animals and humans. There was no apparent concentration dependency of plasma protein binding over this concentration range in human plasma. Following repeated oral administration of pomalidomide to pregnant rabbits, foetal plasma pomalidomide concentrations were approximately 50% of the maternal C_{max}, indicating that pomalidomide crosses the placenta. Following oral administration of pomalidomide to lactating rats, transfer into milk was observed, with milk to plasma ratios of 0.63 to 1.46.

In hepatocytes from rabbit and human, and in vivo in rat, monkey and human, pomalidomide was metabolized primarily via hydroxylation of the phthalimide ring (M14, M16 and M17) followed by glucuronidation (M12 and M13), hydrolysis of the glutarimide ring (M10 and M11), and hydrolysis of the phthalimide ring (M2). There were no unique or disproportionate metabolites observed in humans, compared to rats and monkeys.

Following oral or IV administration of ^{14}Cpomalidomide to rats or monkeys, excretion of radioactivity was rapid and nearly complete (>90%). In rats, the predominant route of elimination was in the faeces following oral administration, mostly from unabsorbed parent, but in urine following IV administration. In monkeys, the primary route of elimination was via the urine, which contained >70% of the radioactive dose following either oral or IV administration. These data indicate that urine is the primary route of elimination for systemic pomalidomide-related material in both species. Urinary radioactivity consisted primarily of metabolites and hydrolysis products, indicating urinary excretion of unchanged compound was a minor clearance pathway.

Pomalidomide was not a CYP inhibitor or inducer in vitro. While pomalidomide is a substrate for P-glycoprotein (P-gp), its intestinal absorption did not appear to be limited by P-gp transport.

2.3.4. Toxicology

Single dose toxicity

Single-dose oral and intravenous studies in mice and rats indicated that the acute oral minimum lethal dose was >2000 mg/kg, and acute IV minimum lethal dose was >80 mg/kg for mice, and >50 mg/kg for rats.

Repeat dose toxicity

Repeated dose toxicity studies were conducted in the rat and monkey using the oral gavage route of administration except for the 13 week and 9 month monkey studies in which the nasogastric route was used. Toxicokinetics were conducted in all studies.

In the rat, pomalidomide was well-tolerated up to the top dose tested in all the studies. No adverse effects were observed up to 5000 mg/kg/day in the 7-day study, 2000 mg/kg/day in the 28-day study, 1500 mg/kg/day in the 90-day study and 1000 mg/kg/day in the 6-month study. In the 7 day study, toxicokinetics revealed no increase in parameters (Tmax, Cmax, AUC24h) with increasing dose 2000 to 5000mg/kg. In the 6-month study, the dosage of 1000 mg/kg/day resulted in AUC_{24h} of 42530 and 98010 ng•h/mL in males and females, respectively on Day 180.

In the monkey, pomalidomide was evaluated in repeat-dose studies with durations of 14 days at doses from 50 to 1200 mg/kg/day, 28 days at doses from 30 to 300 mg/kg/day and from 0.2 and 2 mg/kg/day, 90 days at doses from 0.05 to 10 mg/kg/day and 9 months at doses from 0.05 to 1 mg/kg/day. In these studies, the monkey appeared to be more sensitive to pomalidomide effects compared to the rat, and morbidity and mortality occurred at doses of 1 and 10 mg/kg/day in the 9-month and 3-month studies, respectively. The main toxic effects

were associated with the hematopoietic/lymphoreticular systems. The major findings were decreased RBC parameters (red blood cell count, haemoglobin, and haematocrit), decreased white blood cell (WBC) counts (neutrophils, lymphocytes, and monocytes), and histologic lymphoid depletion (lymph nodes, spleen, thymus, and GALT). In addition, increased incidence of loose and watery stool leading to weight loss were often observed and contributed to poor clinical conditions.

In the 28 day study, administration of pomalidomide to monkeys at 30, 100, and 300 mg/kg/day was associated with mortality and poor clinical condition that led to study termination by Day 19. The principle target organs were the hematopoietic and lymphoid systems that may have caused secondary effects in other tissues. The NOAEL for pomalidomide was <30 mg/kg (AUC_{16h} <48771 and 51858 ng•h/mL for male and female monkeys, respectively).

In the 13 week study, all animals were to be dosed once daily for 13 weeks. However, dosing at 10 mg/kg/day was discontinued after 5 weeks due to adverse clinical signs and haematological findings. In that group, 3 animals/sex were euthanized in Week 6, and 2 animals/sex were retained on dosing-free recovery until Week 13.

In the 9-month toxicity study in monkeys, pomalidomide was administered orally at 0.05, 0.1, and 1 mg/kg/day. There were 6 animals/sex/group. Treatment -related morbidity and early euthanasia (3 animals/sex) occurred at 1 mg/kg/day and were attributed to immunomodulation/immunosuppression effects associated with the pharmacology of pomalidomide (decreased peripheral blood lymphocytes, histologic lymphoid depletion, and hypocellularity of bone marrow). These immunosuppressive effects were associated with staphylococcal infection and chronic inflammation of the large intestine. Villous atrophy of the small intestine and minimal or mild bile duct proliferation were also present. In addition, one female monkey at 1 mg/kg/day was euthanized on day 253 and exhibited changes consistent with acute myelogenous leukaemia (AML; extreme leukocytosis, multiple organ infiltrates, and bone marrow blast infiltration).

Pomalidomide has also shown to be capable of inducing death in primary human AML blasts. The 1 mg/kg/day dose resulted in a mean AUC_{24h} of 6540 ng•h/mL in female monkeys on Day 272 (16-fold higher exposure relative to a 4 mg clinical dose). In the surviving animals, there were no treatment-related changes in body weight, electrocardiography, blood pressure measurements, ophthalmology, and urinalysis. Evaluation of recovery animals indicated that all treatment-related findings were reversible after 8 weeks of dosing cessation, except for proliferation of intrahepatic bile ducts observed in 1 animal at 1.0 mg/kg/day. The NOAEL was 0.1 mg/kg/day, corresponding to Day 272 pomalidomide AUC_{24h} of 227 and 211 ng•h/mL for males and females, respectively (approximately 0.5-fold exposure ratio relative to a 4 mg clinical dose).

Cardiovascular assessment (vital signs, ECG, respiration, and heart rate) conducted in the 1-, 3-, and 9-month monkey studies indicated no treatment -related cardiovascular changes at doses up to 2 mg/kg/day for up to 3 months, and up to 1 mg/kg/day after 9 months (Cmax = 1249 and 653 ng/mL; both sexes combined, at 2 and 1 mg/kg/day respectively).

Genotoxicity

Pomalidomide was not mutagenic in bacterial and mammalian mutation assays, and did not induce chromosomal aberrations in human peripheral blood lymphocytes or micronuclei formation in polychromatic erythrocytes in bone marrow of rats administered doses up to 2000 mg/kg/day.

Carcinogenicity

No carcinogenicity studies have been conducted.

Reproduction Toxicity

In a fertility and early embryonic development study in rats pomalidomide was administered to males and females at dosages of 25, 250, and 1000 mg/kg/day. Uterine examination on GD13 revealed a decrease in mean number of viable embryos and an increase in post-implantation loss at all dosage levels. Therefore, the NOAEL for these observed effects was <25 mg/kg/day (AUC_{24h} was 39960 ng•h/mL at this lowest dose tested, and the exposure ratio was 99-fold relative to a 4 mg clinical dose). When treated males on this study were mated with untreated females, all uterine parameters were comparable to the controls. Based on these results, the observed effects were attributed to the treatment of females.

Pomalidomide was teratogenic in both rats and rabbits when administered during the period of major organogenesis. In the rat embryofoetal developmental toxicity study, malformations or absence of urinary bladder, absence of thyroid gland, and fusion and misalignment of lumbar and thoracic vertebral elements (centra and/or neural arches) occurred at all dosage levels (25, 250, and 1000 mg/kg/day). There was no maternal toxicity observed in this study. Therefore, the maternal NOAEL was 1000 mg/kg/day, and the NOAEL for developmental toxicity was <25 mg/kg/day for rats (AUC_{24h} was 34340 ng•h/mL on GD17 at this lowest dose tested, and the exposure ratio was 85-fold relative to a 4 mg clinical dose).

In rabbits, pomalidomide at dosages ranging from 10 to 250 mg/kg produced embryo-foetal developmental malformations stated to be similar to those observed with thalidomide. Increased cardiac anomalies were seen at all doses with significant increases at 250 mg/kg/day. At 100 and 250 mg/kg/day, there were slight increases in post-implantation loss and slight decreases in foetal body weights. At 250 mg/kg/day, foetal malformations included limb anomalies (flexed and/or rotated fore and/or hind limbs, unattached or absent digit) and associated skeletal malformations (not ossified metacarpal, misaligned phalanx and metacarpal, absent digit, not ossified phalanx, and short not ossified or bent tibia), moderate dilation of the lateral ventricle in the brain, abnormal placement of the right subclavian artery, absent intermediate lobe in the lungs, low-set kidney, altered liver morphology, incompletely or not ossified pelvis, an increased average for supernumerary thoracic ribs and a reduced average for ossified tarsals. Slight reduction in maternal body weight gain, significant reduction in triglycerides, and significant decrease in absolute and relative spleen weights were observed at 100 and 250 mg/kg/day. The maternal NOAEL was 10 mg/kg/day, and the developmental NOAEL was <10 mg/kg/day for rabbits (AUC_{24h} was 418 ng•h/mL on GD19 at this lowest dose tested, which was similar to that obtained from a 4 mg clinical dose.

No pre- and postnatal development study has been conducted.

Toxicokinetic data

The toxicokinetics of pomalidomide were evaluated as part of repeat-dose toxicity studies in rats and monkeys.

Local Tolerance

No local tolerance study has been conducted.

Other toxicity studies

Pomalidomide was assessed for immunotoxicity in monkeys after treatment at 2 mg/kg/day for 28 days. Treatment-related effects included increased large unstained cells, decreases in peripheral lymphocytes populations (correlating to bone marrow hypocellularity), alterations to the primary and secondary humoral immune system, thymic organ weight decreases (macroscopic finding of small thymus), and histological findings consistent with general lymphoid depletion in the thymus, spleen, and the mandibular and mesenteric lymph nodes. There were no effects on granulocyte, monocyte, or NK cell function. All findings at 2 mg/kg/day demonstrated full recovery after a 30-day treatment-free period, with the exception of the decreased $CD20^+$ B-lymphocytes (partial recovery observed) and reduced thymus weights; minimal/mild histological changes in the lymph nodes also indicated that there were partial recoveries of these effects.

2.3.5. Ecotoxicity / environmental risk assessment

Table 1 - Summary of main study results

Substance: pomalidomide			
CAS-number: 19171-19-8			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	Shake flask method	log K_{ow} = 0.58	Potential PBT No
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC surfacewater , default or refined (e.g. prevalence, literature)	PEC surfacewater refined 0.000330	µg/L	< 0.01 threshold

Pomalidomide PEC surfacewater value is below the action limit of 0.01 µg/L. and is not a PBT substance as log Kow does not exceed 4.5.

2.3.6. Discussion on non-clinical aspects

The primary pharmacodynamics were evaluated both in vitro and in vivo. The molecular mechanism of action of pomalidomide was evaluated in vitro. Pomalidomide appeared to have a dual mechanism of action, having immunomodulatory activity with direct effects on T and NK-mediated immunity. The data indicates that pomalidomide was directly tumouricidal for MM cells.

Data from some in vitro studies indicated that even though pomalidomide displays inhibitory activities against several MM cell lines, pomalidomide did not display activity against samples obtained from MM patients. This finding suggested that the product might not show efficacy in a number of patients that may display the same type of MM cells. Studies in primary MM CD138+ cells are limited but similar activity in primary cells and cell lines has been reported. Studying the genetic profile of such cells could provide a better understanding of pomalidomide's pharmacology. The Applicant will evaluate markers of response or resistance in MM patients at baseline whilst undergoing treatment with pomalidomide in two clinical studies. The CHMP recommended that this biomarker analysis report based on clinical studies CC-4047-MM-008 and CC-4047-MM-010 is submitted when available (2Q 2016).

In vivo pomalidomide was shown to have anti-tumour, immunomodulatory and anti-angiogenic properties. It also had anti-fibrotic properties. Additionally, pomalidomide affected the regulation of foetal haemoglobin expression by erythroid precursors derived from the blood of healthy adults and adults with SCD. In vitro the combination of pomalidomide + dexamethasone (Dex) was synergistic in both H929 lenalidomide-sensitive and -resistant cells, inhibiting cell proliferation and inducing apoptosis. The mechanism of pomalidomide plus Dex synergy in these H929 lenalidomide-resistant cell lines is not known at present.

The pharmacokinetics of pomalidomide (racemate) were characterised in in vitro and in vivo studies. Analytical methods were developed for the determination of concentrations of pomalidomide and its enantiomers in pharmacokinetic and toxicokinetic studies. Pomalidomide enantiomers readily undergo racemisation. In human and monkey plasma, the S-enantiomer had a higher per cent protein bound than the R-enantiomer suggesting a possible stereoselectivity of the product in plasma protein binding maybe as a consequence of chiral discriminative properties of the binding sites. The data indicates that the distribution of pomalidomide into tissues is not extensive and that differences in enantiomer distribution would be relatively minor.

Following repeated dosing in rats, systemic exposure (AUC) increased in a less than dose-proportional manner and the extent of pomalidomide accumulation was minimal in males and moderate (<2.0-fold) in females. Following repeated dosing to monkeys, systemic exposure (AUC) increased in approximately a dose-proportional manner and accumulation of pomalidomide generally did not occur at doses less 1 mg/kg, but was observed at higher doses (up to 3-fold accumulation). Accumulation occurred in the monkey at a dose ≥1mg/kg/day but this dose resulted in an exposure (AUC) approximately 5 times higher than the clinical exposure, suggesting this accumulation may not be clinically relevant. Also the proposed clinical dose of 4mg/day which equates to 0.067mg/kg is considerably lower than the dose in monkeys at which accumulation occurred. Data submitted showed that accumulation appeared to be minimal in

both healthy and MM subjects, suggesting that significant accumulation of pomalidomide does not occur at clinically relevant doses.

In the rat, pomalidomide was well-tolerated up to the top dose tested in all the studies. No adverse effects were observed up to 5000 mg/kg/day in the 7-day study, 2000 mg/kg/day in the 28-day study, 1500 mg/kg/day in the 90-day study and 1000 mg/kg/day in the 6-month study. In the monkey the main toxic effects were associated with the hematopoietic/lymphoreticular systems. The major findings were decreased RBC parameters (red blood cell count, haemoglobin, and haematocrit), decreased white blood cell (WBC) counts (neutrophils, lymphocytes, and monocytes), and histologic lymphoid depletion (lymph nodes, spleen, thymus, and GALT).

In the nine month repeated dose toxicity study in monkeys, AML was reported in one female. Based upon the known association in humans of AML with immunosuppression and the low incidence of this neoplastic change in cynomolgus macaques, this finding was considered treatment-related. Due to the rarity of this type of neoplasm in nonhuman primates, the absence of genotoxicity, the reported immunotoxicity in the study and the known association of AML and immunosuppression in humans, the Applicant attributed this finding to a secondary effect of the product due to immunosuppression. However, the clinical relevance of this finding is unknown. A warning on second primary malignancies (SPM) has been included in the SmPC and the monitoring of SPM in clinical studies has been included in the pharmacovigilance plan of the risk management plan (RMP).

Pomalidomide was not genotoxic. No carcinogenicity studies have been conducted. This is acceptable in view of the therapeutic indication.

Pomalidomide had adverse effects on fertility and early embryonic development and was teratogenic in both test species. Consequently, a pregnancy prevention programme is implemented as part of the RMP and conditions of the marketing authorisation. Pomalidomide is contraindicated in pregnancy as well as in women of childbearing potential and male patients unless adhering to the conditions of the PPP; warning and relevant information have also been included in sections 4.4, 4.6 and 5.3 of the SmPC.

Based on the environmental risk assessment, pomalidomide is not expected to pose a risk to the environment.

2.3.7. Conclusion on the non-clinical aspects

The non-clinical studies conducted were adequate to support the marketing authorisation of pomalidomide in the treatment of MM.

2.4. Clinical aspects

2.4.1. Introduction

GCP

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

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

Table 2 - Tabular overview of clinical studies

Study Number (phase)	**Objectives**
CC-4047-CP-005 Phase 1	Bioequivalence 2 mg, food effect
CC-4047-CP-007 Phase 1	Bioequivalence 1, 2, 3, 4 mg
CC-4047-1398/132 Phase 1	Safety, tolerability,pharmacokinetics (PK) and pharmacodynamic of ascending oral single doses
CC-4047-CP-004 Phase 1	Absorption, metabolism and excretion of [^{14}C] pomalidomide
CC-4047-CP-006 Phase 1	Safety, tolerability, PK and pharmacodynamic of ascending oral multiple doses, semen concentration
CC-4047-MM-001/CDC-407-00-001 Phase 1	Maximum tolerated dose (MTD), activity and safety of pomalidomide in previously treated multiple myeloma (MM)
CC-4047-MM-002 Phase 1/2	MTD/PK, safety and efficacy of pomalidomide alone and in combination with LD-dex in RRMM
IFM-2009-02 Phase 2	Efficacy and safety of two regimens of oral pomalidomide in combination with LD-dex in RRMM
PO-MM-PI-0010 Phase 2	Efficacy of pomalidomide in combination with LD-dex in RRMM
CC-4047-MM-003 Phase 3	To compare efficacy and safety of pomalidomide in combination with LD-dex against HD-dex in RRMM

2.4.2. Pharmacokinetics

The pharmacokinetic behaviour of pomalidomide was documented in 5 studies in healthy volunteers, 2 studies in multiple myeloma patients and was supplemented by data from 8 in vitro studies.

Absorption

Pomalidomide is a small molecule with low aqueous solubility and low permeability, classified as BCS class IV. The low solubility limits the rate of absorption at higher doses (> 5 mg), but has no discernible impact on the extent of absorption up to doses of 50 mg. Not unexpectedly, given the low aqueous solubility, formulation is an important determinant of the rate of absorption.

Pomalidomide was absorbed with a maximum plasma concentration (Cmax) occurring between 2 and 3 hours and is at least 73% absorbed following administration of single oral dose. The systemic exposure (AUC) of pomalidomide increases in an approximately linear and dose proportional manner. Following multiple doses, pomalidomide has an accumulation ratio of 27 to 31% on AUC.

Coadministration with a high-fat and high-calorie meal slowed the rate of absorption, decreasing plasma Cmax by approximately 25%, but had minimal effect on the overall extent of absorption with an 8% decrease in AUC. In the fasted state tmax ranged between 1 and 4 hours at clinical doses.

The absolute bioavailability of pomalidomide has not been studied.

Distribution

Pomalidomide contains one chiral centre and is manufactured in its racemic form. All clinical studies were performed using the racemic mixture. In vitro plasma protein binding of pomalidomide, determined over a concentration range of 30 to 1000 ng/mL, was stereoselective, with the mean percentage bound of 16% for the R-enantiomer and 42% for the S-enantiomer. Although the lowest concentration was somewhat high relative to therapeutic drug concentrations, given the low to moderate extent of protein binding, it is accepted that protein binding is unlikely to be important over the therapeutic range. There is no concern regarding displacement interactions or impact of disease on drug protein binding.

The apparent volume of distribution of pomalidomide ranged on average from 74 L to 138 L across a dose range of 1 mg to 10 mg in healthy volunteers and from 62 L to 97 L in multiple myeloma patients. In the human AME study (CC-4047-CP-004), blood to plasma ratios for radioactivity ranged from 0.749 ± 0.0357 at 0.5 hours post dose to 0.904 ± 0.0444 at 24 hours post dose, suggesting that radioactivity distributed readily into red blood cells.

Pomalidomide is distributed in semen of healthy subjects at a concentration of approximately 67% of plasma level at 4 hours post-dose after 4 days of QD dosing at 4 mg (CC-4047-CP-006).

Elimination

Pomalidomide is eliminated from plasma with a geometric mean terminal half-life ranging from 5.7 to 10.8 hours and total clearance (CL/F) ranging from 6.5 to 10.8 L/hr, with no apparent dose-related trend.

A mass balance study using radiolabelled pomalidomide was conducted in eight healthy male volunteers to quantify the rates and routes of elimination and to identify and quantify circulating and excreted metabolites. In addition, a chiral bioanalytical method was used to quantify the two enantiomers (the only in vivo data available for the two enantiomers) in plasma. The elimination of total radioactivity in plasma mirrored that of parent drug. There were no circulating major metabolites in plasma. The mean total recovery of radioactivity was lower than ideal (88% of dose) and ranged from 64% to 110%. Metabolism is the primary mechanism of elimination of pomalidomide (less than 10% of dose excreted unchanged in urine and faeces) and urine is the primary route for excretion of pomalidomide metabolites (72% of dose was recovered in urine and 15% in faeces). The predominant metabolites in excreta were the hydrolysis product, M11 (24% of dose), and two glucuronides (M12 and M13; 29% of dose) of a hydroxylated metabolite (M17). The M17 pathway (M17 + glucuronide metabolites) accounts for at least 35% of the dose. Six other minor metabolites were also detected in excreta. As there were no major circulating metabolites, metabolites were not measured in any clinical pharmacology studies.

The mean Cmax and AUC0-t values for the R and S-enantiomers were approximately 50% of those observed for pomalidomide in plasma and the AUC0-∞ ratio was 1.0.

The metabolism of pomalidomide was studied in vitro in human hepatocytes, which showed low rates of metabolism. The principal routes of metabolism were hydroxylation, glucuronidation of hydroxylated metabolites and hydrolysis. An in vitro study with recombinant CYP isozymes also showed low rates of metabolism. The hydrolysis product, M11, appears to be formed by chemical degradation and/or non-P450 metabolism. The relative contribution of each isoenzyme to the formation of M17 was estimated to be 54%, 30%, 11% and 4% for CYP 1A2, 3A4, 2C19 and 2D6, respectively. Given the low turnover (<10%) during these experiments, further evidence to confirm the enzymes responsible for the elimination of pomalidomide is required. Pomalidomide is also a substrate for P-glycoprotein.

Dose proportionality and time dependencies

The low aqueous solubility of pomalidomide results in a less than proportional increase in Cmax over the dose range of 1 to 50 mg, most in evidence for doses > 10 mg, while AUC is proportional to dose. From exploratory analysis, it appears that Cmax is proportional to dose over the dose range of 0.5 to 5 mg, however this should be verified by the Applicant in the planned population pharmacokinetic analysis.

There was very little accumulation of pomalidomide after once daily dosing in healthy volunteers and steady-state concentrations were achieved by Day 3 of multiple dosing. However, there is evidence of greater (and highly variable) accumulation in multiple myeloma patients.

Special populations

No studies have been submitted in patients with renal or hepatic impairment.

The table below shows the number of subjects stratified by age over the total number of subjects from which PK samples were obtained, by study.

Table 3 - Studies that Contributed to the Pharmacokinetic Characterisation of Pomalidomide in the Elderly

Older subjects number /total number	Age 65-74	Age 75-84	Age 85+
PK Trials	0/152	0/152	0/152
Controlled Trials	MM-003 25/80	MM-003 11/80	MM-003 0/80
Non Controlled trials	MM-001 10/28 MM-002 3/14	MM-001 5/28 MM-002 2/14	MM-001 0/28 MM-002 0/14

Pharmacokinetic interaction studies

The Applicant has conducted a comprehensive package of in vitro studies to support inferences regarding the potential impact of co-administration of pomalidomide with other drugs. Pomalidomide was investigated in vitro to determine its potential for induction of CYP enzymes. The predominant metabolic pathways of excreted radioactivity are hydroxylation with subsequent glucuronidation, or hydrolysis. In vitro, CYP1A2 and CYP3A4 were identified as the primary enzymes involved in the CYP-mediated hydroxylation of pomalidomide, with additional minor contributions from CYP2C19 and CYP2D6. Pomalidomide is also a substrate of P-glycoprotein in vitro. The results of the potential for pomalidomide to inhibit P-gp were considered inconclusive. Pomalidomide is not an inhibitor of CYP enzymes and does not appear to inhibit drug transport proteins other than P-gp.

The applicant has also provided results of in vivo interaction studies. Co-administration of pomalidomide with the strong CYP3A4/5 and P-gp inhibitor ketoconazole, or the strong CYP3A4/5 inducer carbamazepine, had no clinically relevant effect on exposure to pomalidomide. Co-administration of the strong CYP1A2 inhibitor fluvoxamine with pomalidomide in the presence of ketoconazole, increased exposure to pomalidomide by 104 % with a 90% confidence interval [88% to 122%] compared to pomalidomide plus ketoconazole.

2.4.3. Pharmacodynamics

Limited pharmacodynamic data from studies on healthy volunteers and MM patients have been submitted.

The exact mechanism of action of pomalidomide is unknown but results in tumouricidal, immunomodulatory, anti-angiogenic, and anti-inflammatory properties seen also with other drugs of the same class. However, pomalidomide exhibits a general greater potency compared to thalidomide or lenalidomide.

Pomalidomide has also shown inhibition of tumour growth in cells resistant to other drugs, including lenalidomide. Combination of pomalidomide and dexamethasone results in a synergy in anti-proliferative activities although the exact mechanism of action is unknown. This synergy was detected earlier in non-clinical studies. Additional clinical data based on the extensive use of dexamethasone with lenalidomide and thalidomide and the expected rapid onset of activity of dexamethasone compared to immunomodulatory agents support the proposed combination.

A dose related decrease in CD4 counts but not in CD8 counts has been observed in healthy subjects while in MM patients' serum paraprotein decreases in a dose related manner.

No data on exposure-response has been submitted.

No formal thorough QT/QTc study in healthy subjects has been conducted.

2.4.4. Discussion on clinical pharmacology

Overall the PK data supported the proposed posology in the target population.

Pomalidomide has been shown to distribute into semen with concentrations approximately 67% of those in plasma. In view of its teratogenicity, the SmPC includes a warning on sperm donation and use of condoms during, between and after treatment with pomalidomide. A specific recommendation is also made regarding contraception in females during, between and after treatment with pomalidomide.

The pharmacokinetics of pomalidomide appeared to be similar in multiple myeloma patients compared to healthy volunteers following single doses. There was very little accumulation of pomalidomide after once daily dosing in healthy volunteers and steady-state concentrations were achieved by Day 3 of multiple dosing. However, there is evidence of greater (and highly variable) accumulation in multiple myeloma patients. Given the limited number of patients contributing pharmacokinetic data and the uncertainty regarding the extent of accumulation, all data collected in healthy volunteers and multiple myeloma patients should be included in a population analysis as an additional pharmacovigilance measure reflected in the RMP, to quantify the multiple dose pharmacokinetics and potential dose and time-dependency of pomalidomide. The impact of gender, race, weight and age should be covariates included in this population pharmacokinetic analysis.

Pomalidomide was investigated *in vitro* to determine its potential for induction of CYP enzymes. Given that pomalidomide is a potential human teratogen and may be used in fertile women, an *in vivo* interaction study with combined oral contraceptives would have been required. However, given the risk of venous thromboembolism and the pregnancy prevention programme that defines suitable methods of contraception (excluding combined oral contraceptives) and concerns about the ethics and feasibility of a clinical drug interaction study, such a study was not deemed necessary. A warning to that effect has been included in the SmPC.

The Applicant has only assessed the potential for P-gp inhibition in one in vitro system whereas two are recommended with strong and less potent inhibitors. In vitro results of the potential for pomalidomide to inhibit P-gp were therefore considered inconclusive. The Applicant will conduct an additional *in vitro* study to assess the potential of pomalidomide as an inhibitor of P

glycoprotein using Caco-2 cells as an additional pharmacovigilance measure reflected in the RMP.

Pomalidomide was not an inhibitor of CYP enzymes and did not appear to inhibit drug transport proteins other than P-gp. More than 25% of pomalidomide is metabolized, therefore the applicant should conduct an in vitro study as an additional pharmacovigilance measure reflected in the RMP to evaluate whether pomalidomide is an OATP1B1 and/or OATP1B3 substrate.

No data in patients with renal or hepatic impairment have been submitted. Patients with renal or hepatic impairment should be carefully monitored. Studies are ongoing in these patients and will be submitted as an additional pharmacovigilance measure reflected in the RMP.

Although pharmacodynamic data is limited and the exact mechanism of action is unknown pomalidomide results in tumouricidal, immunomodulatory, anti-angiogenic and anti-inflammatory effects in line with other drugs of the same class. A synergy when combined with dexamethasone seen in non-clinical studies and further explored later in clinical studies supports the combination. Pomalidomide reduces the paraprotein levels in MM and has secondary effects expected for a drug of this class, with neutropenia as the most frequent toxicity that led to the chosen 4 mg dose.

No data on exposure-response has been submitted as PK data is too limited at present. All data collected in healthy volunteers and multiple myeloma patients will be included in a population analysis to quantify the multiple dose pharmacokinetics and potential dose and time-dependency of pomalidomide. The covariates to be included in the analysis should include, but not be limited to, disease state, dose, formulation, fed state, age, weight, race, gender, creatinine clearance (ml/min) and markers of hepatic function. This will be performed and submitted as an additional pharmacovigilance measure from the RMP.

No formal thorough QT/QTc study in healthy subjects has been conducted. Preclinical data revealed no evidence of an apparent signal for potential QTc prolongation from pomalidomide. QTc interval has been monitored in healthy subjects at single doses up to 50 mg with no evidence of QTc prolongation. In MM subjects, a QTc interval thresholds of concern was considered at > 500 ms and any change from baseline of > 60 ms. While serious adverse events of QTc prolongation have been reported, to date these data have revealed variable QTc values and modest changes that have not exceeded our defined threshold cut-offs of concern in a frequent or consistent manner. These data also do not reveal any clear trend or pattern of QTc prolongation, and do not appear to have significantly translated into symptomatic or clinically meaningful events. However, the Applicant should conduct a thorough QT study in healthy subjects according to regulatory guidelines as an additional pharmacovigilance measure reflected in the RMP.

2.4.5. Conclusions on clinical pharmacology

The clinical pharmacology data is considered sufficient for approval, with additional data to be provided as additional pharmacovigilance measures from the RMP.

2.5. Clinical efficacy

2.5.1. Dose response studies

Study CC-4047-MM-001 was a phase 1b, ascending dose, open-label study conducted in subjects with RRMM to determine the MTD. Pomalidomide at doses of 1, 2, 5, and 10 mg as a single oral agent were evaluated using two different schedules: every day dosing (Cohort 1) or alternate day dosing (Cohort 2). The duration of treatment was four weeks. Subjects were withdrawn on the basis of dose limiting toxicity.

The MTD was determined to be 2 mg daily (cohort 1) and 5 mg alternate days (cohort 2). However, these two cohorts did not evaluate a dose between 2mg and 5 mg.

Myelosuppression was identified as the dose limiting toxicity suggesting a regimen incorporating a rest period would allow recovery of the bone marrow. Consequently, based on experience with other products of the same class in multiple myeloma, a cyclic dosing schedule (Days 1-21 of each 28-day cycle) was studied. Also prior experience with lenalidomide indicated that the addition of low-dose dexamethasone enhanced efficacy and was better tolerated than when combined with a higher dose of dexamethasone.

Consequently, phase 1 part of study CC-4047-MM-002 was designed to determine the MTD after administration of pomalidomide 2, 3, 4 or 5 mg doses given orally once a day for 21 days out of a 28 days cycle. This was a dose escalation study conducted in RRMM patients that had received prior treatment with lenalidomide and bortezomib. Other secondary efficacy endpoints included objective response, time to response, duration of response and overall survival (OS).

Thirty-eight (38) subjects were enrolled and all were included in the ITT population. A majority of subjects had stage III MM (66%) with median time from first diagnosis of 5.5 years and had received a median of 6 prior therapies.

Identification of MTD was to occur within the 1st cycle and after, subjects were allowed to continue study treatment at their assigned dose of pomalidomide. If they developed progressive disease (PD) at any time or fail to achieve minimum reduction of serum paraprotein of 25% (and 50% reduction in urine paraprotein if measurable) after 4 cycles, they had the option to add oral dexamethasone on days 1, 8, 15, 22 of each 28 day cycle and continue on study treatment until PD developed. Those with PD who chose not to add dexamethasone were discontinued.

The MTD was determined to be 4 mg daily based on dose limiting toxicity of neutropenia. Median duration of treatment was higher in the 4 mg cohorts compared with the 2 mg and 3 mg cohorts.

The response rates were higher in the 4 mg cohort with the addition of dexamethasone (CR or PR 29%) and also the 4 mg cohort had more subjects treated for more than 40 weeks, and fewer subjects requiring dose reductions compared with the other dosing cohorts.

Addition of dexamethasone improved the results for 1 year event-free rate. It was also noted that when adding dexamethasone neutropenia was reported less frequently.

Median OS was highest in the 4 mg cohort at 88 weeks although median progression-free survival (PFS) was higher in 3 mg cohort (36weeks) than 4 mg (20 weeks).

Based on results from this study, the posology selected for the phase 2 of the study and for the phase 3 pivotal study was with a starting dose for pomalidomide is 4 mg oral daily on days 1-21 of repeated 28-day cycles, in combination with dexamethasone 40 mg oral (20 mg if > 75 years) on Days 1, 8, 15 and 22 of each 28-day cycle.

2.5.2. Main studies

This application was initially supported by two phase 2 studies, CC-4047-MM-002 (phase 2) and IFM-2009-02. During the evaluation, data from the phase 3 study CC-4047-MM-003 became available and pivotal to this application.

Study CC-4047-MM-003

Methods

This was a phase 3 multicentre, randomized, open-label study designed to compare the efficacy and safety of pomalidomide plus low dose dexamethasone (Pom+LD-dex) versus high dose dexamethasone (HD-dex) in patients with refractory or relapsed and refractory MM.

Study Participants

Inclusion criteria consisted of:

- Adult patients (≥ 18 years)
- Subjects must have documented diagnosis of multiple myeloma and have measurable disease (serum M-protein ≥0.5 g/dL or urine M-protein ≥ 200 mg/24 hours)
- Subjects must have undergone prior treatment with ≥ 2 treatment lines of anti-myeloma therapy. Induction therapy followed by ASCT and consolidation/maintenance will be considered as one line.
- Subjects must have either refractory or relapsed and refractory disease defined as documented disease progression during or within 60 days of completing their last myeloma therapy.
- All subjects must have received at least 2 consecutive cycles of prior therapy with lenalidomide and bortezomib, either alone or in combination regimens, and had also received prior alkylator therapy. All subjects were required to have failed both lenalidomide and bortezomib.

Exclusion criteria applied to subjects eligible for stem cell transplant, creatinine clearance < 45 ml/min, resistance to high-dose dexamethasone used in the last line of therapy, and peripheral neuropathy ≥ Grade 2.

Treatments

All treatments were administered orally in 28-day cycles:

- Arm A: Pom (4 mg daily Days 1-21) + LD-dex (40 mg daily Days 1,8,15 and 22)
- Arm B: HD-dex (40 mg daily Days 1-4, 9-12, 17-20)

Subjects > 75 years in both arms received dexamethasone at a lower dose (20 mg).

During the treatment phase, subjects were permitted to receive bisphosphonate therapy and hematopoietic growth factors, platelet or red blood cell transfusions at the discretion of the investigator. Low-dose aspirin, low molecular weight heparin, or other anti-coagulant was to be given to all subjects assigned to Arm A as well as to any subjects in Arm B with a prior history of deep vein thrombosis or pulmonary embolism.

Subjects in treatment Arm A could participate in a pharmacokinetic study. Subjects were to continue their allocated treatment until confirmed progressive disease (PD), intolerable toxicity, death, withdrawal of consent or loss to follow up.

Treatment phase discontinuation occurred when a subject had confirmed progressive disease (PD) by at least one member of the Independent Response Adjudication Committee (IRAC). Subjects who did not progress or did not have confirmed progressive disease (PD) by IRAC but were intolerant to treatment or no longer wished to receive study treatment remained in the PFS follow-up period of the treatment phase and had efficacy assessments every 28 days until PD.

Subjects in the HD-dex arm who had confirmed PD, had the option to enrol into a companion study (CC-4047-MM-003C) to receive pomalidomide alone.

Following treatment phase discontinuation, subjects were assessed 28 days after and then entered a long-term follow-up period with visits 4 times per year until death or until 5 years after randomization, whichever occurred first. Subjects were followed for overall survival (OS) and occurrence of second primary malignancies (SPM).

Objectives

The primary objective was to compare the efficacy of Pom+LD-dex with that of HD-dex in subjects with refractory or relapsed and refractory MM.

The secondary objective of the study was to compare the safety of Pom + LD-dex with that of HD-dex in subjects with refractory or relapsed and refractory MM.

Exploratory objectives included the relationship between MM response and cytogenetic abnormalities; determination of the population pharmacokinetics of pomalidomide when administered along with LD-dex in subjects with refractory MM or relapsed and refractory MM; pomalidomide exposure and response relationship and mechanism of action of pomalidomide.

Outcomes/endpoints

The primary endpoint was PFS by International Myeloma Working Group (IMWG) criteria (Durie et al. Leukemia; 2006, 1-7).

Secondary endpoints included Overall survival (OS), Overall response (IMWG criteria per IRAC), Objective response (EBMT criteria per Investigators), Time to progression (TTP), Time to response, Duration of response (DOR), Clinical benefit response (time to increased haemoglobin value, time to improvement of bone pain, time to improvement of renal function, time to improvement of Eastern Cooperative Oncology Group (ECOG) performance status), QoL (EORTC QLQ-MY20 and QLQ-C30), as well as safety evaluations..

Sample size

A total of 426 subjects (284 in Treatment Arm A, 142 in Treatment Arm B) were planned for enrolment in the study for the primary analysis of PFS to detect a hazard ratio of 1.5 (HD-dex vs. Pom + LD-dex) between the 2 arms (5 to 7.5 months) at the 2-sided significance level of 0.05..

Randomisation

Randomisation in a 2:1 ratio was conducted using the stratification factors of age ($\leq$ 75 vs. > 75 years), disease population (refractory subjects vs. relapsed and refractory subjects vs. refractory/intolerant subjects) and number (2 vs. > 2) of prior anti-MM therapies.

Blinding (masking)

This was an open-label study.

Statistical methods

The statistical plan had a total of 426 subjects planned for enrolment. The primary analysis for PFS was planned to be performed after 242 subjects progressed or died during the study (PFS events), with 85% power to detect a hazard ratio of 1.5 (HD-dex vs. Pom + LD-dex) for PFS between the 2 treatment arms (5 to 7.5 months) at the 2-sided significance level of 0.05 (equivalent to a 1-sided alpha of 0.025).

An interim analysis for PFS was planned at 50% PFS information for futility only. An interim analysis for OS using the O'Brian-Fleming boundary for superiority was planned at the same time as the final PFS analysis, or at 50% OS information, whichever was later. All efficacy analyses were conducted in the ITT population (all randomized subjects) with additional supportive analyses in the Efficacy Evaluable (EE= all ITT subjects who took at least one dose of study treatment and who had baseline disease measurement and at least one post-baseline efficacy assessment or PFS event) population.

Subgroup analysis were also conducted for gender, race, baseline ECOG, stratification factors, parameters of prognostic significance (e.g. baseline renal impairment), refractoriness to

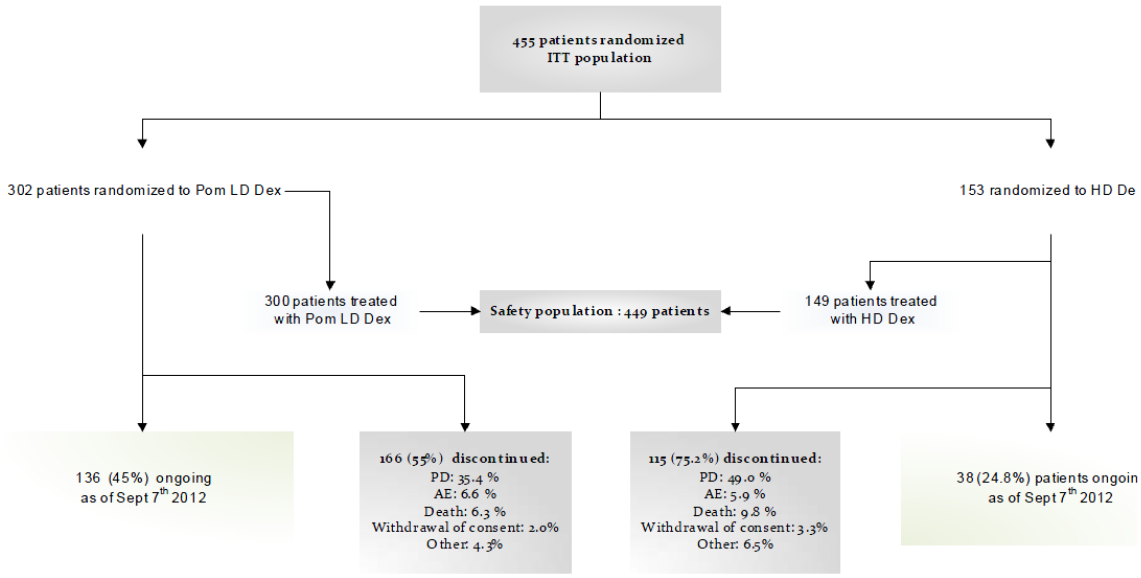
selected prior anti-myeloma therapies, end of Cycle 2 response status, grade 3 or 4 neutropenia/thrombocytopenia at Cycle 2 and for subjects randomized at least 6 months prior to the data cut-off.

A sensitivity analysis of PFS based on FDA guideline for censoring rules as well as comparison of time to treatment failure between the two arms were planned.

Results

Participant flow

Figure 1 – Subject disposition



AE = Adverse event; ITT = Intent-to-treat; PD = Progressive disease
Source: Table 14.1.1
Data cutoff: 07 Sep 2012

Recruitment

The first patient was enrolled on 18 March 2011 and the last patient visit for interim data cut off was 7 September 2012.

Conduct of the study

Based on the results of the final PFS analysis and OS interim analysis, with favourable outcome for Pom+LD-dex arm, the Data Monitoring Committee recommended subjects still on HD-dex arm (with or without PD) to receive pomalidomide, with or without dexamethasone at the discretion of the investigator. Per amendment 4 subjects who cross over prior to PD will

continue the treatment phase until PD, and those who cross over after PD on HD-dex will continue the treatment phase until the next PD. Subjects will then enter the follow up phase.

The interim analysis was performed at 154 PFS events and the DMC recommended that the trial continue as planned. The final analysis of PFS was based on 267 events and an interim analysis of OS was performed with a data cut off of 07 Sep 2012. The database was locked on 17th October 2012. The median follow up was 18.1 weeks.

Baseline data

Table 4 - Demographic and Baseline Characteristics: ITT Population

	Pom+LD-Dex (N=302)	HD-Dex (N=153)	Overall (N=455)
Age (years)			
n	302	153	455
Mean (SD)	63.6 (9.33)	63.7 (9.56)	63.6 (9.40)
Median (min, max)	64.0 (35.0, 84.0)	65.0 (35.0, 87.0)	64.0 (35.0, 87.0)
Age Distribution (years), n (%)			
≤ 65	167 (55.3)	81 (52.9)	248 (54.5)
> 65	135 (44.7)	72 (47.1)	207 (45.5)
Stratification Factor 1: Age			
≤ 75 Years Old	278 (92.1)	141 (92.2)	419 (92.1)
> 75 Years Old	24 (7.9)	12 (7.8)	36 (7.9)
Sex, n (%)			
Male	181 (59.9)	87 (56.9)	268 (58.9)
Female	121 (40.1)	66 (43.1)	187 (41.1)
Race, n (%)			
American Indian or Alaska Native	0 (0.0)	0 (0.0)	0 (0.0)
Asian	4 (1.3)	0 (0.0)	4 (0.9)
Black or African American	4 (1.3)	3 (2.0)	7 (1.5)
Native Hawaiian or Other Pacific Islanders	0 (0.0)	0 (0.0)	0 (0.0)
White	244 (80.8)	113 (73.9)	357 (78.5)
Other	2 (0.7)	2 (1.3)	4 (0.9)
Not Collected[a]	48 (15.9)	35 (22.9)	83 (18.2)
Ethnicity			
Hispanic or Latino	27 (8.9)	14 (9.2)	41 (9.0)
Not Hispanic or Latino	228 (75.5)	104 (68.0)	332 (73.0)
Not Collected[a]	47 (15.6)	35 (22.9)	82 (18.0)

[a] Race/ethnicity was not permitted to be collected by law in some regions

Data cutoff: 07 Sep 2012

Median number of prior anti MM treatments were 5 and the majority (82%) had refractory disease to both lenalidomide and bortezomib. Baseline patient characteristics were balanced across the two arms. Refractoriness status to previous treatments is shown below.

Table 5 - Refractoriness to Selected Prior Anti-Myeloma Drugs by Treatment Arm (ITT Population)

Refractory[a] to:	Pom+LD-Dex (N=302)	HD-Dex (N=153)	Overall (N=455)
Thalidomide	90 (29.8)	49 (32.0)	139 (30.5)
Lenalidomide	281 (93.0)	138 (90.2)	419 (92.1)
Thalidomide and Lenalidomide	84 (27.8)	45 (29.4)	129 (28.4)
Bortezomib	236 (78.1)	118 (77.1)	354 (77.8)
Lenalidomide and Bortezomib	221 (73.2)	108 (70.6)	329 (72.3)
Thalidomide, Lenalidomide and Bortezomib	70 (23.2)	36 (23.5)	106 (23.3)

Data cutoff: 07 Sep 2012

Numbers analysed

Table 6 - Subject disposition (ITT population)

	Pom+LD-Dex (N=302) n (%)	HD-Dex (N=153) n (%)	Overall (N=455) n (%)
Intent-to-Treat Population[a]	302 (100.0)	153 (100.0)	455 (100.0)
Safety Population[b]	300 (99.3)	149 (97.4)	449 (98.7)
Efficacy Evaluable Population[c]	284 (94.0)	139 (90.8)	423 (93.0)
Subjects on Treatment	136 (45.0)	38 (24.8)	174 (38.2)
Subjects Who Discontinued from Treatment	166 (55.0)	115 (75.2)	281 (61.8)
Primary Reason for Discontinuation			
Adverse Event	20 (6.6)	9 (5.9)	29 (6.4)
Withdrawal by Subject	6 (2.0)	5 (3.3)	11 (2.4)
Progressive Disease	107 (35.4)	75 (49.0)	182 (40.0)
Lost to Follow up	1 (0.3)	1 (0.7)	2 (0.4)
Death	19 (6.3)	15 (9.8)	34 (7.5)
Other, Specify[d]	13 (4.3)	10 (6.5)	23 (5.1)

[a] The ITT population is defined as all subjects who are randomized, regardless of whether they receive study treatment or not.
[b] The Safety population is defined as all randomized subjects who receive at least one dose of study drug (either pomalidomide or dexamethasone).
[c] The Efficacy Evaluable population is defined as all ITT subjects who take at least one dose of study treatment, and who have baseline disease measurement and at least one post-baseline efficacy assessment or PFS event.
[d] Reasons include: investigator decision (n=13), progressive disease (n=1); new treatment started (n=1); subject request (n=2); medical decision (n=1); clinical relapse (n=1); subject did not respond to treatment (n=1); deterioration of performance status (n=1); unable to tolerate study medication (n=1); Family notifed the site that the subject had died (n=1) (Listing 16.2.1.1).
Note: Percentage is based on the ITT population.
Source: Table 14.1.1
Data cutoff: 07 Sep 2012

Outcomes and estimation

Efficacy results on the ITT population as of 7 September 2012 have been summarised in the table below. As shown as well in Figure 2, the study met its primary endpoint with PFS was significantly longer with Pom + LD-dex arm compared with the HD-dex arm exceeding the pre-specified difference (observed HR 0.45 versus planned 0.67).

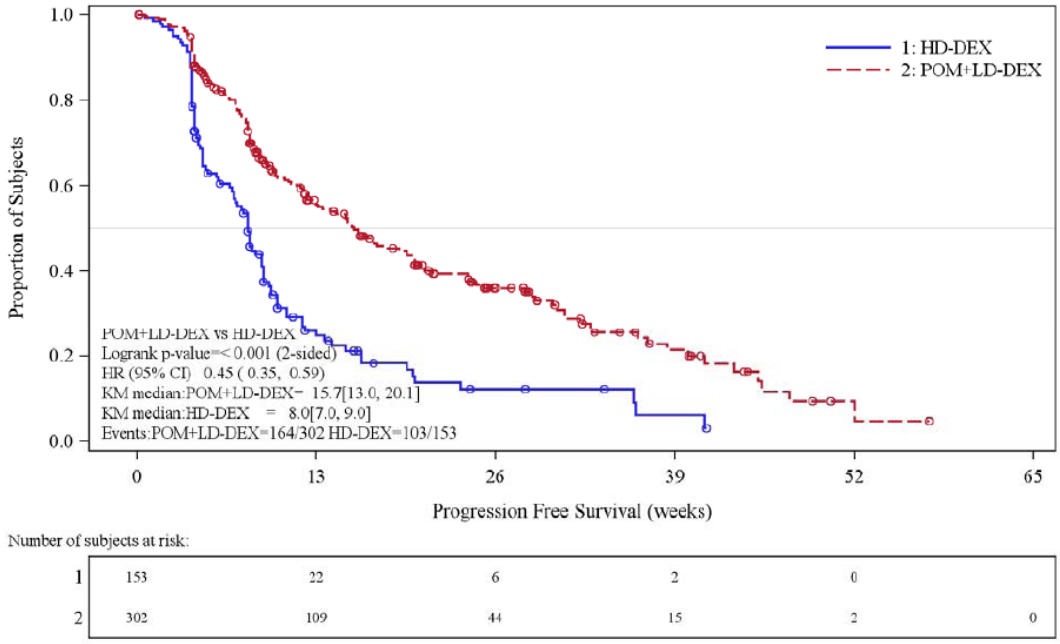
Table 7 - Efficacy endpoints by IRAC assessment, IMWG criteria (ITT population)

Efficacy endpoint		**Pom+LD-dex (n=302)**	**HD-dex (n=153)**
Progression free survival	Censored, n (%)	138 (45.7)	50 (32.7)
	Progressed/Died, n (%)	164 (54.3)	103 (67.3)
	Median (weeks)	15.7	8.0
	Two-sided 95% CI	13.0, 20.1	7.0, 9.0
	Hazard ratio (2 sided 95% CI)	0.45[0.35, 0.59]	
	Log rank test two sided p value	<0.001	
Time to progression	Censored, n (%)	171 (56.6)	69(45.1)
	Progressed, n (%)	131(43.4)	84(54.9)
	Median (weeks)	20.1	8.3
	Two-sided 95% CI	16.1, 28.1	7.7, 9.6
	Hazard ratio (2 sided 95% CI)	0.42[0.31, 0.56]	
	Log rank test two sided p value	<0.001	
Time to treatment failure	Censored, n (%)	115 (38.1)	28 (18.3)
	Treatment failed, n (%)	187 (61.9)	125 (81.7)
	Median (weeks)	15.3	8.0
	Two-sided 95% CI	12.1, 18.1	4.9, 8.1
	Hazard ratio (2 sided 95% CI)	0.441[0.349, 0.557]	
	Log rank test two sided p value	<0.001	
Overall survival	Censored, n (%)	226 (74.8)	95 (62.1)
	Died, n (%)	76 (25.2)	58 (37.9)
	Median (weeks)	NE	34.0
	Two-sided 95% CI	48.1, NE	23.4, 39.9
	Hazard ratio (2 sided 95% CI)	0.53 [0.37, 0.74]	
	Log rank test two sided p value	<0.001	
Response	SCR	0 (0.0)	0 (0.0)
	CR	1 (0.3)	0 (0.0)
	VGPR	4 (1.3)	1 (0.7)
	PR	45 (14.9)	5 (3.3)
	SD	186 (61.6)	81 (52.9)
	PD	35 (11.6)	41 (26.8)
	NE	31 (10.3)	25 (16.3)
	At least one post baseline assessment No post baseline assessment	9 (3.0) 22 (7.3)	10 (6.5) 15 (9.8)
	p value	<0.001	
	Dichotomized response		

	SCR or CR or VGPR or PR SD or PD or NE	50 (16.6) 252 (83.4)	6 (3.9) 147 (96.1)
	p value	<0.001	
	Odds ratio (95% CI)	4.86 [2.03, 11.61]	
	p value	<0.001	
Time to response	Responders (n)	50	6
	Mean (SD) (weeks)	7.8 (4.51)	10.7 (8.13)
	Median (min, max) (weeks)	8.1 (4.0, 24.4)	7.9 (4.1, 24.1)
	p value	0.565	
Duration of response	Subjects with at least PR (%)	50 (100%)	6 (100%)
	Censored, n (%)	37 (74.0%)	4 (66.7%)
	Progressed/Died, n (%)	13 (26.0%)	2 (33.3%)
	Median (weeks) (2 sided 95% CI)	32.0 [24.1, NE]	28.6 [20.1, 43.9]

SCR: stringent complete response; CR: complete response; VGPR: very good partial response; PR: partial response; SD: stable disease; PD: progressive disease; NE: not evaluable
Data cut off: 7 Sep 2012

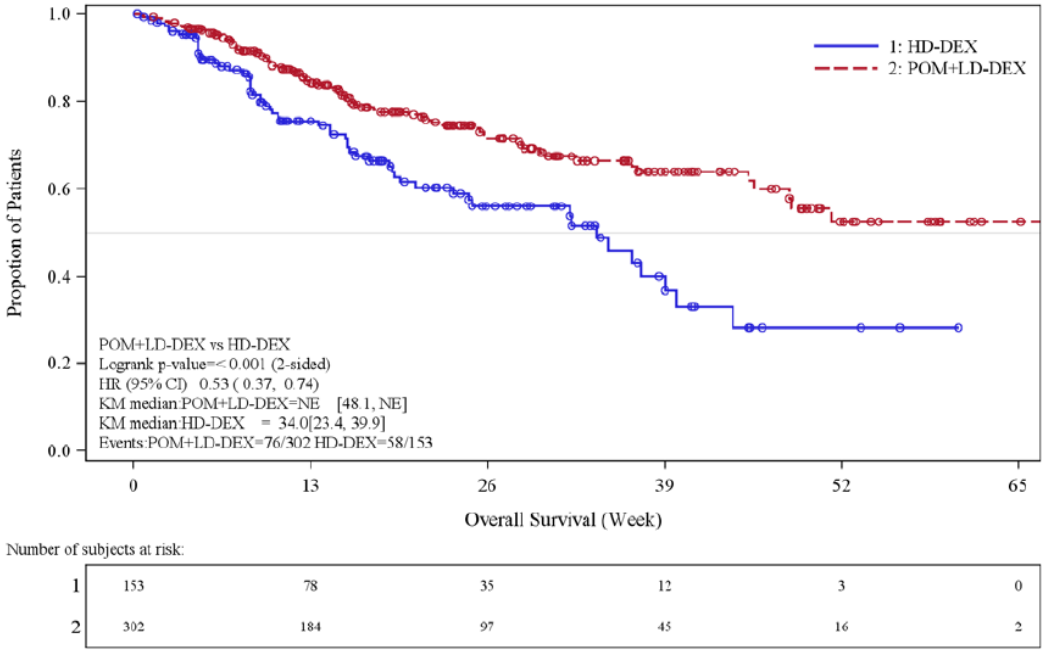
Figure 2 – Progression Free Survival based on IRAC review of responses by IMWG criteria (stratified log rank test) (ITT population)



Source: Figure 14.2.1.1a
Data cutoff: 07 Sep 2012

The difference in OS between the two treatment arms was also statistically significant (HR 0.53 [95% CI: 0.37, 0.74], p < 0.001) exceeding the pre-specified OS difference (observed HR 0.53 versus planned 0.67) (see figure below). The median (min, max) OS follow up was 19.2 weeks (1.4, 70.0) in the Pom + LD-dex arm and 16.3 weeks (0.3, 60.6) in the HD-dex arm.

Figure 3 – Kaplan-Meier curve Overall Survival (ITT population)



Source: Figure 14.2.2.1

Data cutoff: 07 Sep 2012

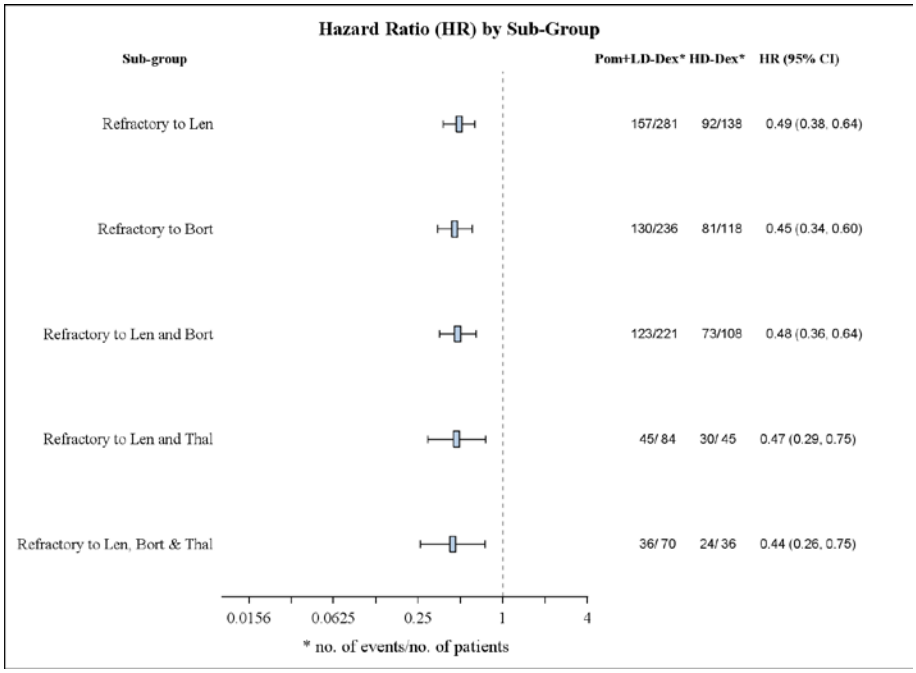
Response rates based on IRAC review of ITT population (IMWG criteria) demonstrated favourable outcome for Pom+LD-dex group. Consistent results were obtained from other response rates analysis including subgroup analysis.

Ancillary analyses

Results for the efficacy evaluable population were consistent with those observed in the ITT population.

Similar PFS results were obtained by IRAC review based on EBMT criteria. Other analyses, including sensitivity analysis, were consistent with the primary analysis. In addition, subgroup PFS and OS analyses were consistently favourable for Pom+LD-dex group in all subgroups. Results of the subgroup analysis based on refractory status (ITT) are shown in the figure below.

Figure 4 – Hazard Ratios (95% CI) of Effect of Pom + LD-Dex on PFS by IRAC Review Based on IMWG Criteria in Subgroups (ITT Population)



Summary of main study

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

Table 8 - Summary of Efficacy for trial MM-003

Title: A Phase 3, Multicentre, Randomised, Open-label Study to compare the Efficacy and Safety of Pomalidomide in Combination with Low-Dose Dexamethasone versus High-Dose Dexamethasone in Subjects with Refractory or Relapsed and Refractory Multiple Myeloma		
Study identifier	CC-4047-MM-003 EUDRACT 2010-019820-30 IND 066188	
Design	Phase 3, randomised, open-label, multicentre	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	Until disease progression not applicable not applicable
Hypothesis	Non-inferiority	
Treatments groups	Pom+LD-dex	pomalidomide (4 mg) on Days 1- 21 of each 28-day treatment cycle. Low-dose dexamethasone (40 mg) on Days 1, 8, 15, and 22 of a 28-day cycle (subjects > 75 years received 20 mg). Until disease progression 302 patients enrolled

	HD-dex		dexamethasone (40 mg) on Days 1 through 4, 9 through 12, and 17 through 20 of a 28-day cycle. Until disease progression 153 patients enrolled
Endpoints and definitions	Primary endpoint	PFS	Progression-Free Survival (by IMWG criteria)
	Secondary endpoint	OS	Overall survival
Database lock	7 September 2012		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat		
Descriptive statistics and estimate variability	Treatment group	Pom+LD-dex	HD-dex
	Number of subject	302	153
	PFS Median (weeks)	15.7	8.0
	Two-sided 95% CI	13.0, 20.1	7.0, 9.0
	HR (2 sided 95% CI)	0.45 (0.25, 0.59)	
	P value (log rank test 2 sided)	<0.001	
	OS Median (weeks)	NE	34.0
	Two-sided 95% CI	48.1, NE	23.4, 39.9
	HR (2 sided 95% CI)	0.53 (0.37, 0.74)	
	P value (log rank test 2 sided)	<0.001	

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

Not applicable.

Clinical studies in special populations

No studies have been conducted in special populations.

Supportive studies

An overview of the study design of the phase 2 studies is shown below.

Table 9 – Overview of Study design of Study CC-4047-MM-002 and Study IFM-2009-02

	CC-4047-MM-002 (Phase 2 Segment)	IFM-2009-02
Study Design	Phase 1b/2, multicentre, randomised, open label, dose-escalation study to determine the MTD and evaluate safety and efficacy of pomalidomide alone and in combination with low-dose dexamethasone.	Phase 2, multicentre, randomised, open label study to evaluate the safety and efficacy of two regimens of oral pomalidomide in combination with low-dose dexamethasone
Population	Subjects with RRMM who had received prior treatment that included lenalidomide and bortezomib and were refractory to their last treatment	Subjects with RRMM who had received prior treatment with lenalidomide and bortezomib and had been non-responsive or refractory to the last course of treatment with both drugs.
Analysis Dataset (ITT)	Total (N=221) Arm A (n=113) Arm B (n=108) **45 remain on treatment**	Total (N=84) Arm A (n=43) Arm B (n=41) **23 remain on treatment**
Dose Regimens	2 arms randomised (1:1) **Arm A (21/28 d, with Dex)**: Pom at 4 mg daily Days 1-21 of 28-day cycle + low-dose dexamethasone (20 mg [subjects >75 yr] or 40 mg [subjects ≤ 75 yr]) daily on Days 1, 8, 15, and 22 of each 28-day cycle vs. **Arm B (21/28 d)**: Pom at 4 mg daily Days 1-21 of 28-day cycle[i)] Oral administration	2 arms randomised (1:1): **Arm A (21/28 d)**: Pom at 4 mg daily Days 1-21 of 28-day cycle + low-dose dexamethasone (40 mg) daily on Days 1, 8, 15, and 22 of each 28-day cycle vs. **Arm B (28/28)**: Pom at 4 mg daily Days 1-28 of 28-day cycle + low-dose (40 mg) dexamethasone weekly Oral administration
Study Endpoints	Objective response (EBMT and IMWG criteria)[ii)] Duration of response Time to response **Progression free survival** [b,iii)] Time to progression Overall survival Relationship between response and cytogenetic abnormalities Safety	**Response rate** (IMWG criteria)[b,c] Duration of response Time to response Progression free survival [b] Time to progression Overall survival Event-free survival Relationship between response and cytogenetic abnormalities Safety

Eligibility Criteria	Documented diagnosis of MM and had relapsed and refractory disease. Received at least 2 prior therapies. Undergone prior treatment with at least 2 cycles of lenalidomide and at least 2 cycles of bortezomib (either in separate regimens or within the same regimen). Relapsed after having achieved at least stable disease for at least one cycle of treatment to at least one prior regimen and then developed PD. Documented evidence of PD during or within 60 days (measured from the end of the last cycle) of completing treatment with the last anti-myeloma drug regimen used just prior to study entry (refractory disease). Measurable levels of myeloma paraprotein in serum (≥ 0.5 g/L) or urine (≥ 0.2 g/24 hours) ECOG performance status score of 0, 1 or 2 None of the following laboratory abnormalities: ANC < 1,000/µL. Platelet count < 75,000/µL for subjects in whom < 50% of bone marrow nucleated cells were plasma cells; or a platelet count < 30,000/µL for subjects in whom ≥ 50% of bone marrow nucleated cells were plasma cells. Serum creatinine > 3.0 mg/dl	Symptomatic and progressive myeloma (per IMWG criteria) following bortezomib and/or lenalidomide treatment, defined as follows: Subjects must have undergone prior treatment with at least 2 cycles of lenalidomide and at least 2 cycles of bortezomib: At diagnosis or at relapse Either in separate regimens or within the same regimen Any number of prior therapies Course of treatment with bortezomib and/or lenalidomide did not need to be the very last line of therapy administered At best, stable disease (per IMWG criteria) (i.e., not achieving a partial response), with the last course of bortezomib and lenalidomide administered to the subject during any line of anti-myeloma therapy. Subjects might have responded initially to either bortezomib and/or lenalidomide but did not respond again at rechallenge with bortezomib and/or lenalidomide. A clearly detectable and quantifiable monoclonal M-component value ECOG performance status of 0, 1 or 2 Adequate bone marrow function, documented within 72 hours prior to treatment without transfusion or growth factor support, defined as: ANC ≥ 1000/mm^3, Platelets ≥ 75000/mm^3 Haemoglobin ≥ 8.5g/dl Serum creatinine clearance (Cockcroft-Gault formula) ≥ 50 ml/min

ANC = absolute neutrophil count; CC-4047 = pomalidomide; d – days; Dex = dexamethasone; ECOG = Eastern Cooperative Oncology Group; EBMT = European Group for Blood and Marrow Transplantation; IFM = Intergroup Francophone du Myélome; IMWG = International Myeloma Working Group; ITT = Intent to treat; MM = multiple myeloma; MTD = maximum tolerated dose; PD = progressive disease; Pom = pomalidomide; QD = once daily.
[i)] Subjects in the single agent pomalidomide treatment arm who develop confirmed PD at any time have the option to receive oral dexamethasone in addition to their current dose of pomalidomide.; [ii)]Independently assessed; [iii)] Primary endpoint

Study CC-4047-MM-002

Subjects in both arms could continue study treatments until disease progression (PD) or intolerable toxicity or discontinuation for any other reason. Subjects in arm B who developed PD at any time had the option to receive oral dexamethasone in addition to pomalidomide at the

same recommended dose of arm A. Subjects with PD who chose not to add dexamethasone were discontinued from study treatment and those who chose to add dexamethasone could continue treatment until PD developed again.

The pomalidomide and dexamethasone doses could be reduced or stopped due to toxicity according to pre-specified instructions in the protocol. All subjects received prophylactic anti-thrombotic treatment and the use of bisphosphonates and growth factors were allowed.

Upon discontinuation from study treatment subjects were to be assessed for up to five years, for survival and subsequent anti-myeloma therapies.

A total of 221 subjects were enrolled and as of 01 April 2011, 45 (20.4%) subjects remain active in the study (23 arm A and 22 in arm B) and the most common reason for premature discontinuation is disease progression.

The majority of subjects were male and white below the age of 75 years with MM stage III and had received a median of 5 prior regimens that included lenalidomide and bortezomib as per protocol, and had prior exposure to thalidomide (67%) and stem cell transplant (75%). Only 33 patients were of black origin. Overall baseline characteristics were balanced between the two arms. More than half of the subjects were refractory to lenalidomide and/or bortezomib and 95% were refractory to last prior regimen.

Study IFM 2009-02

Subjects in both arms could continue study treatments until disease progression (PD) or relapse or intolerable toxicity or discontinuation for any other reason.

The pomalidomide and dexamethasone doses could be reduced due to toxicity according to pre-specified instructions in the protocol. All subjects received prophylactic anti-thrombotic treatment and the use of bisphosphonates and growth factors (except first cycle) were allowed.

84 subjects were randomized patients and comprise the ITT population. At the time of cut-off analysis (1st March 2011) 61 patients had discontinued from the study and 23 patients are still receiving study treatment. The most common cause for discontinuation was disease progression.

Baseline characteristics were in general balanced in both arms. The majority of patients were male, median age 60 years and had stage III disease. Race was not recorded in this study. Median number of prior regimens was 5 and in line with the protocol all patients had received lenalidomide and bortezomib. Other frequently used therapies apart from steroids included thalidomide (73%) and autologous stem cell transplant (81%).

More than half of the subjects were refractory to lenalidomide and bortezomib and the last regimen prior to study entry.

The following table summarise the efficacy results from the supportive studies.

Table 10 –Study CC-4047-MM-002 and Study IFM-2009-02 - Efficacy Endpoints (Based on Best Response Assessment EBMT/IMWG Criteria)- ITT

Efficacy endpoint	Statistic	CC-4047-MM-002			IFM-2009-02		
		Pom [(i)] (21/28) (N = 108)	Pom + Dex (21/28) (N = 113)	Total (N = 221)	Arm A (21/28) (N = 43)	Arm B (28/28) (N = 41)	Total (N = 84)
Response (Best response)	Overall response rate (CR, VGPR or PR)[(ii)], n (%) [95% CI]	10 (9.3)	34 (30.1)[(iii)]	44 (19.9)	15 (34.9) [21.0, 50.9]	14 (34.1) [20.1, 50.6]	29 (34.5) [24.5, 45.7]
	Complete response (n [%])	0 (0.0)	1 (0.9)	1 (0.5)	1 (2.3)	2 (4.9)	3 (3.6)
	Very good partial response (n [%])	3 (2.8)	9 (8.0)	12 (5.4)	1 (2.3)	1 (2.4)	2 (2.4)
	Unconfirmed CR (n [%]) [(iv)]	1 (0.9)	1 (0.9)	2 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)
	Partial response (n [%])	7 (6.5)	24 (21.2)	31 (14.0)	13 (30.2)	11 (26.8)	24 (28.6)
	Stable disease (n [%])	67 (62.0)	57 (50.4)	124 (56.1)	19 (44.2)	21 (51.2)	40 (47.6)
	Progressive disease (n [%])	17 (15.7)	7 (6.2)	24 (10.9)	5 (11.6)	3 (7.3)	8 (9.5)
Duration of Response (weeks)	Median[(v)] duration of ≥ PR (95% CI)[(vi)]	NE (NE, NE)	32.1 (22.1, 39.9)	33.1 (24.7, 44.1)	45.7 (15.1, 54.7)	31.6 (16.1, NE)	35.3 (24.1, 54.7)
Progression Free Survival (weeks)[(vii)]	Median (95% CI)	10.7 (8.3, 16.1)	16.6[(viii)] (14.1, 21.1)	15.1 (12.1, 16.6)	25.1 (16.3, 41.7)	25.1 (13.3, 36.0)	25.1 (16.3, 36.1)
Time to Response (weeks) (with at least PR)	Median (Min, Max)	8.9 (4.1, 49.6)	8.1 (3.7, 45.1)	8.1 (3.7, 49.6)	11.6 (3.6, 41.1)	4.9 (2.6, 36.0)	8.0 (2.6, 41.1)
Overall Survival (weeks)	Median (95% CI)	59.3 (41.6, NE)	62.6 (53.6, NE)	62.6 (53.6, NE)	58.4 (38.7, 60.6)	66.4 (39.9, NE)	58.4 (42.7, NE)

CI = confidence interval; CR = complete response; Dex = dexamethasone; EBMT = European Group for Blood and Marrow Transplantation; IMWG = International Myeloma Working Group; ITT = intent to treat; max = maximum; min = minimum; NA = not available, NE = not estimable; Pom = pomalidomide; PR = partial response; VGPR = very good partial response

[(i)] Responses in the overall pomalidomide arm including 61 subjects who added dexamethasone to their treatment. [(ii)] Values according to EBMT and IMWG criteria are identical for Study CC-4047-MM-002 . [(iii)] Fisher Exact Test p < 0.001 Pom + Dex vs. pomalidomide. [(iv)] M-protein not detected by immunofixation but no bone marrow confirmation of response: uCR is a subcategory of VGPR. [(v)] The median is based on Kaplan-Meier estimate. [(vi)] 95% confidence interval (CI) about the median. [(vii)] Cutoff date: 01 Apr 2011 (CC-4047-MM-002); 01 Mar 2011 (IFM-2009-02). [(viii)] log rank p-value = 0.019 (2-sided) Pom + Dex vs. pomalidomide overall (including Pom/Dex added).

Results of subgroup analyses performed in both studies were in general in line with those of the ITT population, including the subgroup analysis of patients refractory to different prior regimens. In study CC-4047-MM-002 the subgroup results were in general more favourable for the combination arm except for the patients > 65 years but there was an numerically imbalance in this subgroup (n=51 combination arm versus n=39 in single arm).

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

Dosing of pomalidomide was first studied in two phase 1 adequately designed studies to determine the MTD of pomalidomide. The activity of pomalidomide in MM was also explored earlier in the development as a single agent and in combination with low dose dexamethasone (LD-dex).

Efficacy of pomalidomide in combination with LD-dex in the proposed indication was based on one pivotal study (CC-4047-MM-003) supported by two phase 2 studies, CC-4047-MM-002 (phase 2) and IFM 2009-02.

The phase 3 study CC-4047-MM-003 was adequately designed to demonstrate the efficacy of pomalidomide in combination with low dose dexamethasone against an appropriate comparator (HD-Dex) in the proposed RRMM target population. The inclusion criteria of the study corresponded to the criteria by the IMWG of primary refractory and relapsed-and-refractory multiple myeloma patients. The choice of endpoints and statistical methods were considered appropriate.

Both phase 2 studies have included a population of RRMM that represents the proposed target population. Study CC-4047-MM-002 phase 2 was designed to compare the efficacy of pomalidomide with or without dexamethasone so any potential differences between arms would represent a benefit of having dexamethasone added to the treatment. Study IFM 2009-02 was a non comparative study looking at the activity of Pom + Dex in two slightly different schedules for pomalidomide (21/28 versus 28/28 days). As exploratory phase 2 trials the choice of endpoints and methodology were considered appropriate.

Efficacy data and additional analyses

Data from the phase 1 studies justified the proposed dose of pomalidomide 4 mg once daily and dosing schedule.

The results of study CC-4047-MM-002 showed pomalidomide as single agent failed to demonstrate efficacy as pre-specified in the analysis plan but when combined with LD-dex there

is significant activity with a documented response rate of 30% and a median OS of 62 weeks. It appeared there was no cross resistance of pomalidomide with other immunomodulatory agents and activity was documented in patients refractory to several prior therapies, including stem cell transplant. This study supported the proposed combination of pomalidomide with low dose dexamethasone.

In study IFM 2009-02 pomalidomide in combination with dexamethasone showed a response rate of around 34% in line with study CC-4047-MM-002. PFS results were more favourable in this study that may be due to having a younger population. There were no significant differences between the two arms although the duration of response was longer with the 21/28 day regimen. This study supported the dose schedule of pomalidomide for 21 days out of a 28-day cycle in combination with low dose dexamethasone.

The pivotal study CC-4047-MM-003 demonstrated that treatment of pomalidomide in combination with low dose dexamethasone was superior to high dose dexamethasone in patients with primary refractory MM and relapsed- and- refractory MM. A statistically significant difference in favour of the experimental treatment was shown for the primary analysis of PFS (median 15.7 weeks versus 8 weeks) and other endpoints of overall survival and response rate. Further subgroup analysis showed consistent results in favour of the combination treatment. A plausible extrapolation of these positive results and a clear clinical benefit to patients with relapsed disease by the IMWG criteria justifies the proposed indication. The indication clearly specifies patients should demonstrate disease progression on the last therapy but does not require to occur within 60 days. In conclusion, this pivotal study has confirmed the efficacy of pomalidomide in the proposed indication.

Based on the results of the final PFS analysis and OS interim analysis, with favourable outcome for Pom+LD-dex arm, the Data Monitoring Committee recommended subjects still on HD-dex arm to receive pomalidomide, with or without dexamethasone at the discretion of the investigator. The companion study CC-4047-MM-003/C is currently ongoing. The CHMP recommends that the final study report is submitted when available.

2.5.4. Conclusions on the clinical efficacy

The efficacy of Pom+LD-dex in the proposed indication has been demonstrated.

2.6. Clinical safety

As of 1st April 2011, the safety of pomalidomide had been studied in 13 studies involving 171 healthy volunteers as well as 522 patients with different oncology indications: MM (N = 386) , myeloproliferative neoplasm associated myelofibrosis (N = 63) and solid tumours (N = 73).

Following the submission of data from phase 3 study CC-4047-MM-03 (cut off 7 Sep 2012), a total of 300 additional patients had been exposed to pomalidomide in combination with low dose dexamethasone in the proposed posology. Controlled data from this phase 3 trial is pivotal for the safety assessment and is discussed in detail below. Data from other studies will only be mentioned where relevant.

Patient exposure

In Study CC4047-MM-003, the median duration of treatment in the Pom + LD-dex arm (12.4 weeks) was longer than that in the HD-dex arm (8.0 weeks). The median number of treatment cycles was 3 in the Pom + LD-dex arm (min, max: 1, 16 cycles) and 2.0 in the HD-dex arm (min, max: 1, 12 cycles).

Subjects in the Pom + LD-dex arm were exposed to pomalidomide for a median (min, max) of 63 (2, 327) days at a median daily dose of 4.0 mg. The median relative dose intensity was 0.90.

Subjects in the Pom + LD-dex arm were exposed to dexamethasone for a median of 12 days at a median daily dose of 40 mg. Subjects in the HD-dex arm were exposed to dexamethasone for a median of 20 days at a median daily dose of 40 mg. The difference in dexamethasone exposure (in days) reflects the difference in planned dexamethasone dose regimens used in the 2 treatment arms The median relative dose intensity for dexamethasone was similar (0.9 in the Pom + LD-dex arm and 1.0 in the HD-dex arm).

Adverse events

Almost all subjects in each treatment arm had at least 1 treatment-emergent AE (TEAE, 97.0% in the Pom + LD-dex arm and 93.3% in the HD-dex arm). The frequencies of any Grade 3/4 or Grade 5 TEAE as well as serious AE (SAE) were in general similar in the 2 treatment arms.

More subjects in the Pom + LD-dex arm had 1 or more TEAEs that led to the discontinuation, dose reduction or dose interruption of either study drug compared to the HD-dex group (9.7%versus 5.4%; 33% versus 23.5%; 64.3% versus 43.6% respectively).

Table 11 – Overview of Treatment-emergent Adverse Events (Safety population)

AE Category [a]	Pom + LD-dex (N=300)	HD-dex (N=149)
Subjects with at Least One AE	291 (97.0)	139 (93.3)
Subjects with at Least One CTCAE[b] **Grade 3-4** AE	234 (78.0)	113 (75.8)
Subjects with at Least One AE Related to:		
Pomalidomide	230 (76.7)	NA
Dexamethasone	170 (56.7)	107 (71.8)
Either Study Drug	252 (84.0)	107 (71.8)
Subjects with at Least One CTCAE[b] Grade 3-4 AE Related to:		
Pomalidomide	170 (56.7)	NA
Dexamethasone	84 (28.0)	64 (43.0)
Either Study Drug	182 (60.7)	64 (43.0)
Subjects with at Least One CTCAE[b] **Grade 5** AE	37 (12.3)	22 (14.8)
Subjects with at Least One Serious AE	153 (51.0)	75 (50.3)
Subjects with at Least One Serious AE Related to:		
Pomalidomide	63 (21.0)	NA
Dexamethasone	43 (14.3)	34 (22.8)
Either Study Drug	71 (23.7)	34 (22.8)
Subjects with at Least One Serious AE Leading to Discontinuation of:		
Pomalidomide	18 (6.0)	NA
Dexamethasone	17 (5.7)	8 (5.4)
Either Study Drug	20 (6.7)	8 (5.4)
Subjects with at Least One AE Leading to Discontinuation of:		
Pomalidomide	24 (8.0)	NA
Dexamethasone	25 (8.3)	8 (5.4)
Either Study Drug	29 (9.7)	8 (5.4)

AE Category [a]	Pom + LD-dex (N=300)	HD-dex (N=149)
Subjects with at Least One Study Drug Related AE Leading to Discontinuation of:		
Pomalidomide	11 (3.7)	NA
Dexamethasone	9 (3.0)	6 (4.0)
Either Study Drug	15 (5.0)	6 (4.0)
Subjects with at Least One AE Leading to Reduction of:		
Pomalidomide	71 (23.7)	NA
Dexamethasone	48 (16.0)	35 (23.5)
Either Study Drug	99 (33.0)	35 (23.5)
Subjects with at Least One Study Drug Related AE Leading to Reduction of:		
Pomalidomide	61 (20.3)	NA
Dexamethasone	43 (14.3)	31 (20.8)
Either Study Drug	87 (29.0)	31 (20.8)
Subjects with at Least One AE Leading to Interruption of:		
Pomalidomide	184 (61.3)	NA
Dexamethasone	151 (50.3)	65 (43.6)
Either Study Drug	193 (64.3)	65 (43.6)
Subjects with at Least One Study Drug Related AE Leading to Interruption of:		
Pomalidomide	131 (43.7)	NA
Dexamethasone	46 (15.3)	44 (29.5)
Either Study Drug	136 (45.3)	44 (29.5)

NA=not applicable.
[a] A subject with multiple occurrences of an AE is counted only once in the AE category.
[b] CTCAE=Common Terminology Criteria Adverse Events (version 4.0).
Note: Treatment-emergent adverse events (TEAEs) are defined as any AE occurring or worsening on or after the first treatment of the study medication and within 30 days after the end date of study drug.

All Treatment Emergent Adverse Events

TEAEs occurred in the following system organ classes (SOCs) in descending order of frequency in the Pom + LD-dex arm (percentages in parentheses are Pom + LD-dex vs. HD-dex): blood and lymphatic system disorders (69.7% vs. 57.0%); general disorders (64.0% vs. 55.0%); infections and infestations (55.0% vs. 48.3%); gastrointestinal disorders (52.3% vs. 36.9%); musculoskeletal and connective tissue disorders (43.3% vs. 48.3%); respiratory, thoracic, and mediastinal disorders (41.7% vs. 25.5%); nervous system disorders (33.0% vs. 30.2%); metabolism and nutrition disorders (31.7% vs. 40.3%); skin and subcutaneous tissue disorders (24.3% vs. 14.8%); and psychiatric disorders (22.3% vs. 33.6%). A summary of the most frequent TEAEs is displayed below.

Table 12 – TEAE by Any NCI-CTCAE Grade That Occurred in ≥ 5% of Subjects and Grade 3/4 Reported in ≥ 2% of Subjects in Either Treatment Arm by SOC and Preferred Term (Safety Population)

System Organ Class/Preferred Term[i)]	Any Grade		Grade 3/4	
	Pom + LD-Dex (N=300)	HD-Dex (N=149)	Pom + LD-Dex (N=300)	HD-Dex (N=149)
Number of subjects with at least 1 TEAE	291 (97.0)	139 (93.3)	234 (78.0)	113 (75.8)
Blood and lymphatic system disorders	**209 (69.7)**	**85 (57.0)**	**176 (58.7)**	**68 (45.6)**
Anaemia	137 (45.7)	63 (42.3)	81 (27.0)	43 (28.9)
Neutropenia	136 (45.3)	29 (19.5)	125 (41.7)	22 (14.8)
Thrombocytopenia	81 (27.0)	40 (26.8)	62 (20.7)	36 (24.2)
Leukopenia	37 (12.3)	8 (5.4)	26 (8.7)	5 (3.4)
Febrile neutropenia	20 (6.7)	0 (0.0)	20 (6.7)	0 (0.0)
Lymphopenia	13 (4.3)	8 (5.4)	11 (3.7)	6 (4.0)
General disorders and administration site conditions	**192 (64.0)**	**82 (55.0)**	**52 (17.3)**	**28 (18.8)**
Fatigue	85 (28.3)	36 (24.2)	14 (4.7)	7 (4.7)
Pyrexia	63 (21.0)	29 (19.5)	9 (3.0)	4 (2.7)
Asthenia	41 (13.7)	24 (16.1)	10 (3.3)	9 (6.0)
Oedema peripheral	39 (13.0)	16 (10.7)	4 (1.3)	3 (2.0)
General physical health deterioration	27 (9.0)	14 (9.4)	16 (5.3)	10 (6.7)
Infections and infestations	**165 (55.0)**	**72 (48.3)**	**72 (24.0)**	**34 (22.8)**
Pneumonia	32 (10.7)	14 (9.4)	27 (9.0)	11 (7.4)
Upper respiratory tract infection	28 (9.3)	9 (6.0)	3 (1.0)	2 (1.3)
Bronchitis	24 (8.0)	6 (4.0)	1 (0.3)	0 (0.0)
Nasopharyngitis	19 (6.3)	1 (0.7)	0 (0.0)	0 (0.0)
Respiratory tract infection	17 (5.7)	5 (3.4)	3 (1.0)	0 (0.0)
Urinary tract infection	14 (4.7)	8 (5.4)	2 (0.7)	3 (2.0)
Sepsis	7 (2.3)	4 (2.7)	6 (2.0)	3 (2.0)
Lower respiratory tract infection	8 (2.7)	7 (4.7)	5 (1.7)	3 (2.0)
Gastrointestinal disorders	**157 (52.3)**	**55 (36.9)**	**19 (6.3)**	**10 (6.7)**
Constipation	58 (19.3)	18 (12.1)	5 (1.7)	0 (0.0)
Diarrhoea	55 (18.3)	24 (16.1)	3 (1.0)	2 (1.3)
Nausea	35 (11.7)	13 (8.7)	2 (0.7)	2 (1.3)
Vomiting	23 (7.7)	6 (4.0)	4 (1.3)	0 (0.0)
Musculoskeletal and connective tissue disorders	**130 (43.3)**	**72 (48.3)**	**39 (13.0)**	**25 (16.8)**

System Organ Class/Preferred Term[i)]	Any Grade		Grade 3/4	
	Pom + LD-Dex (N=300)	HD-Dex (N=149)	Pom + LD-Dex (N=300)	HD-Dex (N=149)
Back pain	44 (14.7)	20 (13.4)	11 (3.7)	5 (3.4)
Bone pain	44 (14.7)	15 (10.1)	19 (6.3)	4 (2.7)
Muscle spasms	30 (10.0)	9 (6.0)	1 (0.3)	1 (0.7)
Pain in extremity	12 (4.0)	8 (5.4)	4 (1.3)	1 (0.7)
Muscular weakness	8 (2.7)	16 (10.7)	3 (1.0)	4 (2.7)
Myopathy	2 (0.7)	11 (7.4)	0 (0.0)	5 (3.4)
Respiratory, thoracic and mediastinal disorders	**125 (41.7)**	**38 (25.5)**	**29 (9.7)**	**11 (7.4)**
Dyspnoea	50 (16.7)	17 (11.4)	14 (4.7)	7 (4.7)
Cough	45 (15.0)	12 (8.1)	1 (0.3)	0 (0.0)
Epistaxis	27 (9.0)	14 (9.4)	2 (0.7)	3 (2.0)
Nervous system disorders	**99 (33.0)**	**45 (30.2)**	**22 (7.3)**	**15 (10.1)**
Dizziness	27 (9.0)	9 (6.0)	2 (0.7)	1 (0.7)
Headache	15 (5.0)	7 (4.7)	0 (0.0)	0 (0.0)
Peripheral sensory neuropathy	15 (5.0)	4 (2.7)	1 (0.3)	0 (0.0)
Tremor	15 (5.0)	2 (1.3)	2 (0.7)	0 (0.0)
Metabolism and nutrition disorders	**95 (31.7)**	**60 (40.3)**	**48 (16.0)**	**29 (19.5)**
Decreased appetite	30 (10.0)	11 (7.4)	0 (0.0)	0 (0.0)
Hypokalaemia	20 (6.7)	10 (6.7)	9 (3.0)	4 (2.7)
Hypercalcaemia	19 (6.3)	16 (10.7)	11 (3.7)	8 (5.4)
Hyperglycaemia	15 (5.0)	12 (8.1)	9 (3.0)	10 (6.7)
Dehydration	13 (4.3)	9 (6.0)	3 (1.0)	2 (1.3)
Hypocalcaemia	10 (3.3)	9 (6.0)	2 (1.7)	1 (0.7)
Hyponatraemia	7 (2.3)	3 (2.0)	6 (2.0)	3 (2.0)
Hyperuricaemia	8 (2.7)	6 (4.0)	3 (1.0)	3 (2.0)
Skin and subcutaneous tissue disorders	**73 (24.3)**	**22 (14.8)**	**8 (2.7)**	**1 (0.7)**
Pruritus	21 (7.0)	4 (2.7)	0 (0.0)	0 (0.0)
Rash	20 (6.7)	1 (0.7)	3 (1.0)	0 (0.0)
Psychiatric disorders	**67 (22.3)**	**50 (33.6)**	**12 (4.0)**	**10 (6.7)**
Insomnia	24 (8.0)	31 (20.8)	1 (0.3)	4 (2.7)
Confusional state	11 (3.7)	8 (5.4)	7 (2.3)	2 (1.3)
Agitation	8 (2.7)	6 (4.0)	1 (0.3)	3 (2.0)
Investigations	**64 (21.3)**	**25 (16.8)**	**31 (10.3)**	**11 (7.4)**
Neutrophil count decreased	14 (4.7)	1 (0.7)	12 (4.0)	1 (0.7)

System Organ Class/Preferred Term[i)]	Any Grade		Grade 3/4	
	Pom + LD-Dex (N=300)	HD-Dex (N=149)	Pom + LD-Dex (N=300)	HD-Dex (N=149)
Platelet count decreased	10 (3.3)	3 (2.0)	8 (2.7)	2 (1.3)
White blood cell count decreased	8 (2.7)	1 (0.7)	8 (2.7)	0 (0.0)
Blood creatinine increased	13 (4.3)	6 (4.0)	2 (0.7)	3 (2.0)
Renal and urinary disorders	**25 (15.8)**	**12 (15.6)**	**19 (6.3)**	**6 (4.0)**
Renal failure	8 (5.1)	2 (2.6)	9 (3.0)	2 (1.3)
Renal failure acute	5 (3.2)	3 (3.9)	9 (3.0)	4 (2.7)

[i)] System organ classes and preferred terms are coded using the MedDRA dictionary version 14.0. System organ classes and preferred terms are listed in descending order of frequency of Pom + LD-Dex group. A subject with multiple occurrences of an AE is counted only once in the AE category.

Cutoff date: 07 Sep 2012.

Pom = pomalidomide; Dex = dexamethasone. TEAE = Treatment-emergent adverse event

AE Grade 3/4 (National Cancer Institute Common Terminology Criteria (NCI.CTCAE))

Similar percentages of subjects in each treatment arm had at least 1 Grade 3/4 TEAE (78.0% of Pom + LD-dex subjects and 75.8% of HD-dex subjects). Many of these events, including anaemia and thrombocytopenia (the most frequently occurring Grade 3/4 events), occurred in similar proportions of subjects in the 2 treatment arms.

Events that occurred notably more frequently in the Pom + LD-dex arm than in the HD-dex arm included Grade 3/4 neutropenia (41.7% vs. 14.8%); Grade 3/4 febrile neutropenia (6.7% vs. 0%); Grade 3/4 bone pain (6.3% vs. 2.7%); and neutrophil count decreased (4.0% vs. 0.7%).

Events that occurred notably more frequently in the HD-dex arm than in the Pom + LD-dex arm included hyperglycaemia (6.7% vs. 3.0%), asthenia (6.0% vs. 3.3%) and myopathy (3.4% vs. 0.0%).

A total of 170 subjects (56.7%) in the Pom + LD-dex arm had at least one Grade ¾ TEAE considered to be related to pomalidomide, particularly neutropenia (35.7%), thrombocytopenia (13.7%), and anaemia (13.0%).

Drug Related Adverse Events

A total of 230 subjects (76.7%) in the Pom + LD-dex arm had at least 1 TEAE considered to be related to pomalidomide. The most common adverse drug reactions (ADRs) included neutropenia (38.7%), anaemia (22.7%), thrombocytopenia (18.7%), and fatigue (17.7%). An overview of all ADRs is presented in the following tables.

Table 13 – TEAE considered related to pomalidomide by SOC and Preferred Term (Safety population)

System Organ Class/Preferred Term [a]	Pom + LD-dex (N=300)
Number of Subjects with at least 1 TEAE Related to Pomalidomide	230 (76.7)
Blood and lymphatic system disorders	**157 (52.3)**
Neutropenia	116 (38.7)
Anaemia	68 (22.7)
Thrombocytopenia	56 (18.7)
Leukopenia	31 (10.3)
General disorders and administration site conditions	**82 (27.3)**
Fatigue	53 (17.7)
Asthenia	18 (6.0)
Gastrointestinal disorders	**62 (20.7)**
Constipation	25 (8.3)
Diarrhoea	22 (7.3)
Nausea	15 (5.0)
Nervous system disorders	**45 (15.0)**
Dizziness	15 (5.0)
Respiratory, thoracic and mediastinal disorders	**30 (10.0)**
Dyspnoea	15 (5.0)
Musculoskeletal and connective tissue disorders	**19 (6.3)**
Muscle spasms	15 (5.0)

[a] System organ classes and preferred terms are coded using the MedDRA dictionary version 14.0. System organ classes and preferred terms are listed in descending order of frequency of Pom + LD-dex group. A subject with multiple occurrences of an AE is counted only once in the AE category.
Note: Treatment-emergent adverse events (TEAEs) are defined as any AE occurring or worsening on or after the first treatment of the study medication and within 30 days after the end date of study drug.
Source: Table 14.3.2.4.2
Cutoff date: 07 Sep 2012

Table 14 – Adverse reactions and Grade 3 or 4 adverse reactions with pomalidomide by SOC and frequency grouping

System Organ Class / Preferred Term	All Adverse Reactions / Frequency	Grade 3–4 Adverse Reactions / Frequency
Infections and infestations	**Very Common** Pneumonia **Common** Neutropenic sepsis Bronchopneumonia Bronchitis Respiratory tract infection Upper respiratory tract infection Nasopharyngitis	 **Common** Neutropenic sepsis Pneumonia Bronchopneumonia Respiratory tract infection Upper respiratory tract infection **Uncommon** Bronchitis

System Organ Class/ Preferred Term	All Adverse Reactions /Frequency	Grade 3–4 Adverse Reactions /Frequency
Blood and lymphatic system disorders	**Very Common** Neutropenia Thrombocytopenia Leucopenia Anaemia **Common** Febrile neutropenia	**Very Common** Neutropenia Thrombocytopenia Anaemia **Common** Febrile neutropenia Leucopenia
Metabolism and nutrition disorders	**Very Common** Decreased appetite **Common** Hyperkalaemia Hyponatraemia	 **Common** Hyperkalaemia Hyponatraemia **Uncommon** Decreased appetite
Psychiatric disorders	**Common** Confusional state	**Common** Confusional state
Nervous system disorders	**Common** Depressed level of consciousness Peripheral sensory neuropathy Dizziness Tremor	**Common** Depressed level of consciousness **Uncommon** Peripheral sensory neuropathy Dizziness Tremor
Ear and labyrinth disorders	**Common** Vertigo	**Common** Vertigo
Vascular disorders	**Common** Deep vein thrombosis	 **Uncommon** Deep vein thrombosis
Respiratory, thoracic and mediastinal disorders	**Very Common** Dyspnoea Cough **Common** Pulmonary embolism	 **Common** Dyspnoea **Uncommon** Pulmonary embolism Cough
Gastrointestinal disorders	**Very Common** Diarrhoea Nausea Constipation **Common** Vomiting	 **Common** Diarrhoea Vomiting Constipation **Uncommon** Nausea

System Organ Class/ Preferred Term	All Adverse Reactions /Frequency	Grade 3–4 Adverse Reactions /Frequency
Hepatobiliary disorders	**Uncommon** Hyperbilirubinaemia	**Uncommon** Hyperbilirubinaemia
Skin and subcutaneous tissue disorders	**Common** Rash Pruritus	**Common** Rash
Musculoskeletal and connective tissue disorders	**Very Common** Bone pain Muscle spasms	**Common** Bone pain **Uncommon** Muscle spasms
Renal and urinary disorders	**Common** Renal failure Urinary retention	**Common** Renal failure **Uncommon** Urinary retention
Reproductive system and breast disorders	**Common** Pelvic pain	**Common** Pelvic pain
General disorders and administration site conditions	**Very Common** Fatigue Pyrexia Oedema peripheral	**Common** Fatigue Pyrexia Oedema peripheral
Investigations	**Common** Neutrophil count decreased White blood cell count decreased Platelet count decreased Alanine aminotransferase increased	**Common** Neutrophil count decreased White blood cell count decreased Platelet count decreased Alanine aminotransferase increased

Frequencies are defined as: very common (≥ 1/10), common (≥ 1/100 to <1/10); and uncommon (≥ 1/1,000 to <1/100).

The proportion of subjects with at least 1 TEAE considered by the investigator to be related to dexamethasone was higher in the HD-dex arm (71.8%) than in the Pom + LD-dex arm (56.7%), particularly insomnia (17.4% in the HD-dex arm and 3.3% in the Pom + LD-dex arm), myopathy (7.4% in the HD-dex arm and 0.3% in the Pom + LD-dex arm), and muscular weakness (7.4% in the HD-dex arm and 1.7% in the Pom + LD-dex arm).

A higher proportion of subjects in the HD-dex arm (43.0%) than in the Pom + LD-dex arm (28.0%) had at least one Grade 3/4 TEAE considered to be related to dexamethasone.

With the exception of hyperglycaemia in the HD-dex arm, no particular dexamethasone-related Grade 3/4 TEAE occurred in more than 5% of subjects in either treatment arm. Grade 3/4 dexamethasone-related hyperglycaemia occurred more frequently in the HD-dex arm (6.7%) than in the Pom + LD-dex arm (3.0%) as did asthenia (4.7% in the HD-dex arm and 0.7% in the Pom + LD-dex arm).

Serious adverse event / deaths / other significant events

Deaths

As of 7 September 2012, the proportion of subjects in the Pom + LD-dex arm who had died (75 of 300 subjects [25.0%]) was lower than in the HD-dex arm (56 of 149 subjects [37.6%]). The most common cause of death in both treatment arms was MM followed by infection. An overview of deaths in all randomized subjects is shown figure below.

Figure 5 – Deaths among all subjects

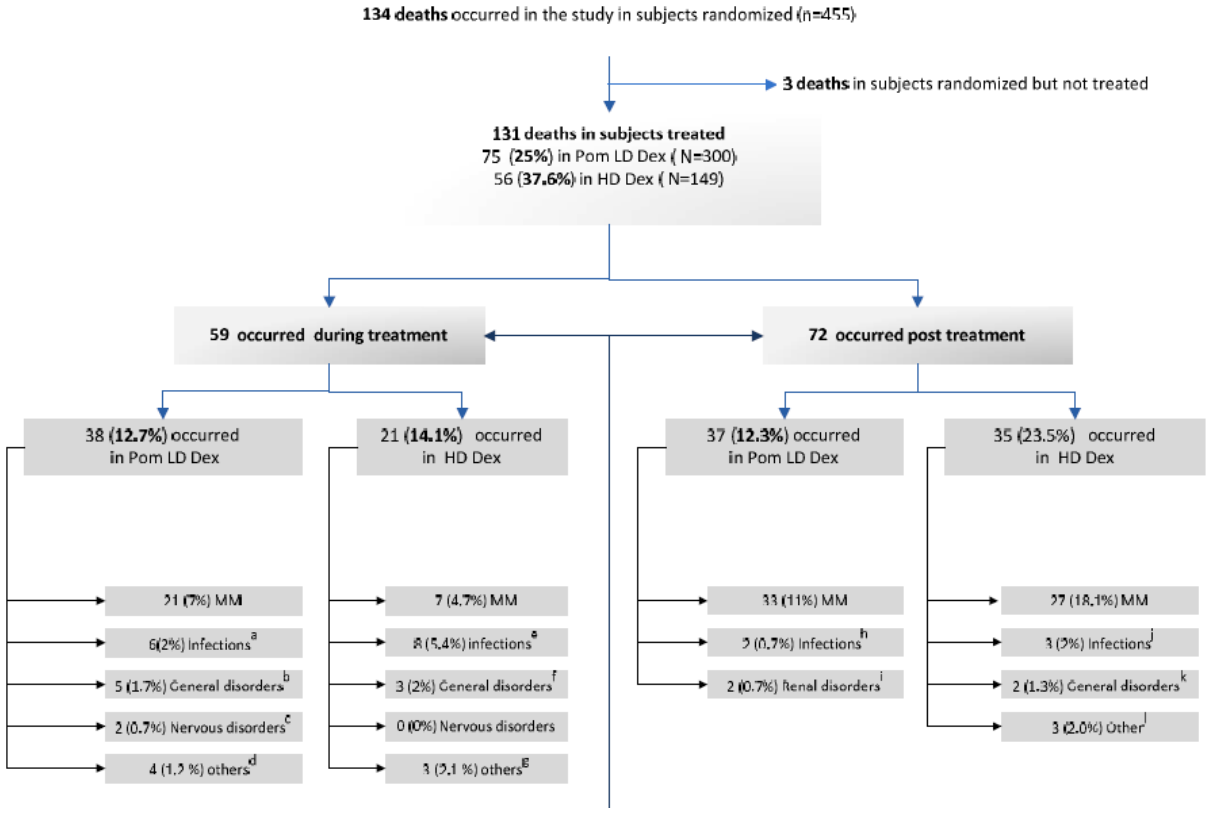


Table 15 – Cause of death for all deaths (Safety Population)

System Organ Class/Preferred Term [a]	Pom + LD-dex (N=300)	HD-dex (N=149)	Overall (N=449)
Total Number of Subjects who Died	75 (25.0)	56 (37.6)	131 (29.2)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**54 (18.0)**	**34 (22.8)**	**88 (19.6)**
Multiple myeloma	54 (18.0)	34 (22.8)	88 (19.6)
Infections and infestations	**8 (2.7)**	**11 (7.4)**	**19 (4.2)**
Pneumonia	3 (1.0)	1 (0.7)	4 (0.9)
Sepsis	2 (0.7)	3 (2.0)	5 (1.1)
Bronchopneumonia	1 (0.3)	0 (0.0)	1 (0.2)
Lower respiratory tract infection	1 (0.3)	1 (0.7)	2 (0.4)
Septic shock	1 (0.3)	5 (3.4)	6 (1.3)
Lung infection pseudomonal	0 (0.0)	1 (0.7)	1 (0.2)
General disorders and administration site conditions	**5 (1.7)**	**5 (3.4)**	**10 (2.2)**
General physical health deterioration	3 (1.0)	3 (2.0)	6 (1.3)
Multi-organ failure	1 (0.3)	0 (0.0)	1 (0.2)
Sudden death	1 (0.3)	0 (0.0)	1 (0.2)
Death (cause unknown)	0 (0.0)	2 (1.3)	2 (0.4)
Renal and urinary disorders	**3 (1.0)**	**0 (0.0)**	**3 (0.7)**
Renal failure	2 (0.7)	0 (0.0)	2 (0.4)
Renal failure acute	1 (0.3)	0 (0.0)	1 (0.2)
Nervous system disorders	**2 (0.7)**	**0 (0.0)**	**2 (0.4)**
Ischaemic cerebral infarction	1 (0.3)	0 (0.0)	1 (0.2)
Subarachnoid haemorrhage	1 (0.3)	0 (0.0)	1 (0.2)
Cardiac disorders	**1 (0.3)**	**2 (1.3)**	**3 (0.7)**
Cardiac arrest	1 (0.3)	1 (0.7)	2 (0.4)
Cardiac failure	0 (0.0)	1 (0.7)	1 (0.2)
Injury, poisoning and procedural complications	**1 (0.3)**	**0 (0.0)**	**1 (0.2)**
Subdural haematoma	1 (0.3)	0 (0.0)	1 (0.2)
Not coded	**1 (0.3)**	**2 (1.3)**	**3 (0.7)**
Chest infection	1 (0.3)	0 (0.0)	1 (0.2)
Patient dead in another country	0 (0.0)	1 (0.7)	1 (0.2)
Sepsis, lower respiratory tract infection	0 (0.0)	1 (0.7)	1 (0.2)
Gastrointestinal disorders	**0 (0.0)**	**1 (0.7)**	**1 (0.2)**
Gastrointestinal haemorrhage	0 (0.0)	1 (0.7)	1 (0.2)
Respiratory, thoracic and mediastinal disorders	**0 (0.0)**	**1 (0.7)**	**1 (0.2)**
Pulmonary embolism	0 (0.0)	1 (0.7)	1 (0.2)

[a] System organ classes and preferred terms are coded using the MedDRA dictionary version 14.0. System organ classes and preferred terms are listed in descending order of frequency of Pom + LD-dex group.

As of 7 September 2012, 38 of 300 (12.7%) subjects in the Pom + LD-dex arm and 21 of 149 (14.1%) subjects in the HD-dex arm died during the treatment period (which includes deaths occurring on or after the date of first study drug dose and within 30 days of the last study drug dose). 37 subjects (12.3%) in the Pom + LD-dex arm and 35 subjects (23.5%) in the HD-dex arm died after 30 days from the end of treatment.

Serious adverse events

The proportion of subjects with at least one SAE was similar between the two arms, 153 subjects (51.0%) in the Pom + LD-dex arm and 75 subjects (50.3%) in the HD-dex arm. The

most frequently occurring SAEs in both treatment arms were pneumonia (9.3% in the Pom + LD-dex arm and 8.7% in the HD-dex arm) and general physical health deterioration (7.3% in the Pom + LD-dex arm and 7.4% in the HD-dex arm).

The majority of SAEs occurred in similar proportions of subjects in the 2 treatment arms. Exceptions include septic shock, which occurred more frequently in HD-dex subjects (4.0%) than Pom + LD-dex subjects (1.0%), and febrile neutropenia, which occurred more frequently in Pom + LD-dex subjects (4.0%) than in HD-dex subjects (none).

Table 16 – Treatment-emergent Serious Adverse Events that Occurred in 2% or more Subjects in either treatment arm by SOC and Preferred Term (Safety Population)

System Organ Class/Preferred Term [a]	Pom + LD-dex (N=300)	HD-dex (N=149)	Overall (N=449)
Number of Subjects with at Least One Serious Adverse Event	153 (51.0)	75 (50.3)	228 (50.8)
Infections and infestations	**73 (24.3)**	**38 (25.5)**	**111 (24.7)**
Pneumonia	28 (9.3)	13 (8.7)	41 (9.1)
Sepsis	7 (2.3)	4 (2.7)	11 (2.4)
Lower respiratory tract infection	5 (1.7)	3 (2.0)	8 (1.8)
Septic shock	3 (1.0)	6 (4.0)	9 (2.0)
Urinary tract infection	1 (0.3)	4 (2.7)	5 (1.1)
General disorders and administration site conditions	**46 (15.3)**	**20 (13.4)**	**66 (14.7)**
General physical health deterioration	22 (7.3)	11 (7.4)	33 (7.3)
Pyrexia	17 (5.7)	6 (4.0)	23 (5.1)
Blood and lymphatic system disorders	**26 (8.7)**	**13 (8.7)**	**39 (8.7)**
Febrile neutropenia	12 (4.0)	0 (0.0)	12 (2.7)
Anaemia	6 (2.0)	7 (4.7)	13 (2.9)
Neutropenia	6 (2.0)	1 (0.7)	7 (1.6)
Thrombocytopenia	5 (1.7)	4 (2.7)	9 (2.0)
Renal and urinary disorders	**23 (7.7)**	**9 (6.0)**	**32 (7.1)**
Renal failure acute	10 (3.3)	6 (4.0)	16 (3.6)
Renal failure	8 (2.7)	1 (0.7)	9 (2.0)
Musculoskeletal and connective tissue disorders	**20 (6.7)**	**8 (5.4)**	**28 (6.2)**
Bone pain	8 (2.7)	1 (0.7)	9 (2.0)
Back pain	6 (2.0)	2 (1.3)	8 (1.8)
Metabolism and nutrition disorders	**19 (6.3)**	**12 (8.1)**	**31 (6.9)**
Hypercalcaemia	11 (3.7)	6 (4.0)	17 (3.8)
Hyperglycaemia	1 (0.3)	3 (2.0)	4 (0.9)

[a] System organ classes and preferred terms are coded using the MedDRA dictionary 14.0. System organ classes and preferred terms are listed in descending order of frequency of Pom + LD-dex group. A subject with multiple occurrences of an AE is counted only once in the AE category.
Note: Treatment-emergent adverse events (TEAEs) are defined as any AE occurring or worsening on or after the first treatment of the study medication and within 30 days after the end date of study drug.

Adverse Events of Special Interest

Neutropenia

In the Pom + LD-dex arm, 154 of 300 subjects (51.3%) of subjects had at least 1 neutropenia. In the HD-dex arm, 30 of 149 subjects (20.1%) had at least 1 neutropenia. Grade 3/4 neutropenia occurred in 47.7% of Pom + LD-dex subjects and in 15.4% of HD-dex subjects. Serious neutropenia occurred in 2.0% of Pom + LD-dex subjects and 0.7% of HD-dex subjects. No subject in either treatment arm had their treatment discontinued due to neutropenia. Neutropenia was not considered to have been the cause of death for any subject.

Febrile neutropenia occurred in 20 of the 300 subjects (6.7%) in the Pom + LD-dex arm and in none of the HD-dex subjects. Febrile neutropenia was considered by the investigator to be related to pomalidomide in 14 subjects (4.7%). For all 20 of these subjects, febrile neutropenia was Grade 3/4. Twelve subjects (4.0%) in the Pom + LD-dex arm had serious febrile neutropenia.

Infections

In the Pom + LD-dex arm, 165 of 300 subjects (55.0%) of subjects had at least 1 infection. In the HD-dex arm, 72 of 149 subjects (48.3%) had at least 1 infection. The proportions of subjects with at least 1 Grade 3/4 infection were similar in the 2 treatment arms (24.0% of Pom + LD-dex subjects and 22.8% of HD-dex subjects). The proportions of subjects with at least 1 serious infection were also similar in the 2 treatment arms (24.3% of Pom + LD-dex subjects and 25.5% of HD-dex subjects). In the Pom + LD-dex arm, 2.0% of subjects had infections that led to discontinuation of pomalidomide and 2.3% of subjects had infections that led to discontinuation of dexamethasone. In the HD-dex arm, 1.3% of subjects had infections that led to discontinuation of dexamethasone. Infections were the cause of death for 8 of 300 (2.7%) Pom + LD-dex subjects and 11 of 149 (7.4%) HD-dex subjects. The higher rate of death due to infections in the HD-dex arm is largely accounted for by the higher proportions of deaths due to septic shock and sepsis in the HD-dex arm (3.4% and 2.0%, respectively) than in the Pom + LD-dex arm (0.3% and 0.7%, respectively).

Pneumonia was the most frequently occurring infection, and it occurred in similar proportions of subjects in each arm (10.7% of Pom + LD-dex subjects and 9.4% of HD-dex subjects). Other respiratory tract infections, including upper respiratory tract infection, bronchitis, and nasopharyngitis, occurred more frequently in the Pom + LD-dex arm than in the HD-dex arm.

Lower respiratory tract infections occurred more frequently in HD-dex subjects (4.7%) than in Pom + LD-dex subjects (2.7%). Septic shock and sepsis occurred more frequently in the HD-dex arm (4.0% and 2.7%, respectively) than in the Pom + LD-dex arm (1.3% and 2.3%, respectively), as did oral herpes (3.4% and 1.0%, respectively). Urinary tract infections occurred in similar proportions of subjects in the 2 arms.

Thrombocytopenia

In the Pom + LD-dex arm, 90 of 300 subjects (30.0%) of subjects had at least 1 thrombocytopenia. In the HD-dex arm, 43 of 149 subjects (28.9%) had at least 1 thrombocytopenia. At least one Grade 3/4 thrombocytopenia occurred in 23.0% of Pom + LD-dex subjects and in 25.5% of HD-dex subjects. The proportions of subjects with at least 1 serious thrombocytopenia were similar in the 2 treatment arms (2.0% of Pom + LD-dex subjects and 2.7% of HD-dex subjects). In the Pom + LD-dex arm, 0.7% of subjects had thrombocytopenia that led to discontinuation of pomalidomide or dexamethasone. In the HD-dex arm, 1.3% of subjects had thrombocytopenia that led to discontinuation of dexamethasone. No subject died as a result of thrombocytopenia; however, it is noted that haemorrhage was the cause of death for 2 subjects in the Pom + LD-dex arm and 1 subject in the HD-dex arm.

Haemorrhage

Haemorrhages occurred in 16.3% of Pom + LD-dex subjects and 21.5% of HD-dex subjects. Epistaxis and hematoma were the most frequently occurring types of haemorrhage, and these

events occurred in similar proportions of subjects in each treatment arm. Among subjects with haemorrhage, 21 of 49 (42.9%) Pom + LD-dex subjects and 10 of 32 (31.3%) HD-dex subjects had thrombocytopenia concurrently with the haemorrhage. Few subjects had Grade 3+ haemorrhages: 9 of 300 (3.0%) Pom + LD-dex subjects and 7 of 149 (4.7%) HD-dex subjects. Among subjects with Grade 3+ haemorrhages, 5 of 9 Pom + LD-dex subjects and 4 of 7 HD-dex subjects had thrombocytopenia concurrently. Serious haemorrhages occurred in 2.7% of Pom + LD-dex subjects and 2.7% of HD-dex subjects. Haemorrhage was the cause of death in 2 Pom + LD-dex subjects and 1 HD-dex subject.

Peripheral Neuropathy

In the Pom + LD-dex arm, 37 of 300 subjects (12.3%) had at least 1 peripheral neuropathy TEAE. In the HD-dex arm, 16 subjects of 149 subjects (10.7%) had at least 1 peripheral neuropathy TEAE. The proportions of subjects with at least one Grade 3/4 peripheral neuropathy were similar in the 2 treatment arms (1.0% of Pom + LD-dex subjects and 1.3% of HD-dex subjects). There was no serious peripheral neuropathy TEAEs in either treatment arm. One subject in the Pom + LD-dex arm (0.3%) and no subjects in the HD-dex arm had treatment discontinued as a result of peripheral neuropathy.

The most frequently occurring peripheral neuropathy events included peripheral sensory neuropathy (15 Pom + LD-dex subjects [5.0%] and 4 HD-dex subjects [2.7%]); paraesthesia (8 Pom + LD-dex subjects [2.7%] and 5 HD-dex subjects [3.4%]); and peripheral neuropathy (6 Pom + LD-dex subjects [2.0%] and 1 HD-dex subject [0.7%]).

Among subjects with at least 1 occurrence of peripheral neuropathy, 45.9% of Pom + LD-dex subjects and 37.5% of HD-dex subjects had neuropathy present at baseline. Among Pom + LD-dex subjects who did not experience treatment-emergent peripheral neuropathy, the percentage of subjects with neuropathy present at baseline was lower (30.0%). Among HD-dex subjects with no peripheral neuropathy TEAEs, the percentage of subjects with neuropathy present at baseline (37.6%) was similar to that in subjects who experienced treatment-emergent peripheral neuropathy (37.5%).

Thromboembolic Events

In the Pom + LD-dex arm, 3.3% of subjects had at least 1 venous thromboembolism (VTE). In the HD-dex arm, 2.0% of subjects had at least 1 VTE. At least one Grade 3/4 VTE occurred in 1.3% of Pom + LD-dex subjects and in no HD-dex subjects. Serious VTEs occurred in 1.7% of Pom + LD-dex subjects and in no HD-dex subjects. No VTE led to the discontinuation of treatment in either treatment arm. No subject died as a result of a VTE.

Of the 8 Pom + LD-dex subjects with deep vein thrombosis (DVT), 1 subject had a concurrent pulmonary embolism; 7 other Pom + LD-dex subjects had DVT without concurrent pulmonary embolism. None of the 3 HD-dex subjects with DVT had a concurrent pulmonary embolism.

Arterial thrombotic events (ATE) occurred in 1.0% of Pom + LD-dex subjects and 0.7% HD-dex subjects. In the Pom + LD-dex arm, these events included: embolism, ischemic cerebral infarction, and myocardial infarction each occurring in 1 subject. In the HD-dex arm, 1 subject (0.2%) had a transient ischemic attack. With the exception of the embolism in the Pom + LD-dex arm, these ATEs were Grade 3/4 events and were serious. None of these ATEs resulted in the discontinuation of treatment in either treatment arm. No subject died as a result of an ATE.

Second Primary Malignancy (SPM)

Two of 300 (0.7%) Pom + LD-dex subjects and 1 of 149 (0.7%) HD-dex subjects had at least 1 SPM. For all 3 of these subjects, the SPM was basal cell carcinoma of the skin (a non-invasive SPM).

Laboratory findings

Only haemoglobin, leukocytes, lymphocytes, neutrophils, and platelets were recorded with a post baseline Grade of 3 or 4. The percentages of subjects with Grade 3 or 4 haemoglobin, lymphocyte, and platelet values were similar in the Pom + LD-dex and HD-dex treatment arms. Substantially higher percentages of subjects in the Pom + LD-dex arm than in the HD-dex arm experienced Grade 3 or 4 reductions in leukocyte (44.6% vs. 12.4%) and neutrophil (55.1% vs. 16.3%) values. No other haematology parameter had any non-normal CTCAE value at any time during the study.

Biochemical parameters with the largest differences were gamma glutamyl transferase (8 subjects [3.2%] vs. 9 subjects [7.5%]), protein urine (36 subjects [13.4%] vs. 27 subjects [21.6%]), and urate (72 subjects [30.2%] vs. 40 subjects [34.8%]), each of which had a greater percentage of Grade 3 or 4 reports in the HD-dex treatment arm.

The only serum electrolytes reported with post-baseline Grade 3 or 4 values for subjects in either treatment arm (Pom + LD-dex vs. HD-dex) were calcium (corrected) (6 subjects [2.4%] vs. 4 subjects [3.3%]), potassium (16 subjects [6.2%] vs. 3 subjects [2.5%]), and sodium (7 subjects [2.7%] vs. 7 subjects [5.8%]).

No abnormal urinalysis values were recorded for any subject except for urine protein dipstick, for which 3 subjects (1.2%) experienced a Grade 3 abnormality in the Pom + LD-dex arm and 2 subjects (1.8%) experienced a Grade 3 abnormality in the HD-dex arm.

Safety in special populations

No studies in special populations have been conducted.

No relevant differences were found among subsets of patients in the pivotal study, including AE profile by gender, baseline renal impairment and age group.

Safety related to drug-drug interactions and other interactions

No relevant safety drug-drug interactions have been identified.

Discontinuation due to adverse events

Twenty-four subjects (8.0%) in the Pom + LD-dex arm had 1 or more TEAEs that led to the discontinuation of pomalidomide. No single TEAE resulted in the discontinuation of pomalidomide in more than 2 subjects.

Table 17 – TEAE leading to discontinuation of pomalidomide by SOC and Preferred Term (Safety Population)

System Organ Class/Preferred Term [a]	Pom + LD-dex (N=300)
Number of subject with at least one TEAE leading to discontinuation of pomalidomide	24 (8.0)
Infections and infestations	**6 (2.0)**
Bronchopneumonia	2 (0.7)
Pneumonia	2 (0.7)
Bronchopulmonary aspergillosis	1 (0.3)
Meningitis	1 (0.3)
Renal and urinary disorders	**4 (1.3)**
Renal failure acute	2 (0.7)
Renal failure	1 (0.3)
Urinary retention	1 (0.3)
Blood and lymphatic system disorders	**3 (1.0)**
Thrombocytopenia	2 (0.7)
Anaemia	1 (0.3)
Cardiac disorders	**2 (0.7)**
Cardiac amyloidosis	1 (0.3)
Ischaemic cardiomyopathy	1 (0.3)
General disorders and administration site conditions	**2 (0.7)**
General physical health deterioration	2 (0.7)
Metabolism and nutrition disorders	**2 (0.7)**
Hypercalcaemia	2 (0.7)
Nervous system disorders	**2 (0.7)**
Depressed level of consciousness	1 (0.3)
Neuropathy peripheral	1 (0.3)
Respiratory, thoracic and mediastinal disorders	**2 (0.7)**
Chronic obstructive pulmonary disease	1 (0.3)
Lung disorder	1 (0.3)
Injury, poisoning and procedural complications	**1 (0.3)**
Subdural haematoma	1 (0.3)
Musculoskeletal and connective tissue disorders	**1 (0.3)**
Back pain	1 (0.3)
Not Coded	**1 (0.3)**
Status alteration	1 (0.3)
Psychiatric disorders	**1 (0.3)**
Bradyphrenia	1 (0.3)

[a] System organ classes and preferred terms are coded using the MedDRA dictionary 14.0. A subject with multiple occurrences of an AE is counted only once in the AE category.

Note: Treatment-emergent adverse events (TEAEs) are defined as any AE occurring or worsening on or after the first treatment of the study medication and within 30 days after the end date of study drug.

The percentages of subjects with 1 or more TEAEs leading to discontinuation of dexamethasone were 8.3% in the Pom + LD-dex arm and 5.4% in the HD-dex arm.

In the Pom + LD-dex arm, no single TEAE other than pneumonia led to the discontinuation of dexamethasone in more than 2 subjects. Pneumonia led to the discontinuation of dexamethasone in 3 Pom + LD-dex subjects (1.0%) and no HD-dex subjects. In the HD-dex arm, no single TEAE led to the discontinuation of dexamethasone in more than 1 subject.

A total of 71 of 300 subjects (23.7%) in the Pom + LD-dex arm had at least 1 TEAE resulting in pomalidomide dose reduction. The most frequently occurring TEAEs leading to dose reduction were neutropenia (7.7%), thrombocytopenia (6.3%), and febrile neutropenia (1.3%).

A total of 184 of 300 subjects (61.3%) had at least 1 TEAE resulting in interruption of pomalidomide treatment. The most frequently occurring TEAEs leading to interruption of pomalidomide were neutropenia (21.0%); thrombocytopenia (8.0%); pneumonia (4.0%); febrile neutropenia (3.7%) general physical health deterioration (3.7%), pyrexia (3.7%), fatigue (2.3%) and anemia (2.0%).

As expected, the proportion of subjects with at least 1 TEAE resulting in dexamethasone dose reduction was lower in the Pom + LD-dex arm (48 of 300 subjects [16.0%]) than the HD-dex arm (35 of 149 subjects [23.5%]). Hyperglycaemia resulted in dexamethasone dose reduction in 8 of 300 subjects (2.7%) in the Pom + LD-dex arm and 2 of 149 subjects (1.3%) in the HD-dex arm.

The proportion of subjects with at least 1 TEAE resulting in dexamethasone dose interruption was higher in the Pom + LD-dex arm (151 of 300 subjects [50.3%]) than the HD-dex arm (65 of 149 subjects [43.6%]) mainly due to neutropenia (11.0% in the Pom + LD-dex arm and 2.7% in the HD-dex arm); pneumonia (4.3% in the Pom + LD-dex arm and 4.7% in the HD-dex arm)and thrombocytopenia (4.0% Pom + LD-dex arm and 2.0% in the HD-dex arm).

Post marketing experience

Not applicable.

2.6.1. Discussion on clinical safety

A total of 300 patients in the study CC-4047-MM-003 have been treated with Pom+LD-dex and 149 with HD-dex. Subjects who were treated with Pom + LD-dex had a longer duration of treatment compared with subjects treated with HD-dex (median 87 days versus 56 days). This higher duration of the treatment in the experimental arm could intuitively indicate a better tolerability-efficacy of Pom+LD-dex, highlighting the differences between the regimens of dexamethasone and the efficacy of pomalidomide.

In the pivotal study, frequencies of TEAEs were generally similar in both treatment arms. On the one hand, blood and lymphatic system disorders (69.7% vs. 57.0%); general disorders (64.0% vs. 55.0%); infections and infestations (55.0% vs. 48.3%); gastrointestinal disorders (52.3% vs. 36.9%); respiratory, thoracic, and mediastinal disorders (41.7% vs. 25.5%); nervous system disorders (33.0% vs. 30.2%) and skin and subcutaneous tissue disorders

(24.3% vs. 14.8%) were more frequently described in the Pomalidomide arm. On the other hand, musculoskeletal and connective tissue disorders (43.3% vs. 48.3%); metabolism and nutrition disorders (31.7% vs. 40.3%) and psychiatric disorders (22.3% vs. 33.6%) were more frequently described in the HD-dex group. Overall, the experimental arm has reported a higher percentage of TEAE.

The most frequent AEs for pomalidomide arm were anaemia (45.7%), neutropenia (45.3%), fatigue (28.3%), thrombocytopenia (27%), pyrexia (21%), constipation (19.3%), diarrhoea (18.3%), dyspnoea (16.7%), cough (15%), back and bone pain (14.7%) and leucopoenia (12.3%).

This profile of AEs seemed very similar to that previously described for pom+dex in the phase II studies. Importantly, the AEs appeared to occur early after initiation of treatment, during the first cycles, tending to decrease over time.

Neutropenias, infections, thrombocytopenia, haemorrhage, peripheral neuropathy, thromboembolic events and second primary malignancy have been identified as AEs of special interest based on experience and knowledge of others drugs with similar mechanism of action (thalidomide and lenalidomide).

Neutropenia was the most frequently reported Grade 3 or 4 haematological adverse reaction in patients with relapsed/refractory multiple myeloma, followed by anaemia and thrombocytopenia. Patients should be monitored for haematological adverse reactions, especially neutropenia. Patients should be advised to promptly report febrile episodes promptly. Physicians should observe patients for signs of bleeding including epistaxes, especially with use of concomitant medication known to increase the risk of bleeding. Complete blood counts should be monitored at baseline, weekly for the first 8 weeks and monthly thereafter. A dose modification may be required (see section 4.2). Patients may require use of blood product support and /or growth factors.

Infections were also common in both arms of the study (55% vs 48%), with pneumonia as the most frequently infection, though with similar percentage of patients between two groups. Grade 3/4 infections were higher in the HD-dex arm.

Peripheral neuropathy events seemed to be similar between groups. However, pomalidomide appeared to have a lower risk for neuropathy than thalidomide. Patients with ongoing $\geqslant$Grade 2 peripheral neuropathy were excluded from clinical studies with pomalidomide. Appropriate caution should be exercised when considering the treatment of such patients with pomalidomide.

Thromboembolic events seemed to be similar between groups, even though serious VTE were described in 1.7% of Pom + LD-dex subjects, whereas none for HD-dex. Patients receiving pomalidomide in combination with dexamethasone have developed venous thromboembolic events (predominantly deep vein thrombosis and pulmonary embolism) and arterial thrombotic events. Patients with known risk factors for thromboembolism – including prior thrombosis – should be closely monitored. Action should be taken to try to minimize minimise all modifiable risk factors (e.g. smoking, hypertension, and hyperlipidaemia). Patients and physicians are advised to be observant for the signs and symptoms of thromboembolism. Patients should be instructed to seek medical care if they develop symptoms such as shortness of breath, chest

pain, arm or leg swelling. Anti-coagulation therapy (unless contraindicated) is recommended, (such as acetylsalicylic acid, warfarin, heparin or clopidogrel), especially in patients with additional thrombotic risk factors. A decision to take prophylactic measures should be made carefully after a careful assessment of the individual patient's underlying risk factors. In clinical studies, patients received prophylactic acetylsalicylic acid or alternative anti-thrombotic therapy. The use of erythropoietic agents carries a risk of thrombotic events including thromboembolism. Therefore, erythropoietic agents, as well as other agents that may increase the risk of thromboembolic events, should be used with caution.

Haemorrhages appeared to occur more frequently in the HD-dex group of patients.

No differences were found between arms in relation to second primary malignancy (0.7% respectively in each group). Physicians should carefully evaluate patients before and during treatment using standard cancer screening for occurrence of second primary malignancies and institute treatment as indicated.

Because pomalidomide has anti-neoplastic activity the complications of tumour lysis syndrome may occur. The patients at greatest risk of tumour lysis syndrome are those with high tumour burden prior to treatment. These patients should be monitored closely and appropriate precautions taken.

Patients with significant cardiac dysfunction (congestive heart failure [NY Heart Association Class III or IV]; myocardial infarction within 12 months of starting study; unstable or poorly controlled angina pectoris) were excluded from clinical studies with pomalidomide. Appropriate caution should be exercised when considering the treatment of such patients with pomalidomide.

Patients with a prior history of serious allergic reactions associated with thalidomide or lenalidomide were excluded from clinical studies. Such patients may be at higher risk of hypersensitivity reactions and should not receive pomalidomide.

Dizziness, fatigue and confusional state have been reported with pomalidomide. Patients must avoid situations where dizziness or confusion may be a problem and are not to take other medicinal products that may cause dizziness or confusion without adequate first seeking medical advice. Similarly, pomalidomide has minor or moderate influence on the ability to drive and use machines. If affected, patients should be instructed not to drive cars, use machines or perform hazardous tasks while being treated with pomalidomide.

Twenty-nine per cent of the subjects died during the trial. Deaths were more frequent in the HD-dex arm (37.6%) than in the Pom + LD-dex arm (25.0%). The most frequent cause of death in both arms was MM, with infections as second cause (7.4% and 2.7%). Of note, renal failure was the cause of three deaths in the pomalidomide group but two of these 3 subjects had disease progression with baseline creatinine clearance values between 30 and 45 mL/min. Patients with creatinine clearance <45 mL/min were excluded from clinical studies. Renal failure has been identified as a potential safety risk in the RMP in view of the experience in products of the same class. In is recommended in the SmPC to carefully monitor patients with renal impairment. A study in patients with renal impairment is ongoing and results will be submitted as additional pharmacovigilance measure reflected in the RMP.

There is no information on the use in patients with hepatic impairment. Consequently, the SmPC recommends to carefully monitor patients with hepatic impairment. A study in patients with hepatic impairment is ongoing and results will be submitted as additional pharmacovigilance measure reflected in the RMP.

Looking at the SAEs, both arms seem to report a similar incidence of serious AEs (~ 50%). The most common SAEs in the pomalidomide group were pneumonia (9.3%), general physical health deterioration (7.3%), pyrexia (5.7%) and febrile neutropenia (4.0%). Of note, 18 subjects in the experimental arm had renal failure. Of them, pneumonia, febrile neutropenia and pyrexia were considered by the investigator to be related to pomalidomide (most frequently). Serious AEs related to metabolism disorders, including hypercalcaemia and hyperglycaemia, occurred more frequently in the HD-dex arm (8.1%) than in the Pom + LD-dex arm (6.3%).

The group treated with pomalidomide and low dose of dexamethasone had a higher percentage of patients with AEs and SAEs leading to discontinuation, reduction and interruption (9.7% vs 5.4%; 6.7% vs 5.4%; 33% vs 23.5%; 64.3% vs 43.6%; AEs discontinuation, SAEs discontinuation; AEs reduction and AEs interruption for pom+LD-dex vs HD-dex, respectively).

Infections (pneumonia) and renal disorders (renal failure) were the most common AEs leading to discontinuation of pomalidomide, whereas neutropenia, thrombocytopenia and pneumonia were the main cause of dose reductions and interruptions for pomalidomide treatment.

Curiously, more patients (in per cent) had dose interruptions of dexamethasone in the Pom+LDdex than in the HD-dex group (50% vs 43%). Neutropenia, pneumonia and thrombocytopenia were again the reasons. Instructions for dose modification or interruption are included in the SmPC.

Overall, the addition of pomalidomide to dexamethasone was associated with an increase in haematological AEs, specifically neutropenia and febrile neutropenia. In terms of non-haematological safety, there was an increase in the occurrence of fatigue, asthenia, infections, constipation, and diarrhoea.

In view of the risk of teratogenicity (see nonclinical aspects), pomalidomide is contraindicated in pregnancy as well as in women of childbearing potential and male patients unless adhering to the conditions of the PPP; warning and relevant information have also been included in sections 4.4, 4.6 and 5.3 of the SmPC.

In general, the safety profile of Pom + LD-dex remained similar regardless of age (> 65 or $\leqslant$ 65 years old), gender or baseline renal function. However, no clear conclusions can be reached due to the limited sample size of these subgroups.

Consequently, as an obligation of the marketing authorisation, the applicant should conduct a non-interventional post authorisation registry of patients treated with pomalidomide for RRMM. The primary objective of the registry study will be to monitor, characterise and determine the incidence of adverse reaction as well as to monitor implementation and compliance of Celgene PPP and off-label use.

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

2.6.2. Conclusions on the clinical safety

In summary, the combination of pomalidomide + dexamethasone appears to have a similar safety profile to other medicinal products of the same class with some differences, including a lower risk than thalidomide for neuropathy and a lower risk than lenalidomide for thromboembolism. The safety profile of pomalidomide is considered acceptable, especially considering the relevance of the observed effects of this combination and the few therapeutics alternatives for these patients.

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

- To conduct a non-interventional post authorisation registry of patients treated with pomalidomide for RRMM to monitor incidence of ADRs and to monitor the implementation and compliance of Celgene PPP and off label use and controlled distribution system on a country basis in agreement with relevant NCA (Submission of protocol within 1 month of granting of the marketing authorisation; Final clinical study report: 31 April 2020).

2.7. Pharmacovigilance

Summary of the pharmacovigilance system

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

2.8. Risk Management Plan

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

PRAC Advice

Based on the PRAC review of the Risk Management Plan, the PRAC considers by consensus that the risk management system for pomalidomide in the treatment of adult patients with relapsed and refractory MM who have received at least two prior treatment regimens, including both lenalidomide and bortezomib, and have demonstrated disease progression on the last therapy, in combination with dexamethasone is acceptable.

This advice is based on the following content of the Risk Management Plan:

- **Safety concerns**

The applicant identified the following safety concerns in the RMP:

Table 18 – Summary of the Safety Concerns

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

The PRAC agreed with the summary of safety concerns presented above.

- **Pharmacovigilance plans**

Table 19 – Studies in the pharmacovigilance plan

Pharmacovigilance Measure **Type, Title and Category (1-3)**	**Objectives**	**Safety Concern Addressed**	**Status (Planned, Started)**	**Date for Submission of Final Reports or Periodic Reports**
Non-interventional post-authorisation registry of patients treated with pomalidomide for RRMM to monitor incidence of ADRs in "real world situation" Monitoring implementation and compliance of Celgene PPP and off-label use and controlled distribution system on a country basis in agreement with relevant NCA Category 1	– Monitor incidence of ADRs in "real world situation" – Monitor implementation and compliance of Celgene PPP and off-label use	Teratogenicity, neutropenia, infection, TEEs, peripheral neuropathy, thrombocytopenia and bleeding, SPM, somnolence, thyroid disorders, renal failure, QT interactions (prolongation), severe skin reactions, TLS, cardiac failure, cardiac arrhythmia (including bradycardia), off-label use	Planned The MAH commits to submitting a draft study protocol for the proposed Registry for review within 1 month of marketing authorisation by the EC.	Final clinical study report: 31 April 2020 Updates with PSURs
Solicited reporting of SPM in all Celgene-sponsored clinical studies Category 3	– Monitor incidence of SPM in the clinical trial setting	SPM	Planned	PSUR/DSUR cycle
Long-term follow-up of SPM in all Celgene-sponsored clinical studies Category 3	– Long-term follow-up of SPM in the clinical trial setting	SPM	Planned	PSUR/DSUR cycle
Definitive TQT study in healthy volunteers Category 3	– Evaluate the effect of pomalidomide on QTc	QT interactions (prolongation), cardiac failure, and cardiac arrhythmia	Planned	31 March 2015 (Final report)
Renal impairment study in MM subjects[i)] Category 3	– Evaluate pomalidomide use in the subpopulation of patients	Use in subjects with renal impairment	Started Q2 2012	31 March 2016 (Final report)

Hepatic impairment study in non-malignant subjects[ii)] Category 3	– Evaluate pomalidomide use in the subpopulation of patients	Use in subjects with hepatic impairment	Started Q1 2013	31 March 2016 (Final report)
Study CC-4047-DMPK-1586: In vitro assessment of pomalidomide as an inhibitor of P-glycoprotein using Caco-2 cells Category 3	– To assess the potential for pomalidomide to inhibit P-gp using a second test system including a strong known inhibitor and less potent known inhibitor as positive controls	To determine if a clinical drug-drug interaction study evaluating pomalidomide as an inhibitor of P-gp may be necessary	Planned - in scheduling	31 December 2013 (Final Report)
Study CC-4047-DMPK-1653: CC-4047: Substrate potential in OATP1B1 and OATP1B3 expressing HEK293 cells Category 3	– Evaluate pomalidomide as a potential substrate for OATP1B1 and OATP1B3	To determine if a clinical drug-drug interaction study evaluating pomalidomide as a substrate of OATP1B1 or OATP1B3 may be necessary	Planned - in scheduling	31 December 2013 (Final Report)
Clinical Pharmacokinetics population analysis Category 3	All data collected in healthy volunteers and multiple myeloma patients should be included in a population analysis to quantify the multiple dose pharmacokinetics and potential dose and time-dependency of pomalidomide. The covariates to be included in the analysis should include, but not be limited to, disease state, dose, formulation, fed state, age, weight, race, age, gender, creatinine clearance (ml/min) and markers of hepatic function.	– Use in patients with renal impairment – Use in patients with hepatic impairment – Use in patients of different racial origin	Started	31 December 2013 (Final Report)

*Category 1 are imposed activities considered key to the benefit risk of the product.

Category 2 are specific obligations
Category 3 are required additional PhV activity (to address specific safety concerns or to measure effectiveness of risk minimisation measures)

The PRAC, having considered the data submitted, was of the opinion that the proposed post-authorisation PhV development plan is sufficient to identify and characterise the risks of the product.

The PRAC also considered that the studies in the post-authorisation development plan are sufficient to monitor the effectiveness of the risk minimisation measures.

- **Risk minimisation measures**

Table 20 – Summary table of Risk Minimisation Measures

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
Important Identified Risks		
Teratogenicity	Routine risk minimisation activities (SmPC and PL). – Section 4.3: Contraindicated in pregnant women and in women of childbearing potential, except when all the conditions for pregnancy prevention have been met. Pomalidomide is also contraindicated in male patients unable to follow or comply with the required contraceptive measures. – Section 4.4: Warnings o Criteria for women of non-childbearing potential o Counselling o Contraception o Pregnancy testing o Precautions for men o Additional precautions o Prescription duration – Section 4.6: Fertility, pregnancy and lactation – Discussed in Section 4.8 of the SmPC. – Section 5.3: Preclinical safety data – Specific pregnancy reporting forms for collection of the pregnancy exposure and follow-up (Annex 7). o Advice to patients in PL.	Celgene PPP (Annex 10 and Annex 11) – Educational Programme o Direct HCP communication prior to launch o HCP kit to include booklet o Treatment algorithm, pregnancy reporting form, Patient Card and/or equivalent tool, and Patient Brochure. – Therapy management o Criteria for determining women of childbearing potential, contraceptive measures and pregnancy testing for women of childbearing potential o Advice in SmPC, DHPC and educational materials – System to ensure appropriate measures have been completed o Patient Card to document childbearing status, counselling and pregnancy testing

Neutropenia	Routine risk minimisation activities (SmPC and PL). – Section 4.2 of the SmPC: dose modification advice for neutropenia. – Section 4.4 of the SmPC: warning of neutropenia, and advice for blood tests at baseline, weekly for the first 8 weeks and then monthly thereafter. – Listed as an ADR and discussed in Section 4.8 of the SmPC. – An event specific questionnaire for AE collection and follow-up (Annex 7). – Advice to patients in PL.	– HCP Kit included in HCP brochure.
Thromboembolic Events	Routine risk minimisation activities (SmPC and PL). – Section 4.4 of the SmPC highlights the possibility of patients developing VTEs and ATEs, and provides recommendations for the use of anticoagulation prophylaxis. – Listed as an ADR and discussed in Section 4.8 of the SmPC. – An event specific questionnaire for AE collection and follow-up (Annex 7). – Advice to patients in PL.	– HCP Kit included in HCP brochure. – Patient brochure
Peripheral Neuropathy	Routine risk minimisation activities (SmPC and PL). – Section 4.4 of the SmPC advises that appropriate caution should be exercised when considering patients with ongoing ≥ Grade 2 peripheral neuropathy for treatment with pomalidomide. – Listed as an ADR and discussed in Section 4.8 of the SmPC. – An event specific questionnaire for AE collection and follow-up (Annex 7).	– HCP Kit included in HCP brochure. – Patient brochure
Infection	Routine risk minimisation activities (SmPC and PL). – Infections and infestations are listed as ADRs and infection is discussed in Section 4.8 of the SmPC. – An event specific questionnaire for AE collection (Annex 7) and advice to patients in PL.	– HCP Kit included in HCP brochure. – Patient brochure
Thrombocytopenia and Bleeding	Routine risk minimisation activities (SmPC and PL). – Section 4.2 of the SmPC: dose modification advice for thrombocytopenia. – Section 4.4 of the SmPC: warning of thrombocytopenia, and advice for blood tests at baseline, weekly for the first 8 weeks and then monthly thereafter. Advice to monitor for signs of bleeding. – Listed as an ADR and discussed in Section 4.8 of the SmPC. – An event specific questionnaire for AE collection and follow-up (Annex 7). – Advice to patients in PL.	– HCP Kit included in HCP brochure. – Patient brochure
Tumour Lysis Syndrome	Routine risk minimisation activities (SmPC and PL). – An event specific questionnaire for AE collection and follow-up (Annex 7).	– HCP Kit included in HCP brochure.

Somnolence	Routine risk minimisation activities (SmPC and PL). – Section 4.7 of the SmPC: Warning about the use of pomalidomide and driving/operating machinery – An event specific questionnaire for AE collection and follow-up (Annex 7). – Warning in PL.	– HCP Kit included in HCP brochure. – Patient brochure
Important Potential Risks		
Secondary Primary Malignancies	Routine risk minimisation activities (SmPC and PL). – Section 4.4 of the SmPC: Warning that SPM have been reported in patients receiving pomalidomide; physicians should carefully evaluate patients before and during treatment using standard cancer screening for occurrence of SPM and institute treatment. – Preclinical safety data discussed in Section 5.3 of the SmPC. – An event specific questionnaire for AE collection and follow-up (Annex 7).	None proposed
Thyroid Disorders	Routine risk minimisation activities (SmPC and PL). – An event specific questionnaire for AE collection and follow-up (Annex 7).	None proposed
Renal Failure	Routine risk minimisation activities (SmPC and PL). – Listed as an ADR in Section 4.8 of the SmPC. – An event specific questionnaire for AE collection and follow-up (Annex 7). – Listed in PL.	None proposed
QT Interactions (prolongation)	Routine risk minimisation activities (SmPC and PL). – An event specific questionnaire for AE collection and follow-up (Annex 7).	None proposed
Severe Skin Reactions	Routine risk minimisation activities (SmPC and PL). – Skin and subcutaneous tissue disorders are listed as ADRs in Section 4.8 of the SmPC. – Listed in PL. – An event specific questionnaire for AE collection and follow-up (Annex 7).	None proposed
Cardiac Failure	Routine risk minimisation activities (SmPC and PL). – Section 4.4 of the SmPC advises that appropriate caution should be exercised when considering patients with significant cardiac dysfunction (CHF [New York Heart Association Class III or IV]; MI within 12 months of starting study; unstable or poorly controlled angina pectoris) for treatment with pomalidomide. – Cardiac failure congestive listed as an ADR in Section 4.8 of the SmPC – An event specific questionnaire for AE collection and follow-up (Annex 7).	None proposed

Cardiac Arrhythmia	Routine risk minimisation activities (SmPC and PL). – Listed in PL. – An event specific questionnaire for AE collection and follow-up (Annex 7).	None proposed
Off-label Use	Routine risk minimisation activities (SmPC and PL). – The SmPC details the risks associated with pomalidomide and the actions to be taken in the case of a specific AE. – The PL details the risks associated with pomalidomide, their symptoms, and the actions to be taken by the patient.	– Managed distribution – Educational Programme o Therapy management o Prescribing controls o Dispensing controls o Assessment o Monitoring of off-label use – Patient Card and/or an equivalent tool
Important Missing Information		
Use in Patients with Renal Impairment	Routine risk minimisation activities (SmPC and PL). – Use in patients with renal impairment addressed in Sections 4.2 and 5.2 of the SmPC.	None proposed
Use in Patients with Hepatic Impairment	Routine risk minimisation activities (SmPC and PL). – Use in patients with hepatic impairment addressed in Sections 4.2 and 5.2 of the SmPC.	None proposed
Interactions with Drugs Affecting and Metabolised by CYP1A2, 3A4/5, and P-gp	Routine risk minimisation activities (SmPC and PL). Section 4.5 of the SmPC: Highlights that CYP1A2 and CYP3A4/5 partly metabolise pomalidomide and pomalidomide is a substrate for P-gp and discusses the effects of co-administration of strong inhibitors or inducers of CYP1A2, 3A4/5, and P-gp on exposure to pomalidomide. For patients where pomalidomide is co-administered with such inhibitors/inducers, close monitoring of side-effects is advised. – Discussed in Section 5.2 of the SmPC.	None proposed
Interaction with Oral Contraceptives	Routine risk minimisation activities (SmPC and PL). – Section 4.5 of the SmPC: Highlights that the potential impact of pomalidomide on the pharmacokinetics of oral contraceptives has not been evaluated clinically.	None proposed
Use in Patients of Different Racial Origin	Routine risk minimisation activities (SmPC and PL). – None proposed	None proposed
Paediatric Use	Routine risk minimisation activities (SmPC and PL). – Section 4.2 of the SmPC: States that there is no relevant use of pomalidomide in the paediatric population in the indication of MM. – Discussed in Sections 5.1 and 5.2 of the SmPC.	None proposed

Use During Breast-feeding	Routine risk minimisation activities (SmPC and PL). – Section 4.6 of the SmPC: Highlights that, although there is no clinical data regarding pomalidomide excretion in milk, it was detected in the milk of lactating rats. It advises that because of the potential for adverse reactions in nursing infants from pomalidomide, a decision should be made whether to discontinue nursing or to discontinue the medicinal product, taking into account the importance of the medicinal product to the mother. – Advice to patients in PL.	None proposed

The PRAC, having considered the data submitted, was of the opinion that the proposed risk minimisation measures are sufficient to minimise the risks of the product in the proposed indication.

The CHMP endorsed this advice without changes.

2.9. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

The applicant requested to have a combined package leaflet for the 1 mg, 2 mg, 3 mg and 4 mg strengths. This was considered acceptable.

3. Benefit-Risk Balance

Benefits

Beneficial effects

Pomalidomide when used in combination with low dose dexamethasone in the relapsed and refractory MM population at the proposed posology has shown to be superior over the acceptable comparator high-dose dexamethasone for PFS (median 15.7 vs 8 weeks; HR 0.45) and overall survival (median not reached vs 34 weeks; HR 0.53) with a statistical significant difference. These results confirmed the previously encouraging results from the phase 2 studies CC-4047-MM-002 and IFM 2009-02. This beneficial effect was also seen in patients refractory to several lines of therapy or those that had received prior SCT, and showed no apparent cross resistance of pomalidomide with other immunomodulatory agents.

Uncertainty in the knowledge about the beneficial effects.

Based on the final PFS analysis and interim OS analysis the IDMC recommended all subjects in the high dose dexamethasone arm to be offered the possibility to receive pomalidomide. As such, further comparison of survival between the two arms will be compromised by the cross over.

Risks

Unfavourable effects

The most common AE was a non cumulative reversible haematology toxicity with neutropenia (the most frequently grade 3/4 event) anaemia and to a less extent thrombocytopenia. It rarely led to treatment discontinuation or was reported as serious AE. It was managed by first dose interruption and to less extent dose reductions.

Infection was the most commonly reported non-haematology toxicity and serious AE, especially pneumonia and upper respiratory tract infections. In around half of the cases it was of grade 3/4. It was the second most common cause of death. Other common undesirable effects include fatigue, pyrexia and gastrointestinal (constipation, diarrhoea, nausea). Gastrointestinal toxicity was rarely of grade 3/4. Most AE tended to occur during the initial cycles tapering off later on the treatment.

Expected safety characteristics for an immunomodulator such as neuropathy, thromboembolism or constipation were also seen with pomalidomide. Pomalidomide showed a greater myelosuppression compared to thalidomide or lenalidomide but had a lower risk for neuropathy than thalidomide and a lower thromboembolic risk than lenalidomide. A teratogenic effect was observed in non-clinical studies. The risk management plan therefore includes a pregnancy prevention programme.

Uncertainty in the knowledge about the unfavourable effects

Given the limited extent of the safety database, particularly in some subgroup of patients, the applicant should conduct a non-interventional post authorisation registry of patients treated with pomalidomide for RRMM in order to monitor the incidence of adverse reaction as well as to monitor implementation and compliance of Celgene PPP and off-label use.

No data in patients with renal or liver impairment although studies in these special populations are ongoing and will be submitted as additional pharmacovigilance measure from the RMP. A thorough QT/QTc study has not been conducted with pomalidomide but is also planned to be conducted and submitted as additional pharmacovigilance measure from the RMP. So far no risk of secondary primary malignancies has been shown; however this potential risk will be monitored through long term follow-up in clinical studies.

Benefit-risk balance

Importance of favourable and unfavourable effects

Pomalidomide in combination with low dose dexamethasone has been shown to be superior to high dose dexamethasone with a clinically meaningful improvement in PFS and survival in MM patients who have failed lenalidomide and bortezomib. This patient population has very limited treatment options.

The most important unfavourable effects in the proposed indication are haematological toxicity and infection. The safety profile is as expected for a treatment of this class and is considered acceptable in the target population.

Benefit-risk balance

The benefit-risk balance is positive.

Discussion on the benefit-risk balance

The benefit of pomalidomide in the proposed indication has been demonstrated in a controlled study and the safety profile is considered acceptable.

4. Recommendations

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Pomalidomide Celgene is not similar to Thalidomide Celgene and Revlimid within the meaning of Article 3 of Commission Regulation (EC) No. 847/200. See appendix 1.

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Pomalidomide Celgene in the treatment of adult patients with relapsed and refractory multiple myeloma who have received at least two prior treatment regimens, including both lenalidomide and bortezomib, and have demonstrated disease progression on the last therapy, in combination with dexamethasone, is favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, section 4.2).

Conditions and requirements of the Marketing Authorisation

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit the first periodic safety update report for this product within 8 months following authorisation. Subsequently, the marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the

requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

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

- **Risk Management Plan (RMP)**

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

An updated RMP should be submitted:

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

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

- **Additional risk minimisation measures**

1. The MAH shall agree the details of a controlled distribution system with the National Competent Authorities and must implement such programme nationally to ensure that:
    - Prior to launch, all doctors who intend to prescribe pomalidomide and all pharmacists who may dispense pomalidomide receive a Direct Healthcare Professional Communication as described below.
    - Prior to prescribing (where appropriate, and in agreement with the National Competent Authority, dispensing) all healthcare professionals who intend to prescribe (and dispense) pomalidomide are provided with a physician information pack containing the following:
        - Educational Health Care Professional's kit
        - Educational brochures for Patients
        - Patient cards
        - Summary of Product Characteristics (SmPC) and Package Leaflet and Labelling.
2. The MAH shall implement a pregnancy prevention programme (PPP) in each Member State. Details of the PPP should be agreed with the National Competent Authorities in each Member State and put in place prior to the marketing of the product.
3. The MAH should agree the final text of the Direct Healthcare Professional Communication and the physician information pack contents with the National Competent Authority in each Member State and ensure that the materials contain the key elements as described below.

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

5. The MAH should also agree with each Member State prior to the launch of the product:

    - The set-up of national measures to assess the effectiveness of and compliance with the PPP.

Key elements to be included

Direct Healthcare Professional Communication

The Direct Healthcare Professional Communication shall consist of two parts:

- A core text as agreed by the CHMP.
- National specific requirements agreed with the National Competent Authority regarding:
    - Distribution of the product
    - To ensure that all appropriate measures have been performed prior to pomalidomide being dispensed

The Educational Healthcare Professional's Kit

The Educational Health Care Professional's Kit shall contain the following elements:

- Brief background on pomalidomide and its licensed indication
- Posology
- The need to avoid foetal exposure due to teratogenicity of pomalidomide in animals and the expected teratogenic effect of pomalidomide in humans
- Obligations of the health care professional in relation to the prescribing of pomalidomide
    - Need to provide comprehensive advice and counselling to patients
    - That patients should be capable of complying with the requirements for the safe use of pomalidomide
    - Need to provide patients with appropriate patient educational brochure and patient card
- Safety advice relevant to all patients
    - Description and management of neutropenia and thrombocytopenia including incidence rates from clinical trials
    - Description and management of thromboembolic risk including incidence rates from clinical trials and post-marketing experience
    - Description and management of infections, somnolence and tumor lysis syndrome
    - Use in patients with hepatic and/or renal impairment
    - Disposal of unwanted medicine

- Local country specific arrangements for a prescription for pomalidomide to be dispensed
- Explanation of unknown risk of neuropathy with long term use

- Description of the PPP and categorisation of patients based on sex and childbearing potential
  - Algorithm for implementation of PPP
  - Definition of women of childbearing potential (WCBP) and actions the physician should take if unsure
- Safety advice for women of childbearing potential
  - The need to avoid foetal exposure
  - Description of the PPP
  - Need for effective contraception (even if woman has amenorrhoea) and definition of effective contraception
    - Pregnancy test regime
    - Advice on suitable tests
    - Before commencing treatment
    - During treatment based on method of contraception
    - After finishing treatment
  - Need to stop pomalidomide immediately upon suspicion of pregnancy
  - Need to tell treating doctor immediately upon suspicion of pregnancy
- Safety advice for men
  - The need to avoid foetal exposure
  - The need to use condoms if sexual partner is pregnant or a WCBP (even if man has had a vasectomy)
    - During pomalidomide treatment
    - For one week following final dose.
  - That he should not donate semen or sperm during therapy (including during dose interruptions) and for 7 days after discontinuation of pomalidomide treatment
  - That if his partner becomes pregnant whilst he is taking pomalidomide or shortly after he has stopped taking pomalidomide he should inform his treating doctor immediately
- Requirements in the event of pregnancy
  - Instructions to stop pomalidomide immediately upon suspicion of pregnancy

- Need to refer to physician specialised or experienced in dealing with teratology and its diagnosis for evaluation and advice
- Local contact details for reporting of any suspected pregnancy
- Pregnancy reporting form

- Patient confirmation form ensuring that patients receive the appropriate counselling concerning the treatment, contraceptive methods and pregnancy prevention appropriate for their sex and childbearing status
- Adverse event reporting forms

Educational Brochures for patients

The Educational brochures for patients should be of 3 types:

- Brochure for women patients of childbearing potential and their partners
- Brochure for women patients who are not of childbearing potential
- Brochure for male patients

All patient brochures should contain the following elements:

- That pomalidomide is teratogenic in animals and is expected to be teratogenic in humans
- That pomalidomide may cause neutropenia and thrombocytopenia and the need for regular blood tests
- Description of the patient card and its necessity
- Disposal of unwanted medicine
- National or other applicable specific arrangements for a prescription for pomalidomide to be dispensed
- That the patient should not give pomalidomide to any other person
- That the patient should not donate blood during therapy (including during dose interruptions) and for 7 days after discontinuation of pomalidomide treatment
- That the patient should tell their doctor about any adverse events

The following information should also be provided in the appropriate brochure:

Brochure for women patients with childbearing potential

- The need to avoid foetal exposure
- Description of the PPP
- Need for effective contraception and definition of effective contraception
- Pregnancy test regime
  - Before commencing treatment

- During treatment (including dose interruptions), every 4 weeks except in case of confirmed tubal sterilisation
- After finishing treatment

- The need to stop pomalidomide immediately upon suspicion of pregnancy
- The need to contact their doctor immediately upon suspicion of pregnancy

Brochure for male patients

- The need to avoid fetal exposure
- The need to use condoms if sexual partner is pregnant or a WCBP (even if man has had vasectomy)
  - During pomalidomide treatment (including dose interruptions)
  - For 7 days following final dose
- That if his partner becomes pregnant he should inform his treating doctor immediately
- That he should not donate semen or sperm during therapy (including during dose interruptions) and for 7 days after discontinuation of pomalidomide treatment

Patient Card

The patient card shall contain the following elements:

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

• Obligation to conduct post-authorisation measures

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

Description	Due date
To conduct a non-interventional post-authorisation registry of patients treated with pomalidomide for relapsed and refractory multiple myeloma to monitor incidence of adverse reactions and to monitor the implementation and compliance of Celgene pregnancy prevention programme and off-label use and controlled distribution system on a country basis in agreement with relevant National Competent Authorities	Final clinical study report: 31 April 2020

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

The Member States should ensure that all conditions or restrictions with regard to the safe and effective use of the medicinal product described below are implemented:

1. The Member State shall agree the details of a controlled distribution system with the Marketing Authorisation Holder (MAH) and must implement such programme nationally to ensure that:

- Prior to launch, all doctors who intend to prescribe pomalidomide and all pharmacists who may dispense pomalidomide receive a Direct Healthcare Professional Communication as described below.
- Prior to prescribing (where appropriate, and in agreement with the National Competent Authority, dispensing) all healthcare professionals who intend to prescribe (and dispense) pomalidomide are provided with a physician information pack containing the following:
    - Educational Health Care Professional's kit
    - Educational brochures for Patients
    - Patient cards
    - Summary of Product Characteristics (SmPC) and Package Leaflet and Labelling.

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

These conditions fully reflect the advice received from the PRAC.

New Active Substance Status

Based on the CHMP review of data on the quality properties of the active substance, the CHMP considers that pomalidomide is qualified as a new active substance.