Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for pomalidomide

Proprietary Product Name: Pomalyst

Sponsor: Celgene Australia Pty Ltd

October 2014

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <http://www.tga.gov.au>.

About AusPARs

- An Australian Public Assessment Record (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.
- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

List of commonly used abbreviations

Abbreviation	Meaning
ADME	absorption, distribution, metabolism, and excretion
AE	adverse event
AML	acute myeloid leukaemia
ANC	absolute neutrophil count
API	active pharmaceutical ingredient
ASA	Australian Specific Annex
ASCT	autologous stem cell transplantation
ATE	arterial thrombotic event
AUC	area under the plasma concentration-time curve
AUC_{t1-t2}	area under the plasma concentration-time curve within time span t1 to t2
bFGF	basic fibroblast growth factor
BMSC	bone marrow stromal cell
CI	confidence interval
CL/F	apparent total clearance of the drug from plasma after oral administration
Cmax	maximum plasma drug concentration
CMI	Consumer Medicine Information
CNS	central nervous system
COX	cyclooxygenase
CR	complete response
CRBN	cereblon
CrCl	creatinine clearance
CTCAE	Common Terminology Criteria for Adverse Events
DLT	dose limiting toxicity
DLP	Data Lock Point

Abbreviation	Meaning
DVT	deep vein thrombosis
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
ERAUC	exposure ratio based on AUC
ERCmax	exposure ratio based on Cmax
FDA	US Food and Drug Administration
GCSF	granulocyte colony stimulating factor
GCP	Good Clinical Practice
GI	gastrointestinal
GLP	Good Laboratory Practice
HCG	Human Chorionic Gonadotropin
HCT	hematopoietic cell transplantation
HD	high dose
hERG	human Ether-à-go-go-Related Gene
HR	hazard ratio
HRQoL	health related quality of life
HSR	Haematology Specialist Representative
IC50	half maximal effective concentration
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IGF	insulin growth factor
IL	interleukin
IMiD	immunomodulatory drug
IMWG	International Myeloma Working Group
IRAC	Independent Response Adjudication Committee

Abbreviation	Meaning
IRB	Institutional Review Board
ITT	intent to treat
IV	intravenous
KLH	Keyhole Limpet Hemocyanin
LD	low dose
LOEL	Lowest Observed Effect Level
MF	myelofibrosis
MM	multiple myeloma
MPN	myeloproliferative neoplasm
MR	minimal response
MTD	maximum tolerated dose
NK	natural killer
NMT	Not More Than
NOAEL	No Observed Adverse Effect Level
ORR	overall response rate
OS	overall survival
PAR	Provisional ARTG Record
PBS	phosphate buffered saline
PD	progressive disease
PE	pulmonary embolism
PFS	progression free survival
PI	Product Information
PO	per os
PPP	pregnancy prevention plan
PSUR	Periodic Safety Update Report
QD	once daily

Abbreviation	Meaning
QOD	every other day
RRMM	relapsed and/or refractory MM
SAE	serious adverse event
SCLC	small cell lung cancer
SD	stable disease
SOP	standard operating procedure
SPM	second primary malignancy
STS	soft tissue sarcoma
TEAE	treatment emergent adverse event
Tmax	time to reach maximum plasma concentration following drug administration
TTP	time to progression
ULN	Upper Limit of Normal
Vd	apparent volume of distribution
VEGF	vascular endothelial growth factor
VTE	venous thrombotic event
Vz/F	apparent volume of distribution during terminal phase after non intravenous administration
WP	working procedure

I. Introduction to product submission

Submission details

Type of submission:	New chemical entity
Decision:	Approved
Date of decision:	27 June 2014
Active ingredient:	Pomalidomide
Product name:	Pomalyst
Sponsor's name and address:	Celgene Australia Pty Ltd Level 7 607 St Kilda Road Melbourne VIC 3004
Dose form:	Gelatin capsules
Strengths:	1 mg, 2 mg, 3 mg and 4 mg
Container:	Blister packs
Pack size:	21 capsules
Approved therapeutic use:	Pomalidomide, in combination with dexamethasone, is indicated for the treatment of 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.
Route of administration:	Oral
Dosage:	The recommended starting dose of pomalidomide is 4 mg/day taken orally on Days 1-21 of repeated 28 day cycles (21/28 days) until disease progression. The recommended dose of dexamethasone is 40 mg/day on Days 1, 8, 15 and 22 of each 28-day treatment cycle. For patients ≥ 75 years of age, the dose of dexamethasone is 20 mg/day on Days 1, 8, 15 and 22 of each 28-day treatment cycle. For these patients a dose adjustment in Pomalyst is not required. Dosing is continued or modified based upon clinical and laboratory findings (see 'Efficacy' section).
ARTG numbers:	212657 (1 mg), 212654 (2 mg), 212656 (3 mg), 212655 (4 mg)

Product background

This AusPAR describes the application by Celgene Australia Pty Ltd to register pomalidomide (trade name Pomalyst) for the following indication:

Pomalyst in combination with dexamethasone is indicated for the treatment of patients with multiple myeloma who have failed at least two prior therapies including lenalidomide and a proteasome inhibitor.

Pomalidomide is a thalidomide derivative and is the third member of a series of drugs known as immunomodulatory compounds, which also include thalidomide and lenalidomide.

Multiple myeloma (MM) is characterised by the neoplastic proliferation of a single clone of plasma cells producing a monoclonal immunoglobulin. This clone of plasma cells proliferates in the bone marrow and often results in extensive skeletal destruction with osteolytic lesions, osteopenia, and/or pathologic fractures.

Despite the much improved survival outcome since the introduction of novel therapeutic agents including the immunomodulatory drugs (IMiDs) and proteasome inhibitors, MM is still an incurable disease. However, the expansion of effective treatment options over the last two decades, has converted what was once a disease with median overall survival (OS) of 3 years, to now a chronic disease capable of long term control, often for 7 years or more. However, almost all patients will relapse after an initial response.

Various definitions for relapsed and refractory disease exist; however, new definitions have recently appeared in the literature, primarily by the International Myeloma Working Group. This guidance was used to develop definitions for the pivotal Study CC 4047 MM-003 in this submission.

Relapsed disease: Relapsed myeloma is defined as previously treated myeloma, which after a period of being off-therapy, requires salvage therapy but does not meet criteria for "primary refractory" or "relapsed-and-refractory" categories, as outlined below.

Refractory disease: Refractory myeloma is defined as disease that is non-responsive while on therapy or progresses within 60 days of last therapy.

a. Relapsed and refractory myeloma is defined as relapse of disease in patients who achieve Minimal Response (MR) or better, and then either become non-responsive while on salvage therapy, or progress within 60 days of last therapy.

b. Primary refractory myeloma refers to refractory disease in patients who have never achieved an MR with any therapy, and includes 2 subcategories:

    i. Patients who never achieve MR or better in whom there is no significant change in M protein and no evidence of clinical progression.

    ii. Primary refractory Progressive Disease (PD).

Treatment options for patients with relapsed or refractory MM include hematopoietic cell transplantation (HCT), a rechallenge of the previous chemotherapy regimen, or a trial of a new regimen. Factors used to determine the choice of therapy include a risk stratification of myeloma (that is, high or standard risk disease), prior treatments used, and the duration of response to these treatments.

For those not eligible for HCT, salvage treatment regimens include those based upon thalidomide, lenalidomide or bortezomib which are used variously in combination with dexamethasone or cytotoxic agents, or treatment regimens with the alkylating agents, melphalan or cyclophosphamide. Additional options include novel agents available through clinical trial participation.

The mechanism of action of pomalidomide includes a variety of immunomodulatory effects such as induction of immune responses, enhancement of activity of immune cells, alteration and modulation of the induction of pro and anti-inflammatory cytokines, and inhibition of inflammation. These compounds also have tumoricidal and anti angiogenic activities that contribute to their anti-tumour activities.

The multiple pharmacological properties of pomalidomide suggest a potential therapeutic benefit in patients with MM. While it is structurally similar to both thalidomide and lenalidomide and shares a number of potentially therapeutic pharmacological properties, pomalidomide has a distinctly different activity and potency profile. It exhibits greater potency than thalidomide with regard to immune modulation, anti-inflammatory and anti-proliferative activity, and has greater potency than lenalidomide at anti proliferative effects in MM cell lines, augmentation of CD4+ and CD8+ T cell proliferation, Th1 cytokine production and natural killer (NK) T cell activation. These differences allow the administration of pomalidomide at lower relative doses compared with thalidomide or lenalidomide.

In vitro and *in vivo* studies suggest that pomalidomide plus dexamethasone may be effective in MM resistant to lenalidomide/dexamethasone therapy. The mechanism underlying the synergistic responses is not fully understood.

Regulatory status

Pomalidomide has not been considered previously by the Advisory Committee on Prescription Medicines (ACPM).

Pomalidomide was granted orphan drug status by the TGA on 17 October 2012:

> *For the treatment of MM in patients who have failed two or more prior therapies.*

The proposed indication is more restrictive, specifying the actual therapies that must be failed, and includes the use with low dose (LD) dexamethasone.

At the time of the Australian submission to the TGA, three other regulatory agencies had considered pomalidomide.

The European Medicines Agency (EMA) granted marketing authorisation on 5 August 2013 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 US Food and Drug Administration (FDA) granted accelerated approval for pomalidomide on 8 February 2013 for the following indication:

> *Pomalyst is a thalidomide analogue indicated for the treatment of patients with multiple myeloma who have received at least two prior therapies including lenalidomide and bortezomib and have demonstrated disease progression on or within 60 days of completion of the last therapy. Approval is based on response rate. Clinical benefit, such as improvement in survival or symptoms has not been verified.*

The FDA approval comes with a black box warning about embryofetal toxicity and risk of pulmonary venous thromboembolism, and was conditional upon the submission of Study CC-4047-MM-007 (not included in this submission to the TGA), a multicentre, randomised open label study of clinical trial of pomalidomide added to bortezomib and LD dexamethasone compared with bortezomib plus LD dexamethasone in patients with previously treated MM. Approval by the FDA was for treatment with pomalidomide, and the addition of dexamethasone was optional.

In Canada, approval was granted on 11 February 2014 for the following indication:

> *Pomalyst (pomalidomide) in combination with dexamethasone (Pomalyst + LD-dex) is indicated for patients with multiple myeloma (MM) for whom both bortezomib and*

lenalidomide have failed and who have received at least two prior treatment regimens and have demonstrated disease progression on the last regimen.

Swissmedic made a positive pre decision on 23 January 2014, with the final decision approving the application expected later in 2014, for the same indication as approved by the EMA.

Product Information

The approved Product Information (PI) current at the time this AusPAR was prepared can be found as Attachment 1. For the most recent PI, please refer to the TGA website at <http://www.tga.gov.au/hp/information-medicines-pi.htm>.

II. Quality findings

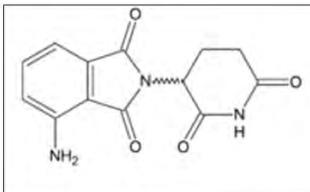
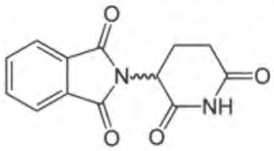
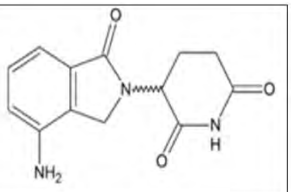
Introduction

In this submission, the sponsor seeks approval for pomalidomide as 1 mg, 2 mg, 3 mg and 4 mg hard gelatin capsules in polyvinyl chloride/polychlorotrifluoroethene (PVC/PCTFE) blister packs of 21 capsules, under the trade name Pomalyst. Clinical comment has been sought regarding the acceptability of the proposed trade name and it has been found acceptable.

Drug substance (active ingredient)

Pomalidomide is a thalidomide derivative and is the third member of a series of drugs known as immunomodulatory compounds, which also include thalidomide and lenalidomide (Figure 1). Thalidomide ('Thalomid') and lenalidomide ('Revlimid') capsules are registered by the sponsor as treatments for MM (cancer of plasma cells).

Figure 1: Structures of immunomodulatory compounds.

		
pomalidomide *POMALYST* capsules 1, 2, 3 and 4 mg Celgene Australia *proposed*	thalidomide *THALOMID* capsules 50, 100, 150 and 200 mg Celgene Australia	lenalidomide *REVLIMID* capsules 5, 10, 15 and 25 mg Celgene Australia

Pomalidomide has one chiral centre. The drug substance is manufactured as a racemic mixture of the R- and S-enantiomers (like thalidomide and lenalidomide). Use of the racemic mixture rather than a specific enantiomer was justified by the company based on the observation that the two enantiomers interconvert *in vitro* in buffer at neutral pH and in plasma. This is further discussed below.

The drug substance is pomalidomide free base, a yellow crystalline powder. The aqueous solubility of pomalidomide is low. The particle size distribution of the active pharmaceutical ingredient (API) is adequately controlled, based on results for batches including that used in the manufacture of finished product batches used in pivotal clinical studies.

Drug product

The strengths are distinguished partly by size (1 mg in size 4 capsule; others in size 2), by capsule body colour (yellow, orange, green or blue respectively; caps are all dark blue), and printing ("POML 2 mg" etc).

The capsule fills all use the same set of excipients, with pomalidomide blended with the diluents mannitol and pre-gelatinised starch and the lubricant sodium stearyl fumarate.

Pomalidomide is sufficiently soluble in aqueous systems to allow dissolution testing without surfactants. Drug is dissolved from capsules quite quickly *in vitro*.

Capsules show good stability and a shelf life of 24 months, when stored below 25°C in original container, has been established.

Biopharmaceutics

Pharmacokinetic profiles are conventional and show little intrasubject variability. Time to reach maximum plasma concentration following drug administration (Tmax) is about 3 h. Pomalidomide is reported to be a substrate of P-glycoprotein but this is claimed to clinically insignificant. Pomalidomide is extensively metabolised via various metabolic pathways, including hydroxylation and hydrolysis. Excretion is primarily renal, largely as metabolites.

Enantiomers

Pomalidomide is a 1:1 mixture of R- and S-enantiomers. The racemisation of each appears to occur via both enzymatic and non-enzymatic pathways since gradual racemisation (approximate half-life of 24 h) was observed *in vitro* in buffer (pH 7) and more rapid racemisation was observed *in vitro* in monkey and human plasma (1:1 ratio achieved after approximately 4 h; elimination half-life of about 7.5 h; Study CC-4047-DMPK-030). Interconversion was also observed in monkeys following oral or intravenous (IV) administration of the individual enantiomers; 18% to 32% conversion based on AUC ratios (Study CC-4047-DMPK-021).

Notwithstanding this, Study CC-4047-DMPK-021 reveals differences in the pharmacokinetic behaviour between the two enantiomers. After IV or oral administration of the racemate in monkeys, the AUC of the R-enantiomer was almost twice that of the S-enantiomer, presumably reflecting the observation that the clearance value for the S-enantiomer is approximately twice that of the R-enantiomer.

Bioequivalence

Bioequivalence Study CC-4047-CP-007 compared the different Formula 3 (proposed commercial formulation) capsule fills (same excipients but in different ratios) used for the different strengths (that is, 1 + 2 mg versus 3 + 4 mg); this showed that a single 4 mg capsule is bioequivalent to two 2 mg capsules and a single 3 mg capsule is bioequivalent to one 1 mg capsule plus one 2 mg capsule when administered under fasted conditions.

Food

Study CC-4047-CP-005 included a study of the effect of food on an experimental formulation which had different ratios of the same excipients compared with those used in the Phase II clinical formulation ('Formula 3' = proposed commercial formulation). These formulations were not bioequivalent with respect to Cmax and 'Formula 4' has not been further developed.

The effect of food has only been measured on this test formulation. A high fat meal slowed the rate of absorption but had minimal effect on overall extent of absorption (Study CC-4047-CP-005). No direct study of the effect of food on the commercial formulation has been submitted, but it is considered reasonable to extrapolate the effect given the similarity of the formulations.

The proposed labelling recommends that the pomalidomide capsules can be administered without regard to food intake.

Absolute bioavailability

An absolute bioavailability study is expected as part of the fundamental pharmacokinetic characterisation of a new chemical entity. This submission does not include such data. The sponsor argues that preparation of a solution formulation of pomalidomide is not feasible because of the instability of the drug and its limited solubility (13 µg/mL at pH 6.8).

The sponsor also argues that the absorption, distribution, metabolism, and excretion (ADME) Study CC-4047-CP-004, in which 2 mg pomalidomide was dosed as a poorly detailed oral suspension in healthy male subjects, showed that at least 73% of the drug was absorbed from the gastrointestinal (GI) tract (that is, seen as urinary radioactivity), so an absolute bioavailability study would offer little additional information about absorption.

Quality summary and conclusions

Registration is recommended with respect to quality and biopharmaceutic aspects. All issues raised during the initial evaluation of this application have been satisfactorily resolved.

As no significant pharmaceutical chemistry issues were identified, the submission was not referred to the Pharmaceutical Subcommittee (PSC) of the ACPM.

III. Nonclinical findings

Introduction

The submitted nonclinical data were in general accordance with the ICH guideline on the nonclinical evaluation of anticancer pharmaceuticals.[1]

Pharmacology

Primary pharmacology

Rationale and mechanism of action

MM is a progressive haematological malignancy of plasma cells which accumulate in the bone marrow resulting in skeletal destruction, renal failure, anaemia and hypercalcaemia. Adhesion of MM cells to bone marrow stromal cells (BMSCs) triggers secretion of cytokines that augment MM cell growth and survival, and confers drug resistance. Pro-inflammatory cytokines such as interleukin (IL)-6, IL-1β, IL-12 and tumour necrosis factor-α (TNF-α) and the anti-inflammatory cytokine IL-10 may influence MM cell growth

[1] European Medicines Agency, "ICH Topic S 9 Nonclinical Evaluation for Anticancer Pharmaceuticals, Step 3: Note for Guidance on Nonclinical Evaluation for Anticancer Pharmaceuticals (EMEA/CHMP/ICH/646107/2008)", December 2008.

and survival. Vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF or FGF2) are secreted by MM and/or BMSCs and may play a role in tumour growth and survival and bone marrow vascularisation and angiogenesis. The overexpression of cyclooxygenase (COX)-2 has been demonstrated to play a role in the pathogenesis of a variety of cancers and in the tumour angiogenesis process.

In vitro

Overall, the pharmacological profile of pomalidomide was similar to lenalidomide. Both pomalidomide and lenalidomide inhibited the proliferation of MM cells (characterised by G1 cell cycle arrest) and induced apoptosis. Both drugs inhibited cytokine production in peripheral blood mononuclear cells (PBMCs) (TNF-α, interleukin (IL)-1β and IL-6) but induced cytokine production from stimulated T cells (IL-2, Interferon gamma (IFN-γ), TNF-α, IL-4, IL-5, IL-13). Both pomalidomide and lenalidomide had anti-angiogenic activity in a human umbilical cord vessel assay and in an *in vivo* angiogenesis plug assay Pomalidomide was shown to inhibit the proliferation of erythroid (but not myeloid) progenitor cells at clinically relevant concentrations: half maximal inhibitory concentration (IC50) 70 nM compared to maximum plasma drug concentration (Cmax) 279 nM.

Expression of cereblon (CRBN) is required for pomalidomide and lenalidomide induction of IL-2 and TNF-α in activated T cells. Lenalidomide resistant MM cells have reduced CRBN levels but were shown to be susceptible to pomalidomide (albeit at higher concentrations than lenalidomide sensitive MM cells). However, a severe reduction in CRBN levels conferred resistance to pomalidomide, and prolonged use of pomalidomide (with or without dexamethasone) led to the generation of pomalidomide resistant cells. The data somewhat supports the use of pomalidomide for lenalidomide resistant MM. However, given the mechanism of lenalidomide resistance is the same as that conferring pomalidomide resistance, the only difference is the threshold; pomalidomide may have limited efficacy in some lenalidomide resistant MM patients, and efficacy may be short lived due to generation of pomalidomide resistance.

The combination of pomalidomide and dexamethasone was synergistic in reducing the growth of lenalidomide sensitive and resistant cell lines, though the efficacy was clearly better in lenalidomide sensitive cell lines (IC50 was 52 times against lenalidomide resistant cells than that seen against lenalidomide sensitive cells).

Together, the *in vitro* data support the use of the combination of pomalidomide and dexamethasone for the treatment of lenalidomide resistant MM. However, reduced efficacy may be seen in some patients and pomalidomide resistance is likely to develop quickly. No *in vitro* studies were conducted to assess efficacy against bortezomib (or any other proteasome inhibitor) resistant lines.

In vivo

The anti-tumour efficacy of pomalidomide was assessed in severe combined immunodeficiency (SCID) mice bearing xenografts of human MM tumours (lenalidomide resistant and combined bortezomib and lenalidomide resistant) and human plasma cell myeloma (lenalidomide resistant). Lower human IgG levels and borderline significant tumour growth inhibition was seen in mice bearing lenalidomide resistant MM xenografts treated with pomalidomide (10 mg/kg/day per os [PO] for 48 days). However, no significant effect on human IgG levels or tumour growth was seen in mice bearing lenalidomide and bortezomib resistant xenografts. In mice bearing lenalidomide resistant human plasma cell myeloma xenografts, both pomalidomide (1 and 3 mg/kg/day PO for 14 to 21 days) and dexamethasone (5 mg/kg/day PO) as single agents inhibited tumour growth (by 26-41% and 51%, respectively). A synergistic effect was seen with the combination of pomalidomide (3 mg/kg/day; 6 mg/m^2/day) and dexamethasone (5 mg/kg/day; 15 mg/m^2/day) (75% tumour growth inhibition). The efficacious doses of

pomalidomide and dexamethasone are similar to those proposed to be used clinically (2.6 mg/m^2 pomalidomide and 26.4 mg/m^2 dexamethasone), thus supporting the proposed use of pomalidomide in combination with dexamethasone in patients with lenalidomide resistant MM. No animal data were provided to support the combined use of pomalidomide and dexamethasone in patients with lenalidomide and bortezomib resistant MM. Pomalidomide alone had no efficacy in mice bearing xenografts of lenalidomide and bortezomib resistant MM.

Pharmacological activity of metabolites

In cell proliferation assays using MM cells, all pomalidomide metabolites and hydrolysis products tested had little or no activity, with IC50 values >1 μM. Therefore, metabolites of pomalidomide are not expected to contribute significantly to the pharmacological action of the drug (at least with respect to apoptotic activity).

Secondary pharmacodynamics and safety pharmacology

A standard set of secondary pharmacology tests (against an array of enzymes and receptors) was not conducted. This is considered acceptable given that pomalidomide is structurally similar to lenalidomide and thalidomide and is likely to have a similar off-target profile. Pomalidomide showed a range of other effects that could be useful for treatment of indications other than myeloma. Among these are effects on the regulation of haemoglobin, inhibition of fibrosis and analgesic/anti-inflammatory effects.

Safety pharmacology studies were conducted investigating effects of pomalidomide on the central nervous system (CNS) (rats), respiratory (rats, dogs) and cardiovascular system (dogs, monkeys and human Ether-à-go-go-Related Gene [hERG] inhibition *in vitro*). All studies were Good Laboratory Practice (GLP) compliant. No neurological or respiratory effects were observed in rats after a single oral dose of up to 2000 mg/kg pomalidomide (estimated Cmax 94 times the clinical Cmax).[2] No respiratory effects were observed in dogs after an IV infusion of ≤10 mg/kg pomalidomide (exposure ratio based on Cmax [ERCmax] 32). A higher dose of pomalidomide (25 mg/kg IV) increased respiratory rate (approximately 2 fold compared to pre-dose) in dogs. Pomalidomide (up to 87.5 μM; 314 times the clinical Cmax) did not block the hERG potassium channel current *in vitro*. Therefore, pomalidomide is not predicted to prolong the QT interval.[3] No adverse cardiovascular effects were observed in dogs after an IV infusion of ≤10 mg/kg pomalidomide (ERCmax 32) or in Cynomolgus monkeys following oral gavage administration of ≤2 mg/kg pomalidomide (estimated Cmax 14 times the clinical Cmax).[4] Overall, no adverse effects on CNS, respiratory or cardiovascular function are predicted from the animal data.

Pharmacokinetics

Absorption

Pomalidomide showed a reasonably rapid rate of absorption after oral administration, Tmax 4 h in rats and 2-3 h in monkeys and human subjects when the racemate or the individual enantiomers were administered. Oral bioavailability was low in rats and monkeys given high doses (100 mg/kg; 13-15%). The absorption of pomalidomide appeared to saturate with higher concentrations since a lower oral dose of pomalidomide (2 mg/kg PO) in monkeys was associated with almost complete bioavailability. In humans,

[2] Based on pharmacokinetic data in the 7 day repeat dose toxicity study (Study 1398/114).
[3] In cardiology, the QT interval is a measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle.
[4] Based on pharmacokinetic data in the absorption study (Study CC-4047-DMPK-021).

oral bioavailability was >70% after administration of a single dose of 2 mg. Following oral dosing, plasma half-lives of pomalidomide were generally similar for rats, monkeys (2 mg/kg dose) and human subjects (5-7.5 h). The plasma half-life was longer in monkeys given higher oral doses (100 mg/kg; 25 h), which may be associated with saturation of the absorption process. Enantiomeric interconversion was demonstrated in monkeys; S/R AUC ratio of 3.3 and 0.215 following oral dosing of the S and R enantiomer, respectively. Following oral dosing of pomalidomide racemate (1:1 R enantiomer to S enantiomer) to monkeys exposure (area under the plasma concentration-time curve [AUC]) to the R enantiomer was 1.5 times higher than exposure to the S enantiomer, though the half-life was slightly shorter for the R enantiomer. The R and S enantiomers of pomalidomide presented similar patterns of degradation or racemisation in phosphate buffered saline (PBS) or monkey and human plasma, suggesting the extent of racemisation in monkeys may be similar to that seen in human subjects. AUC increased approximately dose proportionally in monkeys at low doses (≤1 mg/kg) but increased in a less than dose proportional manner in rats and monkeys at high doses (≥30 mg/kg), consistent with a saturation of absorption. Exposure was dose proportional in human subjects with pomalidomide doses of 0.5 to 2 mg. Following daily oral dosing, the extent of accumulation was minimal in male rats and moderate (<2 fold) in female rats. Accumulation was not observed in monkeys at doses up to 1 mg/kg/day, but was observed at higher doses (≥30 mg/kg/day) (up to 3 fold increase in exposure). Accumulation after repeated dosing with pomalidomide was considered minimal in humans. Sex differences were observed in rats but not monkeys. Female rats had up to 2.5 fold greater exposure than male rats at the same dose level. The pharmacokinetics of pomalidomide in combination with dexamethasone was not investigated in animals. Exposure to pomalidomide was not affected by co-administration of dexamethasone in humans.

Distribution

In vitro, plasma protein binding ranged from 16 to 40% and from 17 to 55% for the pomalidomide R- and S-enantiomers, respectively, in human, monkey, rat, mouse and rabbit plasma. Protein binding of the pomalidomide R- and S-enantiomers was similar in mouse and rabbit plasma, the binding of R- was higher than the S-enantiomer in rat plasma, and the protein binding of S- was higher than the R-enantiomer in monkey and human plasma. The volume of distribution was moderate (2 to 4 fold body water volume, suggesting good tissue distribution in rats). As expected, a tissue distribution study in pigmented rats (Long-Evans) demonstrated that after a single oral dose of radioactive pomalidomide, pomalidomide derived radioactivity was widely distributed to most tissues. The highest concentrations were measured in the alimentary canal (GI tract) and organs of excretion (kidney, liver, bile, and urinary bladder). Moderate concentrations were found in the endocrine glands, secretory glands, brown adipose, and pigmented skin, lymph nodes and thymus. Only low amounts of radioactivity were detected in the seminal vesicles and testes. The clinical overview reports that pomalidomide is distributed in semen of healthy subjects at a concentration of approximately 67% of plasma level at 4 h post dose (Tmax) after 4 days of once daily dosing at 4 mg, suggesting the rat may not be the best model to assess seminal transfer of pomalidomide. A low amount of radioactivity was detected in the spinal cord and brain. It is concluded that pomalidomide crosses the blood-brain barrier to some degree but does not accumulate in the brain.

Metabolism

Pomalidomide underwent both non-enzymatic (hydrolysis) and enzymatic (hydroxylation, N-acetylation) degradation. CYP1A2, 2C19, 2D6 and 3A4 were involved in the enzymatic degradation of pomalidomide. Following oral administration, unchanged drug was the predominant drug related species in the plasma of rats, monkeys and humans. All metabolites detected in human plasma were also seen in the plasma of rats and monkeys.

The excretion pattern of drug related material was similar in animal species and humans: drug related material in urine consisted predominantly of metabolites (though urinary excretion of unchanged drug was also significant in rats), while drug related material in faeces was both unchanged drug and metabolites.

Excretion

Following oral administration, excretion of drug related material was largely in the urine of monkeys and humans (72-73%) and in the faeces of rats. The latter is primarily due to unabsorbed drug. Biliary excretion was demonstrated in rats.

Conclusion

The pharmacokinetic profile of rats and monkeys was considered adequately similar for these species to serve as animal models for the toxicity assessment of this drug.

Pharmacokinetic drug interactions

Pomalidomide was not a cytochrome P450 (CYP450) inducer in human hepatocytes (CYP1A2, 2B6, 2C9, 2C19 and 3A4/5). There was no significant inhibition of CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1 or 3A4/5 at concentrations up to 30 μM (108 times the clinical Cmax). Therefore, pomalidomide is not predicted to alter the exposures of CYP450 substrates. Pomalidomide was shown to be a substrate of P-glycoprotein. However, given the high oral bioavailability of pomalidomide in human subjects (>70%), suggesting P-glycoprotein has a minimal impact on pomalidomide absorption, P-glycoprotein inhibitors are not expected to significantly alter the exposure to pomalidomide. No significant inhibition of P-glycoprotein, **Breast Cancer Resistance Protein (**BCRP), Organic Anion Transporter subtypes OATP1B1, OATP1B3, OAT1 and OAT3 and Organic. Cation Transporter OCT2, transporter activities was seen at high concentrations of pomalidomide (at least 2 μM; 7 times the clinical Cmax). Therefore, pomalidomide is not expected to alter the disposition of substrates for these transporters. According to the clinical overview, no pharmacokinetic interactions were observed between pomalidomide (4 mg) and dexamethasone (20 to 40 mg), a weak to moderate inducer of CYP3A, in MM subjects.

Toxicology

Acute toxicity

The acute toxicity of pomalidomide was investigated in mice and rats by the oral and IV route. The conduct of the studies was appropriate and an adequate observation period was used (14 days). Maximum non-lethal doses were 2000 mg/kg PO in both species and 80 mg/kg IV in mice and 50 mg/kg IV in rats. No clinical signs were evident after oral dosing. Clinical signs following IV dosing (80 mg/kg in mice, 50 mg/kg in rats) were similar in both species: lethargy, piloerection, tachypnoea and palpebral closure. No target organs for toxicity were evident at necropsy at the maximum non-lethal doses. Pomalidomide was considered to have a low order of acute toxicity by the clinical route.

Repeat dose toxicity

Nine repeat dose toxicity studies were submitted; all were conducted under GLP conditions and used the clinically proposed route. Studies in rats were conducted up to 6 months, studies in monkeys up to 9 months. Shorter term studies investigated higher concentrations than the pivotal studies. None of the studies examined pomalidomide in

combination with dexamethasone, as proposed clinically. This is considered acceptable for an anticancer pharmaceutical.[5] The duration of the pivotal studies and inclusion of recovery period, the species used (rats and monkeys, based on pharmacokinetic parameters), group sizes and the use of both sexes were consistent with guidelines. The doses used were appropriate: up to or exceeding the limit dose in rats (and saturation of exposure) and achieving multiples of the clinical AUC in monkeys (Table 1).

Table 1: Relative exposure in repeat dose toxicity studies.

Species	Study duration	Dose mg/kg/day	sex	AUC ng·h/mL	Exposure ratio#
Rat (SD)	1 week	2000	♂	104423[c]	248
		3000	♂	80620[c]	191
		5000	♂	87563[c]	208
	6 months CC-4047-TOX-013	50	♂	21440[a]	51
			♀	40420[a]	96
		250	♂	31120[a]	74
			♀	70170[a]	167
		1000	♂	42530[a]	101
			♀	98010[a]	233
Monkey (Cynomolgus)	1 month (terminated early after 18 days) 1398/117	30	♂	48771[b]	116
			♀	51858[b]	123
		100	♂	41822[b]	99
			♀	96600[b]	229
		300	♂	143388[b]	341
			♀	127655[b]	303
	9 months CC-4047-TOX-006	0.05	♂	132.7[a]	0.3
			♀	169.9[a]	0.4
		0.1	♂	227.3[a]	0.5
			♀	211.4[a]	0.5

[5] European Medicines Agency, "ICH Topic S 9 Nonclinical Evaluation for Anticancer Pharmaceuticals, Step 3: Note for Guidance on Nonclinical Evaluation for Anticancer Pharmaceuticals (EMEA/CHMP/ICH/646107/2008)", December 2008.

Species	Study duration	Dose mg/kg/day	sex	AUC ng·h/mL	Exposure ratio#
		1	♂	5640 [a]	13
			♀	6540 [a]	16
Human (multiple myeloma patients)	steady state	[4 mg]		421[a]	–

= animal:human plasma AUC; [a] AUC_t Area under the curve from the time of dosing (time zero) to the last quantifiable concentration; [b] AUC_{0-16} it is anticipated that the AUC exposure is underestimated in this experiment since only 16 of 24h were measured; [c] AUC_{0-24h}

Major toxicities

There was no clear sign of toxicity in rats treated with up to 1000 mg/kg/day pomalidomide for 6 months (AUC exposure ratio up to 101 in males and 233 in females). Monkeys were more sensitive to pomalidomide, likely consistent with a more appropriate pharmacological response in this species. Therefore, the monkey is considered to be the better species for predicting the potential toxicity of pomalidomide. The toxicity profile in monkeys was similar to that reported previously for lenalidomide with the major target organs identified as the lymphoid/haematopoietic system and the gastrointestinal tract.

Lymphopenia and thrombocytopenia were seen in monkeys treated with 1 mg/kg/day PO pomalidomide for 9 months. These haematological effects correlated with bone marrow hypocellularity and lymphoid depletion (lymph nodes, spleen and thymus). Exposure at the No Observed Adverse Effect Level (NOAEL) was subclinical, suggesting lymphopenia and thrombocytopenia may be seen in patients.

Effects considered secondary to the immunosuppressive action, a severe *Staphylococcus aureus* infection in one male (infection involved the tissues surrounding the thoracic and lumbar vertebrae, marrow cavity and meninges of the spinal cord and brain) and acute myeloid leukaemia (AML) in one female, were seen at 1 mg/kg/day.

Chronic inflammation of the large intestine was seen in monkeys treated with 1 mg/kg/day PO pomalidomide (exposures at the NOAEL were subclinical). This was accompanied by villous atrophy of the small intestine and minimal to mild bile duct proliferation in some animals. Clinical signs in these animals included watery faeces and dehydration.

The severity of the effects associated with the immunomodulatory action of pomalidomide necessitated the early termination of a number of animals.

Genotoxicity

The potential genotoxicity of pomalidomide was investigated in the standard battery of tests: Ames test, mouse lymphoma assay *in vitro*, chromosomal aberration assay *in vitro* in human lymphocytes, forward mutation tk mouse lymphoma assay *in vitro*, rat micronucleus assay *in vivo*. The conduct of the studies was in accordance with ICH guidelines. Concentrations/doses used were appropriate. A suitable set of *S. typhimurium* strains was used in the bacterial mutation assay. The upper dose level in the *in vivo* assay for clastogenicity in rats (2000 mg/kg PO) is estimated to have resulted in exposures

(AUC) 248 times the clinical exposure.[6] All assays were appropriately validated and gave negative results. Pomalidomide is considered to have a low genotoxic potential.

Carcinogenicity

No carcinogenicity studies were conducted, which is considered acceptable according to published guidelines.[7] Given the immunosuppressive activity of pomalidomide and the finding of AML in a pomalidomide treated monkey, secondary malignancies may be seen in patients.

Reproductive toxicity

Submitted reproductive toxicity studies covered all stages except the pre/postnatal development stage. This is acceptable for an anticancer pharmaceutical. Fertility was investigated in rats and embryofetal development in rats and rabbits. All studies were conducted by the clinical route (oral). Numbers of animals and timing/duration of treatment were appropriate.

Relative exposure ratios were very high in rats and reached adequate levels in rabbits (Table 2). In a dose ranging study in rabbits, fetal pomalidomide plasma concentrations were shown to be approximately 50% of maternal plasma concentration indicating that pomalidomide crosses the placenta barrier. Mean milk to plasma ratios ranged from 0.63 to 1.5 for up to 24 h after dosing indicating that pomalidomide is absorbed and excreted into milk in rats. Breast feeding should be avoided when taking pomalidomide.

Table 2: Relative exposure in the reproductive toxicity studies.

Species	Study	Dose mg/kg/day	sex	AUC_{0-24h} ng·h/mL	Exposure ratio# ER
Rat (SD)	Fertility (CC-4047-TOX-020) Sampling: ♀(day14); ♂ (day 28)	25	♂	21070 [b]	50
			♀	39960 [b]	95
		250	♂	43550 [b]	103
			♀	65280 [b]	155
		1000	♂	53890 [b]	128
			♀	92810 [b]	220
	Embryofetal development (CC-4047-TOX-020) Sampling GD17	25	♀	34340 [b]	82
		250	♀	70000 [b]	166
		1000	♀	92610 [b]	220
Rabbit (NZW)	Embryofetal development (CC-4047-TOX-008)*	10	♀	417.9 [a]	1
		100	♀	2787 [a]	7

[6] Based on pharmacokinetic data in the 7 day repeat-dose toxicity study (Study 1398/114).
[7] European Medicines Agency, "ICH Topic S 9 Nonclinical Evaluation for Anticancer Pharmaceuticals, Step 3: Note for Guidance on Nonclinical Evaluation for Anticancer Pharmaceuticals (EMEA/CHMP/ICH/646107/2008)", December 2008.

Species	Study	Dose mg/kg/day	sex	AUC_{0-24h} ng·h/mL	Exposure ratio# ER
	sampling day 19	250	♀	3328 [a]	8
Human (multiple myeloma patients)	steady state	[4 mg]	♂+ ♀	421[a]	-

= animal:human plasma AUC_{0-24h}; [a] AUC_t Area under the curve from the time of dosing (time zero) to the last quantifiable concentration, [b] AUC_{0-24h}; * toxicokinetics not conducted in CC-4047-TOX-008, values from range finding study CC-4047-TOX-007

In a fertility and early embryonic study in rats, a decreased mean number of viable embryos was seen at all doses when treated males were paired with treated females. This finding correlated with increases in the mean number of resorption sites and postimplantation loss. The findings were attributed to female exposure as no effects on embryo viability were seen when treated males were paired with untreated females. Based on these findings, the NOAEL for embryolethality was <25 mg/kg/day (exposure ratio based on AUC [ERAUC] 95) in females and 1000 mg/kg/day in males (ERAUC 128). Pomalidomide is distributed in the semen of human subjects (levels were 67% of the plasma level). Pomalidomide levels were not assessed in the semen of animals, but the tissue distribution study suggested only low levels of drug related material in the seminal vesicles of rats. Rats may not be the best species to assess the effects of paternal exposure on embryo viability. The structurally similar thalidomide has been suggested to adsorb to sperm and there have been reports of thalidomide developmental effects mediated through sperm delivery of the chemical.[8] Therefore, it is recommended that males taking pomalidomide use appropriate measures to avoid seminal transfer.

Pomalidomide was teratogenic in rats and rabbits when administered during the period of organogenesis. Increases in visceral and skeletal malformations where observed in rats at all tested doses (ERAUC 82 at the Lowest Observed Effect Level [LOEL]). Visceral malformations included absent urinary bladder, absent thyroid gland. Skeletal malformations consisted of fusion and misalignment of lumbar and thoracic vertebral elements (centra or neural arches). Embryofetal loss was also observed in rats at all tested doses. These effects occurred in the absence of maternotoxicity, confirming a direct drug related effect.

In rabbits, pomalidomide induced similar effects to the positive control, thalidomide. Increased fetal malformations (gross, external, visceral and skeletal) were observed at all doses (from 10 mg/kg/day; ERAUC 1). Increased cardiac anomalies principally the malformation of intraventricular septal defect was observed. Other visceral malformations included 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 and altered liver morphology. Skeletal malformations or variations included flexed and rotated fore and/or hind limbs, unattached or absent digit, incomplete or unossified metacarpal, phalanx, pelvis, tarsals and tibia; misaligned phalanx and metacarpal, short or bent tibia and an increased average for supernumerary thoracic ribs. Embryofetal lethality was also observed at ≥100 mg/kg/day (ERAUC 7), which may be associated with extreme teratogenicity. Teratogenicity occurred in the absence of maternotoxicity. Given the observed teratogenicity and the relationship of pomalidomide to thalidomide, use in pregnancy should be avoided and sufficient measures should be taken to avoid pregnancy.

[8] Klemmt L, Scialli AR. (2005) The transport of chemicals in semen. *Birth Defects Res B Dev Reprod Toxicol.* 74: 119-131.

Pregnancy classification

The sponsor has proposed Pregnancy Category X. Pregnancy category X is for:

> *drugs which have such a high risk of causing permanent damage to the foetus that they should not be used in pregnancy or when there is a possibility of pregnancy.*

This is considered appropriate due to the teratogenic effect of pomalidomide at clinically anticipated exposures and the relationship of the drug to the known human teratogen, thalidomide. The boxed warning for teratogenic effects included in the PI document is consistent with that for thalidomide and lenalidomide and is considered appropriate.

Immunotoxicity

Pomalidomide was assessed for its immunotoxic potential after treatment of monkeys for 28 days with a 30 day recovery period. Pomalidomide did not induce changes to granulocyte, monocyte or NK cell function (measured as granulocyte and monocyte phagocytosis and oxidative burst activity or NK cell lysis). Treatment related findings included lymphoid depletion of the spleen, thymus and mandibular and mesenteric lymph nodes. Decreases in circulating peripheral lymphocytes correlated with bone marrow lymphocyte hypocellularity and reduced thymus weight. These changes were reversed at the end of the recovery period with the exception of the reduction in thymus weights. Pomalidomide induced alterations to the primary and secondary humoral immune response demonstrated by reductions in anti Keyhole Limpet Hemocyanin (KLH) IgM and anti KLH IgG antibody production following either primary or secondary KLH immunisation. Immunophenotyping showed that pomalidomide treatment was associated with reductions in CD20+ B lymphocytes, CD3+ T lymphocytes, CD3+/CD4+ T helper lymphocytes, CD3+/CD8+ T cytotoxic lymphocytes, CD3-/CD16+ NK cells and CD3-/CD14+ monocytes after 27 days of treatment. Reversal was observed in all populations by the end of the recovery phase, with the exception of CD20+ B lymphocytes in 1 of 3 pomalidomide dosed animals, where only partial reversal was observed. Overall, some impairment of the immune system may be seen in patients, but the effect is not expected to be significantly different to lenalidomide.

Paediatric use

Pomalidomide is not proposed for paediatric use, the proposed PI document states under precautions that

> *there is no experience in treating children and adolescents with pomalidomide. Therefore, pomalidomide should not be used in the paediatric age group (0-18 years)*

No specific studies in juvenile animals were submitted.

Nonclinical summary

- The submitted nonclinical data were in general accordance with the ICH guideline on the nonclinical evaluation of anticancer pharmaceuticals.[9] No studies assessed potential pharmacokinetic or toxicological interactions with pomalidomide and dexamethasone. This is fairly standard for an anticancer pharmaceutical.
- The pharmacological profile of pomalidomide was similar to the structural analogue, lenalidomide. Pomalidomide inhibited the proliferation of lenalidomide resistant MM cell lines *in vitro* and inhibited tumour growth in mice bearing lenalidomide resistant MM xenografts. The combination of pomalidomide and dexamethasone was

[9] European Medicines Agency, "ICH Topic S 9 Nonclinical Evaluation for Anticancer Pharmaceuticals, Step 3: Note for Guidance on Nonclinical Evaluation for Anticancer Pharmaceuticals (EMEA/CHMP/ICH/646107/2008)", December 2008.

synergistic in both systems. The efficacious doses of pomalidomide and dexamethasone in mice were similar to those proposed to be used clinically.

- The mechanism of lenalidomide and pomalidomide resistance is similar but with different thresholds.
- Based on findings in standard safety pharmacology studies, no adverse effects on CNS, respiratory or cardiovascular function are predicted.
- Oral absorption of pomalidomide was reasonably rapid. Absorption appeared to saturate at high doses in rats and monkeys. Enantiomeric conversion was shown to occur in monkeys. The interconversion rate was similar in monkey and human plasma. Tissue distribution studies in rats were unremarkable. Pomalidomide underwent both non-enzymatic and enzymatic degradation. CYP1A2, 2C19, 2D6 and 3A4 were involved in the enzymatic degradation of pomalidomide. There were no human specific metabolites. Biliary excretion was demonstrated in rats.
- Pomalidomide is not expected to alter the exposures of CYP450 or P-glycoprotein substrates. Pomalidomide was a substrate of P-glycoprotein, but based on the high oral bioavailability of this drug, P-glycoprotein inhibitors are not expected to alter the pharmacokinetic of pomalidomide.
- Oral pomalidomide had a low order of single dose toxicity in rodents.
- Oral treatment with pomalidomide over 6 months was well tolerated in rats. Monkeys were more sensitive to pomalidomide induced toxicity (likely associated with pharmacological responsiveness). Major target organs in monkeys were the lymphoid and haematopoietic system (lymphopenia, thrombocytopenia, bone marrow hypocellularity and lymphoid depletion) and the GI tract (chronic inflammation of the large intestine and villous atrophy of the small intestine). *Staphylococcus aureus* infection and acute myeloid leukaemia seen in individual animals and was attributed to the immunosuppressant action of pomalidomide. The toxicity profile of pomalidomide was similar to lenalidomide.
- Pomalidomide was examined for potential genotoxicity in the standard battery of tests with negative results in all assays. Carcinogenicity studies were not conducted and are not required for this anticancer medication. However, given the immunosuppressive activity of pomalidomide and the finding of AML in a pomalidomide treated monkey, secondary malignancies may be seen in patients.
- Pomalidomide crossed the placenta and was detected in fetal blood following administration to pregnant rabbits. Maternal exposure to pomalidomide induced embryo/fetal lethality and teratogenicity in rats and rabbits. A NOAEL was not established. Pomalidomide was detected in the milk of lactating rats following administration to the mother. Breast feeding should be avoided when taking pomalidomide. Adverse embryonic effects following seminal transfer of pomalidomide cannot be ruled out. The animal studies are inadequate to address this.
- Pomalidomide is an immunomodulator with some immunosuppressant activity. The activity is expected to be similar to that for lenalidomide (based on pharmacological studies).

Nonclinical conclusions and recommendation

- Pomalidomide had a similar pharmacological/toxicological profile to lenalidomide.
- The primary pharmacology studies support the combined use of pomalidomide with dexamethasone for the treatment of patients with lenalidomide resistant MM. No

animal studies assessed the efficacy of this combination against lenalidomide and bortezomib resistant MM.

- The main toxicity findings of clinical relevance were:
  - immunosuppression and secondary effects (infections, secondary malignancies)
  - teratogenicity and embryo/fetal lethality, thus warranting a Pregnancy Category X
- There are no nonclinical objections to the registration of pomalidomide for the indication sought
- The nonclinical evaluator recommended amendments to the draft PI but the details of these are beyond the scope of this AusPAR.

IV. Clinical findings

A summary of the clinical findings is presented in this section. Further details of these clinical findings can be found in Attachment 2.

Introduction

Pomalyst in combination with dexamethasone is indicated for the treatment of patients with MM who have failed at least two prior therapies including lenalidomide and a proteasome inhibitor.

> *Comment: The inclusion of "a proteasome inhibitor" as one of the required prior therapies is more general than the approved indication by the FDA and the EU where the proteasome inhibitor is specified as bortezomib. While bortezomib was the first FDA approved proteasome inhibitor (2003), carfilzomib has since been approved for relapsed or refractory MM (July 2012).*

Clinical rationale

Multiple myeloma

Disease background

MM is an incurable disease that is characterised by the accumulation of clonal plasma cells in the bone marrow and accounts for 10% of all haematological malignancies. The disease follows a relapsing course in the majority of patients, regardless of treatment regimen or initial response to treatment. While relapsed and/or refractory MM (RRMM) patients may achieve responses to subsequent anti myeloma therapies, the duration of response typically decreases with successive relapses until resistant disease develops reflecting changes in disease biology, with more tumour cells expressing a more aggressive phenotype, higher rates of proliferation, and lower rates of apoptosis.

The clinical features of MM are varied and can arise from the effects of the tumour itself, the toxicity of the tumour products, or the host's own response. The most common criteria used in diagnosis of symptomatic MM are the presence of neoplastic plasma cells comprising greater than 10% of bone marrow 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 hypercalcemia, renal insufficiency, anemia, and bone lesions (CRAB), which are clinical features of malignant disease associated with active MM. This deterioration leads to progressive morbidity and eventual mortality by lowering resistance to infection and causing significant skeletal destruction, and less commonly, neurological complications and hyperviscosity.

The prognosis of patients with MM depends on a variety of factors including a patient's age and stage of MM at time of diagnosis. These factors are typically described by the International Staging System and Durie Salmon staging system. Poor prognostic factors include Stage III disease (β2-microglobulin level ≥ 5.5 mg/L), hypodiploidy, deletion of 17p, translocation of chromosomes 4 and 14 (t[4:14]), translocation of chromosomes 14 and 16 (t[14;16]); and light chain and Immunoglobulin A (IgA) disease.

Treatment

All patients with MM eventually relapse and may benefit from certain salvage therapies. Various definitions for relapsed and refractory disease exist; however, new definitions have recently appeared in the literature, primarily by the International Myeloma Working Group. This guidance was used to develop definitions for the pivotal Study CC 4047 MM-003.

Current definition of relapsed disease

Relapsed myeloma is defined as previously treated myeloma, which after a period of being off-therapy, requires salvage therapy but does not meet criteria for "primary refractory" or "relapsed and refractory" categories, as outlined below.

Definition of refractory disease

Refractory myeloma is defined as disease that is non responsive while on therapy or progresses within 60 days of last therapy.

a. Relapsed and refractory myeloma is defined as relapse of disease in patients who achieve MR or better, and then either become non responsive while on salvage therapy, or progress within 60 days of last therapy.

b. Primary refractory myeloma refers to refractory disease in patients who have never achieved an MR with any therapy, and includes 2 subcategories:

    - Patients who never achieve MR or better in whom there is no significant change in M protein and no evidence of clinical progression.

    - Primary refractory PD.

Treatment options upon relapse

There is no single standard treatment for patients with relapsed myeloma. Determining which treatment to use should be individualised and depends for example on prior therapy, including the patient's duration of remission since the initial therapy, as well as current physical status, and the presence or risk of side effects. The choice of agent to use at relapse not only depends on availability in a given region of the world, but also on individual preference and, importantly, co-morbidities.

At first relapse, the first choice might be to use a new class of drug or a drug combination different from that used for induction, unless the first remission was long enough to merit consideration of retreatment with the same or a similar regimen, with the possibility of adding another agent. Additionally, the presence or risk of side effects may require a change from the first line treatment.

At second or subsequent relapse treatment options have historically comprised combination therapies with corticosteroids and cytotoxic chemotherapeutic agents.

The approvals of bortezomib and lenalidomide based regimens, plus thalidomide in certain countries, for the treatment of previously treated MM have provided effective therapeutic options that give patients with relapsed or refractory MM the prospect for a longer progression free survival (PFS) and OS. These agents are generally used in combination with corticosteroids (pulsed or weekly dexamethasone), and sometimes with an alkylator (either melphalan or most commonly, in certain countries, cyclophosphamide), or with an anthracycline (adriamycin or liposomal pegylated

adriamycin), with selected patients undergoing autologous stem cell transplantation (ASCT). The various regimens can be used in different combination or sequences. No best sequence has been identified. Of note, it is recommended to use steroids in combination with all products with a few exceptions. Miscellaneous antineoplastic agents including a number of investigational drugs may be used.

Product background and scientific rationale for pomalidomide as treatment for MM

The mechanism of action of pomalidomide includes a variety of immunomodulatory effects such as induction of immune responses, enhancement of activity of immune cells, alteration and modulation of the induction of pro and anti-inflammatory cytokines, and inhibition of inflammation. These compounds also have tumoricidal and anti angiogenic activities that contribute to their anti tumour activities.

The multiple pharmacological properties of pomalidomide suggest a potential therapeutic benefit in patients with MM. While it is structurally similar to both thalidomide and lenalidomide and shares a number of potentially therapeutic pharmacological properties, pomalidomide has a distinctly different activity and potency profile making it a unique compound in the immunomodulatory class in both the nonclinical and clinical settings. Pomalidomide exhibits greater potency than thalidomide with regard to immune modulation, anti-inflammatory and anti-proliferative activity, and has greater potency than lenalidomide at anti proliferative effects in MM cell lines, augmentation of CD4+ and CD8+ T cell proliferation, Th1 cytokine production, and NK T cell activation. These differences allow the administration of pomalidomide at lower relative doses compared to thalidomide or lenalidomide.

Initial treatment of MM with dexamethasone effectively induces MM cell apoptosis; however prolonged drug exposures result in the development of chemoresistance, which is associated with defective apoptotic signalling in response to drugs, over expression of anti-apoptotic proteins such as Bcl-2 or inhibitors of apoptosis protein, expression of multidrug resistance gene, the presence of growth promoting cytokines within the bone marrow microenvironment such as IL-6 and insulin growth factor-1 (IGF-1).

Pomalidomide inhibits the proliferation of MM cell lines *in vitro* including the dexamethasone resistant MM1R cell line. Nonclinical studies have shown that the observed activity of the combination of pomalidomide and dexamethasone is greater than that of single agent pomalidomide or dexamethasone. Moreover, the combination of pomalidomide and dexamethasone is synergistic at inhibiting cell proliferation and inducing apoptosis in both lenalidomide sensitive and lenalidomide resistant H929 cell lines, suggesting that it may similarly be effective in MM patients who have become refractory or resistant to lenalidomide. The exact mechanism of pomalidomide + dexamethasone synergy is not known at present although the combination of pomalidomide + dexamethasone was shown to reduce pRB1 phosphorylation, the expression of Survivin, IRF-4, Bcl-2, and to increase the expression of p27 and BIM when compared to either agent alone.

These data show that pomalidomide is active in dexamethasone resistant cells, and that lenalidomide refractory MM cells are responsive to pomalidomide monotherapy, and the combination of pomalidomide + dexamethasone induces strong synergistic and tumoricidal effects, suggesting that pomalidomide and dexamethasone together have potential therapeutic benefit in the treatment of lenalidomide refractory patients, although the synergy between pomalidomide and dexamethasone is likely cell line dependent. In parallel, preliminary *in vivo* studies have also shown that pomalidomide + dexamethasone may overcome resistance to lenalidomide + dexamethasone.

These findings support the conclusions from clinical studies that showed pomalidomide + dexamethasone is active in RRMM patients who have previously been treated with lenalidomide + dexamethasone.

Clinical rationale for administration of pomalidomide in combination with dexamethasone in RRMM

The combination of pomalidomide + LD dexamethasone has been proposed based on the following clinical considerations.

1. Combination of immunomodulatory drugs with dexamethasone

Synergistic anti myeloma effects have been reported in animal models and in clinical data. Lenalidomide and thalidomide are now used extensively in combination with dexamethasone and are either approved by regulatory authorities and/or recommended in the literature in combination by experts in many countries. Also the combination of lenalidomide plus standard pulsed high dose (HD) dexamethasone has been shown in the relapsed setting to be more effective than either drug taken alone. Initial studies of pomalidomide, when dexamethasone was added in 9 subjects with PD and 2 subjects with stable disease (SD), some activity was shown.

2. Use of LD dexamethasone

Effective regimens containing HD dexamethasone are associated with significant toxicity. In the pivotal lenalidomide Phase III studies, patients receiving combination therapy (lenalidomide + 40 mg dexamethasone) who had their dexamethasone dose reduced owing to a toxicity had a significantly higher overall response rate (ORR), including a higher complete response (CR), compared with those who persisted with standard dexamethasone dose. This was possibly due to reduced complications and improved tolerance, which led to better compliance and a longer duration on therapy. Moreover, it has been described in the literature that HD dexamethasone was not well tolerated in elderly patients.

In a study of 445 patients, as initial therapy for newly diagnosed MM, lenalidomide plus HD dexamethasone was associated with better response (79% versus 68%, p = 0.008), although toxicity was higher (deep vein thrombosis [DVT] 26% versus 12%, infections including pneumonia 16% versus 9%, and fatigue 15% versus 9%). Short term OS was better with lenalidomide + LD dexamethasone (96% versus 87% at 1 year, p = 0.002).

The nonclinical and clinical experience with lenalidomide in combination with dexamethasone provided an additional rationale for the evaluation of the combination of pomalidomide and dexamethasone. LD dexamethasone at 40 mg weekly was proposed to be used in combination with pomalidomide, which had already been shown to be effective in early clinical studies.

> *Comment: The rationale for the clinical study of pomalidomide and LD dexamethasone in patients with relapsed or refractory MM is acceptable although the contribution of LD dexamethasone compared to pomalidomide alone is unknown and was not the object of the pivotal Phase III study.*

Guidance

A number of issues had been identified by the TGA in its planning letter of 12 July 2013. All had been addressed and the submitted documents updated.

Contents of the clinical dossier

- Eight (8) clinical pharmacology studies, including 5 on healthy subjects and 3 on patients with MM provided pharmacokinetic data. Two of the 5 were bioequivalence studies, 2 determined pharmacokinetic properties, and 1 ADME. Three studies included pharmacodynamic assessments of the effect of pomalidomide on CD4 and CD8 cells, cytokine production, serum paraprotein concentration, and neutrophil numbers. Efficacy outcomes reflect the pharmacodynamic properties of pomalidomide

in its effects on the myeloma disease process, while safety issues reflected its pharmacodynamic effects on the body's normal tissues such as bone marrow and the production of normal blood cells. These will be assessed from data in the relevant clinical trials

- Preliminary pharmacokinetic data was obtained in the pivotal Phase III trial but a definitive analysis of population pharmacokinetic is to be completed later
- Two of the 3 pharmacokinetic studies in patients with MM were ascending dose studies to determine the maximum tolerated dose (MTD)
- Two studies of efficacy and safety were Phase II studies (CC-4047-002 and IFM 2009-02) and one was pivotal Phase III trial (CC-4047-MM003). Two additional Phase I studies (CC-4047-MM-001 and CC-4047-MM-002) were also submitted, mainly for safety assessment

Paediatric data

The submission did not include paediatric data. The Paediatric Development Plan stated that the EU had given a waiver for paediatric data. The FDA did not require such data because of the orphan designation of pomalidomide.

Good clinical practice

Ethical conduct of the study

The pivotal Phase III study, CC-4047-MM-003 was conducted in accordance with the sponsor's standard operating procedures (SOPs) and working procedures (WPs), which were designed to ensure adherence to Good Clinical Practice (GCP), as defined in the ICH requirements for GCP[10] and in accordance with the ethical principles outlined in the Declaration of Helsinki.

Patient information and consent

An informed consent form (ICF) explaining the procedures of the study, including the potential hazards, was reviewed and approved by the Institutional Review Board (IRB) and Independent Ethics Committee (IEC) prior to its use. Prior to entering the study, the ICF was read by and explained to all subjects or their legally authorised representative. Each subject had ample opportunity to ask questions and was assured of the right to withdraw from the study at any time without any disadvantage and without having to provide a reason for this decision.

Each subject was required to sign an ICF to participate in the study. If the subject was not capable of providing a signature, an oral statement of consent could have been given in the presence of a witness. Each subject or representative received a signed and dated copy of the ICF.

A sample ICF and the written information given to the subject were provided.

Independent Ethics Committee (IEC) or Institutional Review Board (IRB)

The protocol (and its amendments) were reviewed and approved by each study site's IRB or IEC prior to the start of the study.

Evaluation of compliance with Good Clinical Practice

The Celgene Clinical Research Physician, in conjunction with other study team members, was responsible for assessing the overall compliance of the study with GCP guidelines.

[10] European Medicines Agency, "ICH Topic E 6 (R1) Guideline for Good Clinical Practice, Step 5: Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95)", July 2002.

During the course of the study, compliance with GCP was reviewed by the study monitors on an ongoing basis and investigators were notified when issues were identified. Actions taken to ensure compliance with GCP included follow up with sites to ensure that any departures were corrected in a timely manner, and when necessary, investigators and other site personnel were re-trained on protocol defined procedures. A listing of identified issues was provided. None of the issues had an impact on interpretation of the data or subject safety.

Pharmacokinetics

Studies providing pharmacokinetic data

Submitted pharmacokinetic studies are shown in Table 3.

Table 3: Submitted pharmacokinetic studies.

PK topic	Subtopic	Study ID
PK in healthy adults	General PK Single dose	1398/132
		CC-4047-CP-004
	Multi-dose	CC-4047-CP-006
	Bioequivalence† Single dose	CC-4047-CP-005
	Multi-dose	CC-4047-CP-007
	Food effect	CC-4047-CP-005
PK in special populations	Target population § Single dose	
	Multi-dose	CC-4047-MM-001-PK
		CC-4047-MM-002
		CC-4047-MM-003
	Hepatic impairment	NA
	Renal impairment	NA
	Neonates/infants/children/adolescents	NA
	Elderly	NA
Genetic/gender-related PK	Males versus females	NA
PK inter-actions	NA	
Population PK	Healthy subjects	NA

PK topic	Subtopic	Study ID
analyses	Target population	NA
	Other	NA

† Bioequivalence of different formulations. § Subjects who would be eligible to receive the drug if approved for the proposed indication.

None of the pharmacokinetic studies had deficiencies that excluded their results from consideration.

Evaluator's conclusions on pharmacokinetics

The following conclusions are based on those of the Summary of Clinical Pharmacology, except where the evaluator disagrees with those conclusions as indicated.

- Following single dose administration in the fasted state, pomalidomide was at least 73% absorbed with a median Tmax of approximately 3 h.
- Steady state was reached by Day 3 in healthy subjects. No drug accumulation was seen in these subjects after 5 days, but in MM subjects receiving 1 mg or 2 mg daily doses for 28 days, drug accumulation was shown by a 73% to 98% higher value for AUC0-τ on Day 28 compared to that predicted from Day 1 findings. Drug accumulation was not seen at 5 mg daily dose in MM patients. The difference is unexplained. (The European Summary of Product Characteristics has a different interpretation.)
- Systemic exposure increased after single doses of differing strengths of pomalidomide in both healthy subjects and MM patients. In healthy subjects, the Cmax increase was sub proportional, while the AUC values were approximately proportional. In MM patients, both AUC and Cmax were not dose proportional.
- Food decreased the rate of absorption but had minimal effect on overall extent of absorption (approximately 8% decrease in AUC). Pomalidomide can be administered without regard to food intake.
- Mean (%CV) apparent volume of distribution during terminal phase after non IV administration (Vz/F) of pomalidomide after a single dose ranged from 65 to 138 L.
- Pomalidomide distributed into semen, with the semen concentration at plasma Tmax approximately 67% of plasma concentration.
- Pomalidomide protein binding in human plasma was low to moderate (15.8% and 42.2% for R- and S-enantiomers, respectively).
- Pomalidomide is metabolised in humans via multiple pathways (CYP mediated, enzymatic and non-enzymatic hydrolysis). The metabolites observed were formed primarily via hydroxylation with subsequent glucuronidation, or hydrolysis of the parent compound.
- Pomalidomide was the predominant circulating radioactive component, accounting for approximately 70% of the circulating radioactivity, and no metabolites were present at >10% relative to parent or total radioactivity. There were no unique or disproportionate human metabolites.
- CYP dependent metabolites accounted for approximately 43% of the excreted radioactivity, while non-CYP dependent hydrolytic metabolites accounted for 25%, and excretion of unchanged pomalidomide accounted for 10%.
- Pomalidomide metabolites did not show significant pharmacological activity in-vitro.

- The mean half-life of pomalidomide is approximately 7.5 h, and CL/F generally ranged from 6.5 to 10.8 L/hr. CL/F and half-life in plasma appear to be independent of dose and dosing duration.
- Urine was the primary route of elimination for radioactivity, containing approximately 72% of the dose. Unchanged drug in urine accounted for <3% of the dose, indicating extensive metabolism prior to excretion. The radioactivity in faeces (15.3% of the dose) contained parent compound (approximately 8% of the dose) and several metabolites.
- The pharmacokinetic parameters of single dose pomalidomide in subjects with MM appear similar to those in healthy subjects over the comparable dose range, except for the 1 and 2 mg doses in MM patients (see above). (The European Summary of Product Characteristics has a different interpretation.)
- Pomalidomide is not an inhibitor or inducer of CYP isoenzymes, and did not inhibit P-glycoprotein or other studied transporters *in vitro*. Pomalidomide is not anticipated to cause clinically relevant pharmacokinetic drug-drug interactions at therapeutic doses when co-administered with CYP substrates or substrates of the evaluated transporters and therefore has not been studied in a clinical trial.
- Pomalidomide is partially metabolized by CYP1A2 and CYP3A4, and to a minor extent CYP2C19 and CYP2D6. Pomalidomide is a substrate of P-glycoprotein *in vitro* but well absorbed in humans. Pomalidomide is unlikely to be a significant substrate of other enzymes or transporters. The potential for clinically relevant drug-drug interactions when pomalidomide is co-administered with other drugs is low. A clinical trial evaluating potential drug-drug interactions is clinically complete and data analysis is in progress (CC-4047-CP-008).
- Clinical trials evaluating pharmacokinetics in MM patients with renal insufficiency and in otherwise healthy subjects with hepatic impairment are in progress (CC-4047-MM-008 and CC-4047-CP-009, respectively).

Pharmacodynamics

Studies providing pharmacodynamic data

Studies providing pharmacodynamic data are shown in Table 4.

Table 4: Submitted pharmacodynamic studies.

PD Topic	Subtopic	Study ID
Primary Pharmacology	Effect on CD4 and CD8 count	1398/132 (in part)
	Effect on serum M protein concentration, cytokine production and neutrophils.	CC-4047-00-002 (in part)
Secondary Pharmacology	NA	
Gender other genetic and Age-Related Differences in PD Response	Effect of gender NA	

PD Topic	Subtopic	Study ID
PD Interactions	NA	
Population PD and PK-PD analyses	NA	

NA=Not available

Note: The pharmacodynamic evaluations from Study CC-4047-CC-006 were reported separately, and were not found in this application.

Evaluator's conclusions on pharmacodynamics

- Pharmacological properties of pomalidomide from nonclinical studies are summarised
- Effects of pomalidomide on the CD4 and CD8 counts in Study 1398/132 in healthy subjects were inconclusive
- A reduction in serum paraprotein concentration of at least 25% was seen in 39% of patients treated with pomalidomide (Study CDC-4047-00-001)
- Grade 3 and 4 neutropenia were seen in MM patients treated with pomaildome; and
- Efficacy and safety were not shown to be related to PK data on pomalidomide because of insufficient data.

Dosage selection for the pivotal studies

The proposed clinical starting dose for pomalidomide is 4 mg daily (given as 2 x 2 mg capsules) on Days 1 to 21 of repeated 28 day cycles, in combination with 40 mg dexamethasone on Days 1, 8, 15 and 22 of each 28 day cycle. In the Phase II section of study CC-4047-MM-002, the results from the 14 patients who provided pharmacokinetic data showed a steady state mean exposure (AUC0-t) to pomalidomide in the range of 381-411 ng.hr/mL (CV 28-55%).

The therapeutic dose is consistent with data from the Phase I portion of CC-4047-MM-002, in which the MTD of pomalidomide when administered as single agent once per day orally on Days 1 to 21 of each 28 day cycle (cyclic regimen schedule) was determined to be 4 mg based on the occurrence of dose limiting toxicities (DLTs) of Grade 4 neutropenia in the 5 mg dose cohort. Subjects in the 4 mg cohort had fewer dose reductions than those in the 5 mg cohort and the proportion of subjects who completed ≥ 40 weeks on study was higher in the 4 mg (and 5 mg) cohort compared with the 2 mg and 3 mg cohorts. This implies a balance between tolerability and efficacy. This result is consistent with Study CC-4047-MM-001, which determined an MTD of 2 mg once daily (QD) or 5 mg every other day (QOD), but did not explore a dose between this range. The MTD of 4 mg was used as the recommended starting dose for the Phase II open label randomised segment of the study to determine the efficacy and safety of pomalidomide alone and in combination with LD dexamethasone in the RRMM population.

The proposed usage of pomalidomide is in combination with dexamethasone. However, pomalidomide is active when administered alone, with an overall response rate of 9% (intent to treat [ITT population]), and a response rate of 15.4% in subjects > 65 years old and 23.1% in subjects >75 years old based on an Independent Response Adjudication Committee (IRAC), in the heavily pre-treated subjects in the Phase II Study CC-4047-MM-002. The rationale for the combination of pomalidomide plus LD dexamethasone was based on *in vitro* data that show that pomalidomide inhibits the proliferation of lenalidomide resistant MM cell lines and synergises with dexamethasone in both

lenalidomide sensitive and lenalidomide resistant cell lines to induce tumour cell apoptosis. These data were supported by the overall response rate of 30.1% (ITT population) in subjects treated with the combination of pomalidomide and LD dexamethasone versus 9.3% in subjects treated with pomalidomide alone in Phase II Study CC-4047-MM-002. In addition, compared to treatment with lenalidomide alone lenalidomide (of which pomalidomide is an analogue) demonstrated increased antimyeloma activity when used in combination with dexamethasone. The use of LD dexamethasone as well as a cyclic regimen schedule is also supported by studies using lenalidomide.

A cyclic regimen of pomalidomide 21 of 28 days versus 28 of 28 days was compared in IFM-2009-02. There was no difference in response rate, or any secondary endpoint, between the two different treatment regimens, both of which contained the same dose/schedule of dexamethasone. Since both regimens were well tolerated, and overall treatment duration was longer with the 21 day versus the 28 day regimen, use of the 21 day regimen appears favourable.

Therefore, the available data support a 21 of 28 day cyclic regimen of pomalidomide 4 mg in combination with LD dexamethasone to be the optimal regimen. There were not sufficient PK data currently available to determine an exposure-response relationship.

Comment: The reasons for the dose selections are acceptable.

Efficacy

Evaluator's conclusions on efficacy

- In the pivotal trial Study CC-4407-MM-03, the combination of pomalidomide + LD dexamethasone was effective in the treatment of patients with MM who had failed at least two prior therapies including lenalidomide and bortezomib.

  Comment: The study was not designed to show effectiveness against any other proteosome inhibitor than bortezomib, and only 7 of 455 patients in the trial had received another protesome inhibitor, carfilzomib. It may be argued that because of their similar anti MM action, resistance to all protesome inhibitors is the same as for bortezumib. However, lenalidomide and pomalidome are also structurally and functionally similar, but resistance to lenalidimode still allows response to pomalidomide as shown in the pivotal trial. It is therefore unsafe to extrapolate responses in this disease based on similarities in the agents involved.

- The combination of pomalidomide + LD dexamethasone resulted in a clinically significant improvement of 7.7 weeks in PFS, of more than 12 weeks in OS (20 weeks in the updated analysis), and of 12.7% in response rate. The positive effects were shown in most subgroups, with three exceptions.
- If the two subgroups with very small numbers of patients were excluded, one subgroup with an adequate number of subject with poor renal function (creatinine clearance <45 ml/min) showed no significant difference in endpoints in the two treatment arms.
- The contribution of LD dexamethasone to the combination of pomalidomide + LD dexamethasone remains uncertain in this population of patients. The supporting trials confirmed the activity of pomalidomide in this group of patients, as shown by the response rates achieved with the pomalidomide treatments. The one trial of pomalidomide + LD dexamethasone and pomalidomide alone (CC-4047-MM-002) showed a small clinical benefit of the added dexamethasone with an increase of 4.6 weeks in the PFS in the pomalidomide + dexamethasone arm (16.6 weeks) compared

to the pomalidomide arm (12 weeks) before dexamethasone was added to Arm B, and 6.6 weeks after the addition (16.6 weeks compared with 10 weeks PFS). However, the OS was the same in each arm and the addition of dexamethasone to the pomalidomide treatment in the pomalidomide alone arm did not increase the response rate.

Safety

Studies providing safety data

The following studies provided evaluable safety data:

- Pivotal efficacy Study CC-4047-MM-003

Pivotal studies that assessed safety as a primary outcome

Not applicable.

Dose response and non-pivotal efficacy studies

The dose response and non-pivotal efficacy studies provided safety data as follows:

- Study CC-4047-MM-002 Phase II: The Phase II section of this multicentre, randomised, open label, dose escalation study was designed to determine the MTD, safety, and efficacy of pomalidomide alone and in combination with LD dexamethasone, and provided safety data on 107 subjects and 112 subjects respectively in the two treatment arms.
- Study IFM-2009-02: This Phase II, multicentre, randomised, open label study evaluated the safety and efficacy of oral pomalidomide in combination with two regimens of LD dexamethasone provided data on 43 and 41 subjects in each of the two arms.
- Study CC-4047-MM-001(CDC-407-00-001): This Phase I, single centre, open label study evaluated safety and efficacy of dose escalation of pomalidomide in subjects with relapsed or refractory MM, and provided safety data on 24 subjects on daily dosing and 21 on second daily dosing.
- Study CC-4047-MM-002, Phase I: The Phase I section of this trial (see above) determined the MTD of pomalidomide administered daily and provided safety data on 38 subjects.

Other studies evaluable for safety only

As of 7 September 2012, the safety of pomalidomide had been evaluated in subjects with RRMM, myeloproliferative neoplasm (MPN) associated myelofibrosis (MF), small cell lung cancer (SCLC), metastatic prostate cancer, and advanced soft tissue sarcomas (STSs), as well as in healthy male subjects. The clinical development program included a total of 14 studies, 9 of which were completed and 5 of which included subjects who are still being followed for disease progression and survival status. These 14 studies included 5 studies in MM (one primary Phase III study [CC-4047-MM-003]; two supportive Phase II studies [CC-4047-MM-002 Phase 2 and IFM 2009-02], and two supportive Phase I studies [CC-4047-MM-002 Phase 1 and CC-4047-MM-001] [see above]); four studies in subjects with other tumor types; and five Phase I studies in healthy subjects. The latter two groups were presented in an appendix; three additional ongoing studies are evaluating pomalidomide containing regimens in RRMM (CC-4047-MM-003/C), MPN associated MF (CC-4047-MF-002), and sickle cell disease (CC-4047-SCD-001).

Comment: The studies additional to the 5 above will be checked but not included in this evaluation unless their safety results differ significantly from the pivotal and supportive studies in the application.

Patient exposure

The total numbers of subjects exposed to pomalidomide in the MM studies providing safety data in this review are shown in Table 5 by pomalidomide dose.

Table 5: Number of subjects exposed in MM studies by pomalidomide starting dose (safety population).

MM Subjects	Pomalidomide Dose (mg)						
	1	2	3	4	5	10	Total
Number of subjects [a]	10	19	8	617	26	6	686

[a] Includes studies CC-4047-MM-003, CC-4047-MM-002 Phase 2, IFM 2009-02, CC-4047-MM-001, CC-4047-MM-002 Phase 1

Pivotal Study CC-4047-MM-003

Duration of treatment

The median duration of treatment in the pomalidomide + LD dexamethasone arm (12.4 weeks) was longer than that in the HD dexamethasone arm (8.0 weeks). The distribution of treatment duration in the pomalidomide + LD dexamethasone arm differed from that in the HD dexamethasone arm, with 56.6% of pomalidomide + LD dexamethasone subjects receiving treatment for 12 weeks or longer compared with 28.2% of HD dexamethasone subjects. The median number of treatment cycles was 3.0 in the pomalidomide + LD dexamethasone arm (minimum [min], maximum [max]: 1, 16 cycles) and 2.0 in the HD dexamethasone arm (min, max: 1, 12 cycles). These data reflect the lower rate of discontinuation from treatment seen in the pomalidomide + LD dexamethasone arm.

Dosing and dose reductions and interruptions for pomalidomide

Subjects in the pomalidomide + LD dexamethasone arm were exposed to pomalidomide for a median (minimum, maximum) of 63 (2, 327) days at a median daily dose of 4.0 mg. The median relative dose intensity (that is, observed dose intensity [in mg/day] divided by planned dose intensity [in mg/day]) was 0.90.

Depending on the type of treatment emergent adverse event (TEAE), the dose of pomalidomide was first interrupted and then reduced, or was reduced. In the pomalidomide + LD dexamethasone arm, 24% of subjects had at least 1 pomalidomide dose reduction, among whom the median number of reductions per subject was 1 and the median time to the first dose reduction was 30 days (min, max: 10 to 232 days). In the pomalidomide + LD dexamethasone arm, 58% of subjects had at least 1 pomalidomide dose interruption. Among subjects with at least 1 dose interruptions, the median number of dose interruptions per subject was 2 (min, max: 1 to 14) and the median time to the first interruption was 29 days (min, max: 2 to 253 days). There were more pomalidomide dose interruptions than dose reductions as a result of the occurrence of neutropenia in 45.3% of pomalidomide + LD dexamethasone subjects; neutropenia was one of the TEAEs that required dose interruption before dose reduction.

Dosing and dose reductions and interruptions for dexamethasone

Subjects in the pomalidomide + LD dexamethasone arm were exposed to dexamethasone for a median of 12 days at a median daily dose of 40 mg. Subjects in the HD dexamethasone 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 (that is, observed dose intensity [in mg/day] divided by planned dose intensity [in mg/day]) for dexamethasone was similar (0.9 in the pomalidomide + LD dexamethasone arm and 1.0 in the HD dexamethasone arm).

The percentage of subjects with at least 1 dexamethasone dose reduction was lower in the pomalidomide + LD dexamethasone arm (16.7%) than in the HD dexamethasone arm (26.2%). Among subjects with at least 1 dose reduction, the median number of dose reductions per subject in each treatment arm was 1. The median time to the first dexamethasone dose reduction was longer in the pomalidomide + LD dexamethasone arm (57 days [min, max: 8 to 312 days]) than in the HD dexamethasone arm (33 days [min, max: 28 to 309 days). The percentage of subjects with at least 1 dexamethasone dose interruption was higher in the pomalidomide + LD dexamethasone arm (37.0%) than in the HD dexamethasone arm (22.1%). Among subjects with at least 1 dose reduction, the median number of dexamethasone dose interruptions was 2 in the pomalidomide + LD dexamethasone arm and 1 in the HD dexamethasone arm. The median time to the first dexamethasone interruption was longer in the pomalidomide + LD dexamethasone arm (29 days; min, max: 8 to 261 days) than in the HD dexamethasone arm (17 days; min, max: 9 to 81 days).

Study CC-4047-MM-002 Phase 2

Subjects were randomised 1:1 to treatment arm A or B.

Arm A: Subjects received oral pomalidomide at a dose of 4 mg a day on Days 1 to 21 of a 28 day cycle, and oral dexamethasone 40 mg once per day on Days 1, 8, 15 and 22 of each 28 day cycle for subjects who were ≤ 75 years of age and 20mg once a day for those >75.

Arm B: Subjects received oral pomalidomide at a dose of 4 mg a day on Days 1-21 of a 28 day cycle. Subjects who had confirmed PD at any time had the option to receive a starting dose of dexamethasone was 40 mg once per day on Days 1, 8, 15 and 22 of each 28 day cycle for subjects who were ≤ 75 years of age in addition to pomalidomide. For subjects who were > 75 years of age, the starting dose of dexamethasone was 20 mg once per day on Days 1, 8, 15 and 22 of each 28 day cycle.

Overall, as the data cutoff date, subjects were exposed to pomalidomide for a mean of 121 days with an average daily dose of 3.8 mg/day. Mean treatment duration was approximately 173 days. A total of 26 of the 112 subjects in the pomalidomide + dexamethasone arm and 34 of the 107 subjects in the pomalidomide arm had at least one pomalidomide dose reduction (27.4% of subjects in the overall safety population).

Study IFM-2009-02

Patients were randomised (1:1) to receive in:

- Arm A: 4 mg/day pomalidomide on Days 1 to 21, plus commercial dexamethasone 40 mg on Days 1, 8, 15, and 22 of each 28 day cycle or
- Arm B: 4 mg/day pomalidomide on Days 1 to 28, plus commercial dexamethasone 40 mg on Days 1, 8, 15, and 22 of each 28 day cycle.

Patients remained on treatment for an average of 6 treatment cycles overall. The average number of cycles received was higher amongst patients in Arm A (median: 8) than in Arm B (median: 6). More patients underwent dose reduction in Arm A (19 patients, 44%) than Arm B (14 patients, 34%), but there was no difference between treatment arms in terms of relative dose intensity (88% in each arm).

Safety issues with the potential for major regulatory impact

Haematological toxicity

The addition of pomalidomide to dexamethasone was associated with an increase in haematological adverse events (AEs), specifically neutropenia and febrile neutropenia. Approximately 24% of subjects in the pomalidomide + LD dexamethasone arm in the pivotal study had pomalidomide dose reductions, most of which were due to neutropenia (7.7%), thrombocytopenia (6.3%), and febrile neutropenia (1.3%). Pomalidomide dose

interruptions were more frequent (61.3%) and were due to neutropenia (21.0%); thrombocytopenia (8%).

Therefore, the management of haematological toxicity is an important part of responsible use of pomalidomide + LD dexamethasone treatment in this population of MM patients.

Evaluator's conclusions on safety

The following conclusions are largely from the pivotal Study CC-4047-MM-003 in which the treatment dose and patient population were closest to those in the requested indication.

- TEAEs related to pomalidomide were significantly more frequent (76.7%) than those related to LD dexamethasone (56.7%) in the proposed pomalidomide + LD dexamethasone combination.
- The most frequently occurring TEAEs related to pomalidomide included neutropenia (38.7%), anaemia (22.7%), thrombocytopenia (18.7%), and fatigue (17.7%). The majority of the first three TEAEs were severe (see below).
- Those related to LD dexamethasone included fatigue (10%), asthenia (5%), peripheral oedema (5.3%) and hyperglycaemia (4%).
- Severe TEAEs (Grade 3 and 4) related to pomalidomide occurring in at least one subject were significantly more frequent (56.7%) than those related to LD dexamethasone (28%).
- The most frequently occurring severe TEAEs related to pomalidomide included neutropenia (35.7%), thrombocytopenia (13.7%), and anaemia (13.0%). Febrile neutropenia occurred in 4.7% of subjects.
- The most frequently occurring severe TEAEs related to LD dexamethasone included pneumonia (3.3%), hyperglycemia (3%), and fatigue combined with asthenia (2.4%).

(Note: Investigators classified 3.7% and 2% of subjects with neutropenia and thrombocytopenia as related to dexamethasone respectively. However, since this association would be difficult to make in the presence of a pomalidomide effect on these counts, and since these figures were not increased in the HD dexamethasone arm, the evaluator does not consider they were caused by the LD dexamethasone administered.)

- The proportion of subjects in the pomalidomide + LD dexamethasone arm who had died at the data cut-off date was 25%, 18% of whom died of MM and 12.3% of a TEAE. Of the latter, most (5.3%) were due to "physical health deterioration", while 3 subjects (1%) died of acute renal failure.
- A total of 24 subjects (8.0%) in the pomalidomide + LD dexamethasone arm had 1 or more TEAEs that led to the discontinuation of pomalidomide. Most common were infections (2%) and renal disorders (1.3%). No single TEAE resulted in the discontinuation of pomalidomide in more than 2 subjects.
- The percentages of subjects with 1 or more TEAEs leading to discontinuation of dexamethasone were 8.3% in the pomalidomide + LD dexamethasone 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 subjects (1.0%).
- No unexpected laboratory abnormalities were reported. Neutropenia was significant and also reported as a TEAE (see above), which was severe in most cases.

- As pomalidomide is a thalidomide analogue that is teratogenic in animal models, care was taken in the pomalidomide trials to warn about and monitor possible exposure to female subjects. Strong warnings have been included in the proposed PI and CMI.
- Renal abnormalities (both TEAEs and severe TEAEs) were less frequent in the pomalidomide + LD dexamethasone group of subjects than in those receiving HD dexamethasone.
- A total of 32 subjects receiving pomalidomide have reported 40 second primary malignancies (SPMs) from approximately 3000 patients receiving the drug.
- The safety of pomalidomide + LD dexamethasone compared to pomalidomide alone could not be assessed in the pivotal trial but was assessable in the Phase II trial, CC-4047-MM-002, although complicated by the addition of dexamethasone treatment to the pomalidomide only arm on disease progression. The question is important, given that synergy of the two drugs was shown in laboratory and animal studies. In the trial, the incidence of TEAEs related to pomalidomide was the same (89%) in pomalidomide + dexamethasone and the pomalidomide only arms, and that of severe (Grade 3 and 4) TEAEs similar in both arms for the most frequent events. Grade 5 adverse events were also of similar frequency (12.3% and 14.8%). Pomalidomide was discontinued in 8% of subjects in the pomalidomide + LD dexamethasone and 12% in the pomalidomide only arm. These results show that adverse events were not increased by the addition of dexamethasone to pomalidomide.

Overall, it can be concluded that treatment of this heavily pretreated population of patients with pomalidomide and dexamethasone is associated with frequent and severe neutropenia that was manageable as shown by the relatively low discontinuation rate and Grade 5 events due to neutropenia.

First round benefit-risk assessment

First round assessment of benefits

The benefits of pomalidomide and LD dexamethasone in the proposed usage are:

- a clinically significant improvement of 7.7 weeks in PFS
- a clinically significant improvement of more than 12 weeks in OS (20 weeks in the updated analysis)
- a clinically significant improvement of 12.7% in response rate
- The positive effects were shown in most subgroups, with one possibly significant exception.

Note that these benefits are from comparison with HD dexamethasone treatment, and not to pomalidomide alone. That comparison in the Phase II Study CC-4047-MM-002 showed a smaller clinical benefit in PFS and no benefit in OS or response rates when dexamethasone was added to pomalidomide on disease progression.

First round assessment of risks

The main risks of pomalidomide and LD dexamethasone in the proposed usage are:

- The high frequency (56.7%) of Grade 3 and 4 neutropenia with the associated risks of infection.

Comment: Although of high frequency, severe neutropenia was manageable, and is acceptable for this population of heavily pre-treated patients with advanced disease, provided the treatment is administered and managed by experienced physicians.

- Venous thrombotic event (VTEs) and arterial thrombotic events (ATEs): These events were infrequent. In the pomalidomide + LD dexamethasone arm, 3.3% of subjects had at least 1 VTE. In the HD dexamethasone arm, 2.0% of subjects had at least 1 VTE. At least one Grade 3/4 VTE occurred in 1.3% of pomalidomide + LD dexamethasone subjects and in no HD dexamethasone subjects. Serious VTEs occurred in 1.7% of pomalidomide + LD dexamethasone subjects and in no HD dexamethasone subjects. No VTE led to the discontinuation of treatment in either treatment arm. No subject died as a result of a VTE. DVT and venous thrombosis occurred in similar proportions of subjects in the 2 treatment arms. Pulmonary embolism occurred in 1.0% of pomalidomide + LD dexamethasone subjects and in no HD dexamethasone subjects. Arterial thrombotic events occurred in 1.0% of pomalidomide + LD dexamethasone subjects and 0.7% HD dexamethasone subjects. In the pomalidomide + LD dexamethasone arm, these events included: embolism, ischemic cerebral infarction, and myocardial infarction each occurring in 1 subject. In the HD dexamethasone arm, 1 subject (0.2%) had a transient ischemic attack. With the exception of the embolism in the pomalidomide + LD dexamethasone 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.

  Comment: The data show that the risk of these AEs is low and manageable. It is noted that all subjects in the pivotal trial were required to take prophylactic medication for thrombosis and this recommendation is included in the PI.

- Peripheral neuropathy: The frequency of peripheral neuropathy was significant in both arms of the pivotal trial. In the pomalidomide + LD dexamethasone arm, 12.3% of subjects had at least one occurrence of peripheral neuropathy, and in the HD dexamethasone arm, 10.7%. There were few occurrences of severe neuropathy in either arm.

- Second primary malignancies: the occurrence of a second primary malignancy exists in patients receiving pomalidomide.

  Comment: This risk has to be considered against the seriousness of the disease being treated, and the risk that exists with MM in the absence of pomalidomide treatment. An appropriate warning is included in the PI.

- Teratogenic effects: The risks associated with the teratogenic effects of pomalidomide are addressed by the restricted access program and the TGA approved compulsory *i-access* program, which also apply to thalidomide and lenalidomide.

  Comment: Combined with the related warnings and advice in the PI of Pomalyst, this risk is acceptable.

- The possibility that dexamethasone contributes significantly to toxicity but not to efficacy compared to pomalidomide alone:

  Comment: Although the addition of dexamethasone to treatment with pomalidomide did not increase OS, the small increase in PFS seen and the lack of any synergistic toxicity provide reasons for accepting its use, while noting that its contribution to the efficacy of the combination was not addressed in the pivotal study.

- Whether similar outcomes of both efficacy and safety would be observed with a patient population refractory or resistant to proteosome inhibitors other than bortezomib.

First round assessment of benefit-risk balance

The benefit-risk balance of pomalidomide with dexamethasone remains unfavourable given the proposed usage, but would become favourable if the recommended changes are adopted. The reason is that broadening the patient population to include those who are resistant or refractory to any proteosome inhibitor (including those not yet in clinical trial) introduce a risk of loss of efficacy, because structurally similar drugs, for example, lenalidomide and pomalidomide have different patterns of drug resistance in this patient population. The results can therefore only be applied with safety to patients who have had exposure to the designated proteosome inhibitor, bortezomib.

First round recommendation regarding authorisation

The evaluator recommends that the requested indication be approved if the wording were changed to the following:

> *Pomalyst in combination with dexamethasone is indicated for the treatment of patients with multiple myeloma who have failed at least two prior therapies including lenalidomide and bortezomib*

The wording of the PI and Consumer Medicine Information (CMI) should also be changed as recommended.

Clinical questions

None.

V. Pharmacovigilance findings

Risk management plan

The sponsor submitted a Risk Management Plan (EU-RMP Version 6.0 dated 05/06/2013; Data Lock Point [DLP] 24/05/2013) and Australian Specific Annex (ASA) Version 1.0 (dated 11/09/2013; no DLP given) which was reviewed by the TGA's Office of Product Review (OPR).

Ongoing safety concerns

The sponsor provided a summary of Ongoing Safety Concerns which are shown at Table 6.

Table 6: Ongoing Safety Concerns for Pomalyst.

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 CYP1A2, 3A4/5 and P-glycoprotein – Interaction with oral contraceptives – Use in patients of different racial origin – Paediatric use – Use during breast-feeding

Pharmacovigilance activities

The sponsor proposes routine pharmacovigilance activities for important identified and potential risks and missing information (as stated above). Furthermore, additional activities are planned for some of the risks. These activities are summarised in Table 7.

Table 7: Additional pharmacovigilance activities planned by the sponsor.

Additional activity	Assigned safety concern	Actions/outcome proposed	Estimated planned submission of final data
Non-interventional post-authorisation registry of patients treated with pomalidomide for RRMM to monitor incidence of ADRs in "real world situation" and to monitor implementation and compliance of Celgene PPP and off-label use and controlled distribution system on a country basis in agreement with the relevant NCA CC-4047-EU Registry Protocol synopsis available	• 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)	Primary • To characterise and determine the incidence of important identified and potential risks as outlined in the risk management plan (RMP) among previously treated MM patients who are currently being treated with pomalidomide in a post marketing setting. Secondary • To describe and assess the effectiveness, implementation and compliance of the Celgene PPP for patients recruited in this registry • To describe the type of myeloma treatments administered prior to receiving pomalidomide • To describe the type and duration of myeloma regimens administered prior to receiving pomalidomide • To describe the type and duration of myeloma regimens administered after receiving pomalidomide during follow up period	30 Apr 2020 (Final report) Updates with PSURs

Additional activity	Assigned safety concern	Actions/outcome proposed	Estimated planned submission of final data
	• Off-label use	• To describe risk factors for thromboembolic events and use of prophylactic anticoagulation medications	
Solicited reporting of SPM in all Celgene-sponsored clinical studies	• SPM		PSUR/DSUR cycle
Long-term follow-up of SPM in all Celgene-sponsored clinical studies	• SPM		PSUR/DSUR cycle
Definitive TQT study in healthy volunteers. A Phase 1, Double-Blind, Four-Period Crossover Study To Investigate The Effects Of Pomalidomide (Cc-4047) On The QT Interval In Healthy Male Subjects. CC-4047-CP-010 Protocol available	• QT interactions (prolongation) • Cardiac failure, • Cardiac arrhythmia (including bradycardia)	Primary Objective: To evaluate the effect of pomalidomide on the time-matched changes from placebo in the baseline-adjusted QT interval of the electrocardiogram (ECG) using the Fridericia correction method (QTcF).	Q1 2015 (Final report)
A Phase I multi-center, open-label, dose escalation study to determine the pharmacokinetics and safety of pomalidomide when given in combination with low dose dexamethasone in subjects with relapsed or refractory multiple myeloma and impaired renal	• Use in patients with renal impairment	The primary objective of the study is to determine the PK and safety for the combination of pomalidomide (POM) + low-dose dexamethasone (LD-DEX) in subjects with relapsed or refractory MM (RRMM) and impaired renal function. The secondary objective of the study is to	Q1 2016 (Final report)

Additional activity	Assigned safety concern	Actions/outcome proposed	Estimated planned submission of final data
function. CC-4047-MM-008 Protocol available		evaluate the efficacy of POM + LD-DEX in subjects with RRMM and impaired renal function.	
A Phase I, open-label, two-part study to evaluate the pharmacokinetics of pomalidomide (cc-4047) in hepatically impaired male subjects. CC-4047-CP-009. Protocol available.	• Use in patients with hepatic impairment	Primary Objectives: • Part 1: To evaluate the effect of severe hepatic impairment on the pharmacokinetics (PK) of a single oral dose of pomalidomide in male subjects. • Part 2: To evaluate the effect of moderate and mild hepatic impairment on the PK of a single oral dose of pomalidomide in male subjects. Secondary Objectives: • To evaluate the effect of hepatic impairment on the safety of a single oral dose of pomalidomide in male subjects.	Q1 2016 (Final report)
In vitro assessment of pomalidomide as an inhibitor of P-glycoprotein using Caco-2 cells. CC-4047-DMPK-1586 Final report available	• Interactions with drugs affecting and metabolised by CYP1A2, 3A4/5 and P-glycoprotein	Conclusion: The efflux ratio of digoxin was not reduced in the presence of pomalidomide indicating it is not an inhibitor of P-gp *in vitro*.	Q3 2013 (Final Report)

Additional activity	Assigned safety concern	Actions/outcome proposed	Estimated planned submission of final data
CC-4047: Substrate potential in OATP1B1 and OATP1B3 expressing HEK293 cells. CC-4047-DMPK-1653 Protocol synopsis available	*None assigned.*	• To determine if a clinical drug-drug interaction study evaluating pomalidomide as a substrate of OATP1B1 or OATP1B3 may be necessary.	Q4 2013 (Final Report)
Population pharmacokinetics and exposure response analysis plan of pomalidomide. Protocol available	• Use in patients with renal impairment • Use in patients with hepatic impairment • Use in patients of different racial origin	• Pharmacokinetic data from completed studies in healthy subjects and MM patients will be included in a population pharmacokinetic analysis • The covariates to be included in the analysis will 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, as available.	End of 2013 (Final Report)

Q=quarter

Risk minimisation plan

The sponsor proposes routine and additional pharmacovigilance activities for identified risks, important potential risks and missing information.

Routine and additional risk minimisation activities are proposed for pomalidomide.

Additional risk minimisation activities have been assigned to teratogenicity, neutropaenia, TEEs, peripheral neuropathy, thrombocytopaenia and bleeding, TLS, somnolence, and off-label use. All the aforementioned risks will be covered by health care professional education materials, the risk of teratogenicity will be additionally covered by a pregnancy prevention programme.

Pregnancy prevention programme

The sponsor is proposing a pregnancy prevention programme for patients on pomalidomide. In Australia, this is facilitated through the *i-access*® program for pregnancy prevention. The programme involves prescribers, patients, and pharmacists. All parties involved need to be registered with the programme. Flowcharts of the process for prescribers, patients and pharmacists are in Appendix 3 of the submitted ASA for the EU-RMP.

Reconciliation of issues outlined in the RMP report

Reconciliation of issues outlined in the RMP report is as follows.

Recommendation #1 in RMP evaluation report

The following should be added as Ongoing Safety Concerns, or a compelling justification provided:

- Anaemia;
- Dyspnoea; and
- GI toxicity.

Sponsor response

The sponsor closely monitors all AEs received for pomalidomide on a case by case basis as well as in an aggregate fashion. Based upon experience and medical judgement, the sponsor does not believe that these events need to be incorporation into the RMP, as ongoing safety concerns, at this time. However, the sponsor will continue to monitor these events and will update the EU RMP and the ASA should new data be received.

OPR evaluator's comment

The sponsor has not given a compelling justification why these concerns should not be included.

However, at this stage, the sponsor is not required to include these risks, but this will be reviewed in the future.

Recommendation #2 in RMP evaluation report

The sponsor is advised to submit the final study reports with Periodic Safety Update Reports (PSURs), when they become available.

Sponsor response

The sponsor agrees to submit the final study reports relating to pharmacovigilance activities with the PSURs, when available.

OPR evaluator's comment

This is considered acceptable.

Recommendation #3 in RMP evaluation report

The pregnancy prevention programme seems to adequately prevent the risk of pregnancy during therapy with pomalidomide. Some issues require clarification or further recommendations:

- The sponsor should clarify what constitutes a 'medical practitioner working with a haematologist/oncologist'.

Sponsor response

The treatment with pomalidomide can only be initiated by a haematologist/oncologist specialist who is registered with the *i-access* program. The ongoing management of patients can be conducted by a medical practitioner under the supervision of the haematologist/oncologist specialist. The medical practitioner could be a physician in training to become a specialist in haematology/oncology. He or she could also be a haematology/oncology resident or registrar, working with the specialist at the time, as part of ongoing medical training and experience.

OPR evaluator's comment

This is considered acceptable.

Recommendation #4 in RMP evaluation report

The sponsor should clarify what constitutes a 'medically supervised pregnancy test'.

Sponsor response

A medically supervised pregnancy test, as described in the PI, requires a minimum sensitivity of 25 mIU/mL and needs to be conducted by a healthcare professional in order to ensure that the patient is not pregnant prior to commencement of treatment with pomalidomide. These would typically be blood tests.

OPR evaluator's comment

The sponsor should specify that the pregnancy test should be a blood test.

Recommendation #5 in RMP evaluation report

The sponsor should clarify what patient information material is distributed (other than the CMI document).

Sponsor response

The main information document provided to the patients by the sponsor is the CMI. The prescribers, haematologist/oncologist specialists, who are trained on the pregnancy prevention requirements for pomalidomide and are registered with the *i-access* program will educate and counsel all patients (females of child bearing potential, females of non-child bearing potential and males) on the *i-access* program and the special requirements of the *i-access* program for pregnancy prevention.

OPR evaluator's comment

Based on the information given by the sponsor, it is assumed that no patient information material is distributed (other than the CMI document).

Recommendation #6 in RMP evaluation report

The sponsor should clarify whether the training sessions for health care professionals are delivered online or in person.

Sponsor response

The Celgene Haematology Specialist Representatives (HSRs) provide personal, face to face training to the prescribers (haematologists/oncologists) prior to registration with the *i-access* program and on an ongoing basis, as required. The Celgene Risk Management Specialists provide individual in-service training over the telephone to the prescribers (haematologists/oncologists) who cannot be accessed by the HSRs, and to the main Pharmacists of each pharmacy prior to registration with the *i-access* program. Once training is completed, the prescribers (haematologists/oncologists) and the pharmacists are also able to access online educational material for easy reference.

OPR evaluator's comment

This is considered acceptable.

Recommendation #7 in RMP evaluation report

The sponsor should clarify whether the educational materials (for each prescriber, pharmacist and patients) are supplied in print or online or both.

Sponsor response

The *i-access* program educational materials for prescribers and pharmacists are available in printed form, and are currently being developed as an online resource.

OPR evaluator's comment

This is considered acceptable.

Recommendation #8 in RMP evaluation report

The programme should incorporate the use of a patient card that contains patient details and core information with regard to pomalidomide therapy. The card will be useful for elderly patients.

Sponsor response

The sponsor believes that all core information included in the Patient Cards are captured, recorded and monitored via the *i-access* program and that introduction of such patient cards in Australia will not provide any additional benefit to the patients.

The sponsor uses different tools in different territories to monitor key elements of the pregnancy prevention plan (PPP) including indication, dose, patient demographics and compliance to the PPP. In the EU, each National Competent Agency can choose to include the Patient Card or incorporate the key elements from the patient card within other tools such as the Prescription Form. The Australian *i-access* program has been developed to capture the key core elements of the PPP, which includes all information captured in the patient cards.

OPR evaluator's comment

The use of a patient card additional to the other components of the *i-access* program is the preferred option for the OPR evaluator.

Recommendation #9 in RMP evaluation report

In regard to patients who are females of non-child bearing potential, the program should only authorise a maximum supply for 12 weeks.

Sponsor response

The sponsor agrees to only authorise a maximum supply for 12 weeks of treatment for females of non-child bearing potential and males via the *i-access* program.

OPR evaluator's comment

This is considered acceptable.

Recommendation #10 in RMP evaluation report

The prescriber should be notified, if a pregnancy test is positive to enable further medical management of the issue. This notification needs to be facilitated by the programme.

Sponsor response

The sponsor confirms that in an event of a positive pregnancy test the Celgene Risk Management Centre (CRMC) will contact the prescriber to enable further medical management of the issue. The Celgene Risk Management specialist will:

- request that the prescriber directs the patient to stop therapy immediately
- request the prescriber to confirm if it is a positive/equivocal test
- request the results and clinical interpretation of an additional medically supervised
- pregnancy test conducted immediately and within 48 h of the first test to be sent to Celgene
- not authorise further dispensing of pomalidomide to the patient until a negative pregnancy test result is received by Celgene.

OPR evaluator's comment

Additional to the actions described by the sponsor in their response with regard to a positive pregnancy test, the sponsor should follow up a continuing pregnancy.

Recommendation #11 in RMP evaluation report

The sponsor should provide a plan on how the effectiveness of the education programme measure will be measured.

Sponsor response

The *i-access* program is well established and controls prescribers, pharmacists and patients for every monthly dispense of product. As every dispense of pomalidomide requires the sponsor's authorisation before supply, the sponsor has tight control and monitoring of compliance of the program and educational effectiveness. The well-established program has met its objectives as no fetal exposure has been reported in patients being treated with either Thalomid or Revlimid in Australia; therefore the program and associated education are considered effective and proven in many thousands of patients since the inception of the Pregnancy Prevention RMP in 2002 for Thalomid and 2008 for Revlimid.

OPR evaluator's comment

This is considered acceptable.

Recommendation #12 in RMP evaluation report

All draft education materials should be made available to the TGA.

Sponsor response

The accepted and fundamental consumer document specific for pomalidomide is the CMI, which contains educational material and information about the product, disease and *i-access* program. Currently, the sponsor has not developed any product specific educational material for pomalidomide. As the *i-access* program is a restricted distribution 'process' that is common to a number of the sponsor's products, the following *i-access* materials currently in use will also be applicable to pomalidomide. These documents (provided) will be updated as relevant, to include pomalidomide upon TGA approval of the product.

Introducing *i-access*

- Information for prescribers

- "Prescribing Thalomid or Revlimid for women of childbearing potential"
- Quick guide to using your *i-access* online account for Prescribers
- Quick Guide to Using the *i-access* Online Portal
- Patient consent form

OPR evaluator's comment

This is considered acceptable.

VI. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

The quality evaluator had no objections to registration following the sponsor's response to questions.

The capsule fills all use the same set of excipients, with pomalidomide blended with the diluents mannitol and pregelatinised starch and the lubricant sodium stearyl fumarate.

Bioequivalence Study CC-4047-CP-007 compared the different Formula 3 capsule fills (same excipients but in different ratios) used for the different strengths (that is, 1 + 2 mg versus 3 + 4 mg); this showed that a single 4 mg capsule is bioequivalent to two 2 mg capsules and a single 3 mg capsule is bioequivalent to one 1 mg capsule plus one 2 mg capsule when administered under fasted conditions.

Pomalidomide has one chiral centre. The drug substance is manufactured as a racemic mixture of the R- and S-enantiomers (like thalidomide and lenalidomide). Use of the racemic mixture rather than a specific enantiomer was justified by the company based on the observation that the two enantiomers interconvert *in vitro* in buffer at neutral pH and in plasma.

The drug substance is pomalidomide free base, a yellow crystalline powder. The aqueous solubility of pomalidomide is low. Adequate stability data have been provided to support a retest period for the drug substance of 3 years with storage below 25°C.

Nonclinical

The nonclinical evaluator had no objections to the registration of pomalidomide for the indication sought and recommended the RMP and draft PI are amended as directed. The Delegate is in support of the amendments to the PI recommended and the OPR evaluator will incorporate any RMP changes deemed necessary.

Pomalidomide has a similar pharmacological/toxicological profile to lenalidomide.

The primary pharmacology studies support the combined use of pomalidomide with dexamethasone for the treatment of patients with lenalidomide resistant MM. No animal studies assessed the efficacy of this combination against lenalidomide and bortezomib resistant MM.

The main toxicity findings of clinical relevance were:

> *immunosuppression and secondary effects (infections, secondary malignancies) teratogenicity and embryo/fetal lethality, thus warranting a Pregnancy Category X.*

The pharmacological profile of pomalidomide was similar to the structural analogue, lenalidomide. Pomalidomide inhibited the proliferation of lenalidomide resistant MM cell lines *in vitro* and inhibited tumour growth in mice bearing lenalidomide resistant MM xenografts. The combination of pomalidomide and dexamethasone was synergistic in both systems. The efficacious doses of pomalidomide and dexamethasone in mice were similar to those proposed to be used clinically. The mechanism of lenalidomide and pomalidomide resistance is similar, but with different thresholds.

Based on findings in standard safety pharmacology studies, no adverse effects on CNS, respiratory or cardiovascular function are predicted.

Oral absorption of pomalidomide was reasonably rapid. Enantiomeric conversion was shown to occur in monkeys, which was similar in monkey and human plasma. Tissue distribution studies in rats were unremarkable. Pomalidomide underwent both non-enzymatic and enzymatic degradation. CYP1A2, 2C19, 2D6 and 3A4 were involved in the enzymatic degradation of pomalidomide. There were no human specific metabolites. Biliary excretion was demonstrated in rats.

Pomalidomide is not expected to alter the exposures of CYP450 or P-glycoprotein substrates. Pomalidomide was a substrate of P-glycoprotein, but based on the high oral bioavailability of this drug, P-glycoprotein inhibitors are not expected to alter the pharmacokinetic of pomalidomide.

Oral pomalidomide had a low order of single dose toxicity in rodents, and treatment with pomalidomide over 6 months was well tolerated in rats. Monkeys were more sensitive to pomalidomide induced toxicity (likely associated with pharmacological responsiveness). Major target organs in monkeys were the lymphoid and haematopoietic system (lymphopenia, thrombocytopenia, bone marrow hypocellularity and lymphoid depletion) and the intestinal tract (chronic inflammation of the large intestine and villous atrophy of the small intestine). *Staphylococcus aureus* infection and AML seen in individual animals and was attributed to the immunosuppressant action of pomalidomide. The toxicity profile of pomalidomide was similar to lenalidomide.

Pomalidomide was examined for potential genotoxicity in the standard battery of tests with negative results in all assays. Carcinogenicity studies were not conducted and are not required for this anticancer medication. However, given the immunosuppressive activity of pomalidomide and the finding of AML in a pomalidomide treated monkey, secondary malignancies may be seen in patients.

Pomalidomide crossed the placenta and was detected in fetal blood following administration to pregnant rabbits. Maternal exposure to pomalidomide induced embryo/fetal lethality and teratogenicity in rats and rabbits. A NOAEL was not established. Pomalidomide was detected in the milk of lactating rats following administration to the mother. Breast-feeding should be avoided when taking pomalidomide. Adverse embryonic effects following seminal transfer of pomalidomide cannot be ruled out. The animal studies are inadequate to address this.

Pomalidomide is an immunomodulator with some immunosuppressant activity. The activity is expected to be similar to that for lenalidomide (based on pharmacological studies).

Clinical

The clinical evaluator reviewed the submitted data (see *Clinical findings* above and Attachment 2 for the scope of the sponsor's clinical dossier).

The submitted data was evaluated using TGA adopted EMA guidelines.[11]

Clinical evaluator's recommendation

The clinical evaluator has recommended registration of pomalidomide for the following modified indication:

> *Pomalyst in combination with dexamethasone is indicated for the treatment of patients with multiple myeloma who have failed at least two prior therapies including lenalidomide and bortezomib.*

Paediatric data

The submission did not include paediatric data.

Pharmacokinetics/Pharmacodynamics

Absorption

The pharmacokinetic results were generally similar for healthy and MM subjects following single and multiple dose studies. The oral bioavailability was 73%, and under fasting conditions (and food studies indicated no significant effect of food intake), the median Tmax was 3 h for the dose range used in the clinical studies. The Cmax in the clinical dose range (0.5-5 mg) increases in a dose proportional manner, and steady state is reached by Day 3. The justification for not including an absolute bioavailability study (no plans to develop IV or oral solution due to instability at a neutral pH, limited solubility) is considered acceptable. Bioequivalence was demonstrated across the 4 dosage strengths proposed for registration. The apparent volume of distribution (Vd) in healthy subjects ranged from 102-140 L for doses ranging from 1-50 mg, and plasma protein binding differed for the different enantiomers (R: 15.8%; S: 42.2%). No active metabolites have been identified. Tissue distributions in the nonclinical studies showed detectable levels of radiolabelled pomalidomide in the gastrointestinal tract, organs of excretion (renal tract, bladder and bile) and detectable levels were present in the CNS. In the clinical studies, pomalidomide was measurable in semen.

Metabolism/excretion

In vitro, pomalidomide was metabolised to a limited extent in human hepatocytes, and the principal routes of metabolism were hydroxylation followed by glucuronidation, and hydrolysis, with multiple products also formed due to non-enzymatic hydrolysis. *In vivo*, pomalidomide was detected intact (70% circulating radioactivity) with metabolites formed by hydroxylation with subsequent glucuronidation, or hydrolysis of the parent compound. In the human ADME study, CYP dependent metabolites accounted for approximately 43% of the excreted radioactivity, while non CYP dependent hydrolytic metabolites accounted for 25%, and excretion of unchanged pomalidomide accounted for 10%. CYP3A4 and CYP1A2 were the primary isoenzymes responsible for CYP-450 mediated metabolism. Less than 5% is excreted unchanged in the urine.

Pomalidomide is mainly metabolised at extra renal sites and the metabolites are eliminated predominantly through renal excretion (72.8% of the administered dose but <5% was unchanged drug). Faecal excretion of radioactivity accounted for 15.5% of the administered dose, with unchanged pomalidomide accounting for 7.7% of the dose.

[11] European Medicines Agency, "Guideline on the evaluation of anticancer medicinal products in man (EMA/CHMP/205/95/Rev.4)", 13 December 2012; European Medicines Agency, "Committee for Proprietary Medicinal Products (CPMP), Points to Consider on Application with 1. Meta-analyses; 2. One pivotal study (CPMP/EWP/2330/99)", 31 May 2001.

Pomalidomide parent compound is responsible for the pharmacological response (for example, inhibition of MM cell lines, immunomodulatory effects).

Pharmacokinetic studies in MM patients

While not of sufficient concern to preclude registration, there were several limitations in the pharmacokinetic analyses presented in the submission, which require addressing to characterise pomalidomide fully for use in the proposed population, and to provide optimal advice about safe prescribing in the PI. Most of these are being addressed in studies underway and were not available at the time of submission but it is the Delegate's view that these ought to be submitted, as a condition of registration. These include:

- Studies in subjects with renal impairment. A dedicated study in MM patients with renal impairment is underway (Phase I, dose escalation pharmacokinetic and safety Study CC-4047-MM-008). While pomalidomide is extensively metabolised and <5% of the active parent drug is excreted unchanged in the urine, given the incidence of renal impairment in both this disease, the advanced median age at diagnosis (71), and observed cases of renal failure (see Safety section), submission of this should be a condition of registration (see Conditions of registration). The sponsor is requested to indicate a likely completion date for this study in the pre ACPM response.
- Drug-drug interaction study: information in the PI (mentioned in the EMA European Public Assessment Report [EPAR] and Summary of Product Characteristics) indicates a significant increase in pomalidomide levels (and likely increased efficacy/adverse events) with concurrent administration of a strong CYP3A4 and CYP1A2 inhibitors. There is no discussion about the any potential loss of efficacy with CYP3A4 and CYP1A2 inducers. Data supporting this have not been included in this submission: the Summary of Clinical Pharmacology states that a trial is completed and under analysis (CC-4047- CP-008). The sponsor has indicated that they plan to submit this study post registration. As this pertains to safe prescribing, the sponsor is requested to provide the immediately relevant information to support these findings and submit the study for full clinical evaluation within 3 months of registration (see Conditions of registration).
- Hepatic impairment: no pharmacokinetic trials presented in those with hepatic impairment, and patients with transaminases > 3 x Upper Limit of Normal (ULN) were excluded from the Phase II trials CC-4047-MM-002 and IFM-2009-02. This needs to be reflected in the PI. A clinical trial evaluating pharmacokinetics in MM patients otherwise healthy subjects but with hepatic impairment is in progress (CC-4047-CP-009). Again, given the age at median diagnosis and likelihood of co-morbidities, this trial should be submitted to the TGA upon completion and the PI updated accordingly.
- There was no formal QT/QTc study submitted. The sponsor's Summary of Clinical Pharmacology states:

  '*The applicant has been compiling and reviewing QT data on an annual basis. A summary is provided here, and detailed information can be found in the Summary of Clinical Safety. The nonclinical and clinical data reviewed and analysed to date do not suggest an apparent signal or potential concern regarding QTc prolongation with pomalidomide. However, a formal thorough QT/QTc study in healthy subjects is planned with a target start date of 3Q 2013.*'

The sponsor is requested to indicate the likely completion date in the pre ACPM response, and it should be submitted upon completion as a condition of registration.

Although the pharmacokinetic measurements were generally similar to the healthy subjects' results, there were conflicting results at different dose levels for the two pharmacokinetic studies in MM patients at the dose closest to the proposed clinical dose level. In Study CC-4047-MM-001, the small patient numbers and high between patient

variability meant no statistical analysis was possible, while the pharmacokinetic component of the Phase II Study CC-4047-MM-002 was only an exploratory objective. The Delegate is in agreement with the clinical evaluator's conclusions that the clinical significance of the pharmacokinetic differences is uncertain and better assessed on the basis of the safety of the 4 mg dose in the clinical studies.

- There appeared to be no significant effect of age, body weight, or normal renal function on the pomalidomide pharmacokinetics in healthy males or those with MM. Most of these analyses were done in patients on pomalidomide alone, with only 7 patients evaluable who were on pomalidomide and dexamethasone. No studies were done in healthy female subjects, but there does not appear likely that this would yield different results and the results in the MM subjects confirm this.

A reduction in serum paraprotein concentration of at least 25% was seen in 39% of MM patients treated with pomalidomide (Study CDC-4047-00-001), while Grade 3 and 4 neutropenia were seen in 2.6% and 15.8%, respectively. The lowest point (nadir) was on Day 22 and lasted for 6-8 days. Effects of pomalidomide on the CD4 and CD8 counts in Study 1398/132 in healthy subjects were inconclusive.

- Efficacy and safety were not shown to be related to pharmacokinetic data on pomalidomide because of insufficient data.

Dosage selection

The 4 mg once daily dose was chosen as there were fewer instances of Grade 4 neutropenia requiring dose reduction than with 5 mg in the pomalidomide alone studies. Pomalidomide is active when administered alone: ORR 9% (ITT population), and a response rate of 15.4% in subjects > 65 years old and 23.1% in subjects >75 years old in heavily pre-treated subjects in Phase II Study CC-4047-MM-002. The proposed usage of pomalidomide is in combination with dexamethasone is supported by *in vitro* data, the observed synergy between lenalidomide (pomalidomide is a lenalidomide analogue) and LD dexamethasone and the ORR of 30.1% (ITT population) in subjects treated with pomalidomide/LD dexamethasone, versus 9.3% in subjects treated with pomalidomide alone in Phase II study CC-4047-MM-002. The choice of LD dexamethasone as well as a cyclic regimen schedule comes from studies using lenalidomide, and 21 out of 28 days was well tolerated and as efficacious as 28 of 28 days for pomalidomide.

Efficacy

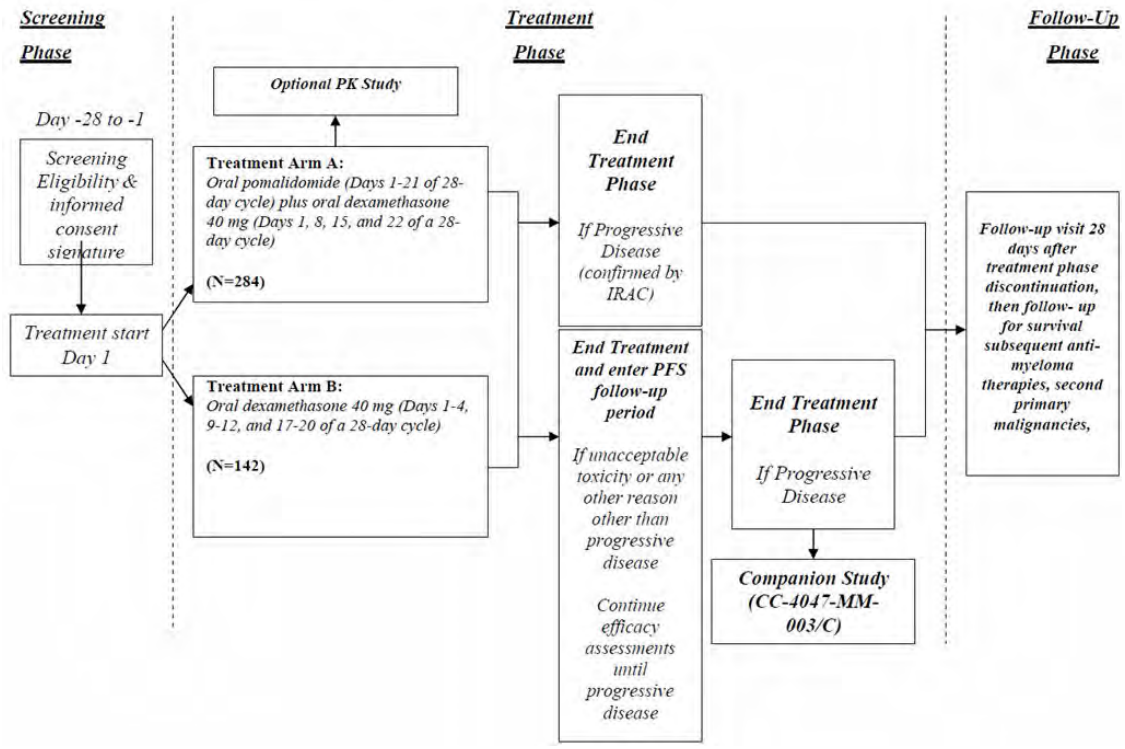
Pivotal Study CC-4407-MM-003 was a multicentre, randomised, open label design to compare PFS as a primary endpoint between pomalidomide + LD dexamethasone versus HD dexamethasone alone in patients with refractory MM or relapsed and refractory MM. In addition, the study was also powered to show an advantage in OS. The control arm was HD dexamethasone, a treatment widely used as a comparator to test novel agents in RRMM. For subjects in the HD dexamethasone arm who had confirmed disease progression, the option to enrol into an ongoing companion study (CC-4047-MM-003C) to receive pomalidomide alone was available.

The primary efficacy endpoint was PFS (as per International Myeloma Working Group [IMWG] criteria) of pomalidomide + LD dexamethasone versus HD dexamethasone. Secondary efficacy endpoints included: OS; Overall Response (using the new IMWG response criteria per IRAC); Objective Response (using European Group for Blood and Marrow Transplantation criteria per investigators); Time to progression (TTP); Time to response; Duration of response; Clinical benefit responses (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) and the European Organisation for Research and Treatment of Cancer

QoL Questionnaire for Patients with Multiple Myeloma (EORTC QLQ-MY20) Module, the Cancer QoL Questionnaire for Patients with Cancer (EORTC QLQ-C30) Module, and the descriptive system of the EQ-5D.

The secondary objective was to determine the safety of the treatment in the study population. Exploratory objectives of the study were to explore the relationship between MM response and cytogenetic abnormalities; to determine the population pharmacokinetics of pomalidomide when administered along with LD dexamethasone in subjects with refractory MM or RRMM; to explore the pomalidomide exposure and response relationship, and to explore the mechanism of action of pomalidomide (Figure 2).

Figure 2: Design of Study CC-4407-MM-003.



The inclusion and exclusion criteria are provided but key inclusion criteria included:

- ≥ 2 regimens that included lenalidomide and bortezomib, either alone or in combination
- adequate prior alkylator therapy, and to have had either refractory or relapsed and refractory disease defined as documented disease progression during or within 60 days of completing their last myeloma therapy
- a ≥ MR response and had developed intolerance/toxicity after ≥ 2 cycles of a bortezomib containing regimen.

  Comment: this pivotal efficacy trial specified bortezomib rather than the more general term, "proteasome inhibitor" as sought in the proposed indication.

Key exclusion criteria:

- absolute neutrophil count (ANC) < 1,000/µl, platelets < 75,000/µL for subjects in whom < 50% of bone marrow nucleated cells were plasma cells; or a platelets < 30,000/µL for subjects in whom ≥ 50% of bone marrow nucleated cells were plasma cells, Hb < 80 g/L (prior red blood cell transfusion or recombinant human erythropoietin use was permitted)

- creatinine clearance (CrCl) < 45 mL/min by Cockcroft-Gault formula: eligible if CrCl calculated from the 24 h urine sample was ≥ 45 ml/min
- Corrected serum calcium > 3.5 mmol/L
- Serum AST or ALT > 3.0 x ULN
- Serum total bilirubin > 34.2 μmol/L; or > 3.0 x ULN if hereditary benign hyperbilirubinaemia
- Prior resistance to HD dexamethasone, defined as disease progression on or within 60 days of receiving the last dose of HD dexamethasone used in the last line of therapy, either as single agent or in combination
- Prior allogeneic bone marrow or allogeneic peripheral blood stem cell transplant < 12 months prior who had not discontinued immunosuppressive treatment for > 4 weeks prior to initiation of study treatment and were currently dependent on such treatment.

Response (efficacy) assessments performed at central laboratories at the start of each cycle are described.

Randomisation was stratified according to the following:

- age (≤ 75 years old versus > 75 years old)
- number of prior anti MM therapies (2 prior anti MM therapies versus > 2 prior anti MM therapies).
- disease population
  - **refractory** subjects who had progressed on or within 60 days of both lenalidomide and bortezomib based treatments
  - versus **relapsed** and **refractory** subjects who achieved at least PR and progressed within 6 months after stopping treatment with lenalidomide and/or bortezomib
  - versus **refractory/intolerant** subjects who had developed intolerance/toxicity after a minimum of 2 cycles of bortezomib)

A total of 455 subjects were randomised in the study: 302 in the pomalidomide + LD dexamethasone arm and 153 in the HD dexamethasone arm. As of the data cut-off date of 7 September 2012, 136 (45.0%) subjects in the pomalidomide + LD dexamethasone arm and 38 (24.8%) subjects in the HD dexamethasone arm were still on treatment. The most common reason for discontinuation was disease progression (35.4% for subjects in the pomalidomide + LD dexamethasone arm; 49.0% in the HD dexamethasone arm).

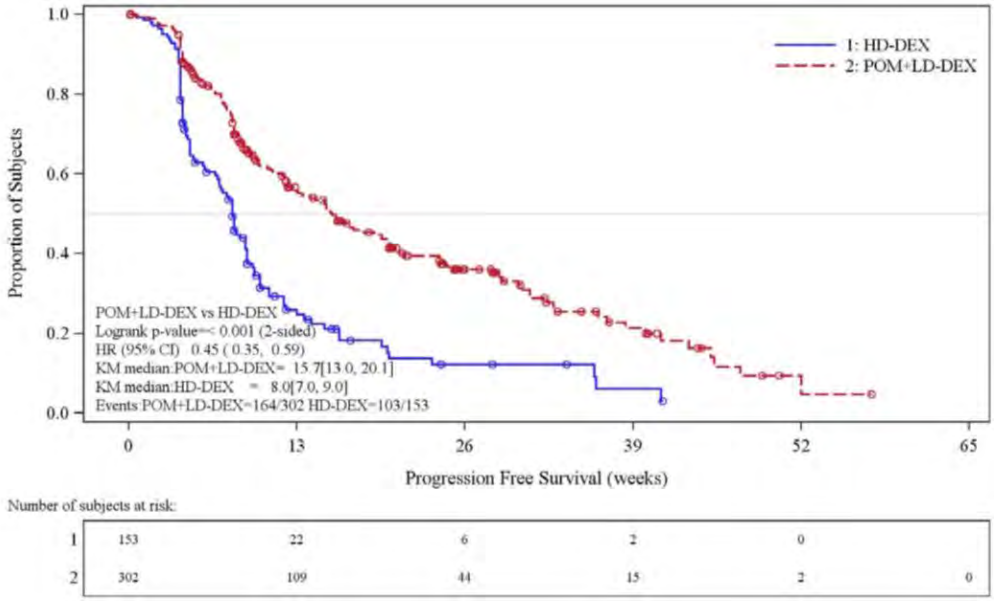
There were 59% of subjects in the ITT population who were male, and the median age was 63 (range 35-87) with 8% >75 years of age. Over 80% of subjects in each treatment arm were refractory, 94% of subjects had > 2 prior anti MM therapies (median number of treatments was 5). The proteosome inhibitor used was mainly with bortezomib (99.8% of total patient population) with only 7 of the total 455 patients treated with carfilzomib.

The demographic and disease characteristics were balanced in the two arms with the following exceptions that favoured the pomalidomide + LD dexamethasone arm: fewer patients with Stage III disease, a shorter median time since diagnosis, a lower incidence of light chain disease, and more subjects with Eastern Cooperative Oncology Group

Performance Status (ECOG PS)[12] 0 (36.4% compared with 23.5%). However, the clinical evaluator also noted there were more high risk/modified high risk subjects based on cytogenetics in the pomalidomide + LD dexamethasone arm (43% + 25.5%) than in the HD dexamethasone arm (37.3% + 22.9%).

As of the 7 September 2012 data cut-off, in the ITT population, PFS by was significantly longer with pomalidomide + LD dexamethasone arm compared with the HD dexamethasone arm (median 15.7 [95% CI: 13, 20.1] versus 8.0 weeks [95% CI: 7-9]; Hazard Ratio [HR] 0.45 ; p < 0.001). The PFS in the two arms of the EE population were very similar. An updated PFS (cut-off 1 March 2013) was provided although was not the primary endpoint and confirmed the median values of 16 weeks (13-19.6 weeks) for the test arm and 8.1 weeks (7.1-9.4 weeks) for the control arm with a HR of 0.49 (0.39-0.61), and a p value <0.001 (Figure 3).

Figure 3: Progression Free Survival based on IRAC Review of Response by IMWG Criteria (Stratified Log Rank Test); ITT Population.



The median time to progression was 20.1 weeks for the pomalidomide + LD dexamethasone arm, and 8.3 weeks for the HD dexamethasone arm, and the median time to treatment failure (PD, discontinuation, death or start of another treatment) was 15.3 weeks in the treatment arm (95% CI: 12.1, 18.1) compared with 8.0 weeks (95% CI: 4.9, 8.1) for the control arm, HR was 0.441 (95% CI: 0.349, 0.557, p < 0.001).

Subgroup analyses

These were generally limited by small numbers, but the following emerged:

12

ECOG PERFORMANCE STATUS*

Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

HR: generally in favour of the treatment arm apart from three subgroups but the numbers were only sufficient for those whose CrCL was <45 ml/minute (48 patients, 30 in treatment arm).

> *Comment: patients with CrCL < 45ml/min were ineligible and the sponsor did not address the clinical evaluator's question about the inclusion of these 48 patients, nor how their CrCL was measured (Cockcroft-Gault versus 24 h urine CrCl). Rather the sponsor reasserted the HR of 0.67 still supported a degree of PFS benefit, but there are wide confidence intervals crossing 1. Significant uncertainty remains about any benefit of the study treatment in this group with impaired renal function; this needs to be reflected in the PI under Special Populations/Precautions.*

The improvement in PFS observed in the ITT population was similar across the groups analysed by the stratification factors, although the numbers were small.

OS

At the interim analysis (primary endpoint), the median OS had not been reached for the pomalidomide + LD dexamethasone, but had been in the HD dexamethasone arm. At the time of the updated analysis (1 Mar 2013 cut-off date), 227 had died (49.9% of the total population: 48% in the pomalidomide + LD dexamethasone arm, 53.6% in the HD dexamethasone arm); median OS was 55.4 weeks (95% CI 45.3, 67.3 weeks) for pomalidomide + LD dexamethasone and 35.1 weeks (95% CI 29.9, 47.1 weeks) for HD dexamethasone (HR = 0.74 [0.56-0.97], log-rank p = 0.028), favouring pomalidomide + LD dexamethasone although the confidence intervals overlap. There was substantial cross over to pomalidomide alone (49.7%) at this analysis with a median follow-up of 43.4 weeks limiting the ability to demonstrate OS.

A subgroup analysis of OS was carried out but using the interim analysis cut-off date when median OS had not been determined for the treatment group. While these are exploratory secondary objectives, a notable finding was the decreased OS for those with CrCl <45 ml/minute.

Response rate

At the 7 September 2012 data cut-off, CR was observed in one subject in the pomalidomide + LD dexamethasone arm. Objective responses were observed in 16.6% (pomalidomide + LD dexamethasone) versus 3.9% (HD dexamethasone). At a later cut-off, 9 November 2012, the ORR based on IMWG criteria in the ITT population was 21.2% (pomalidomide + LD dexamethasone) versus 2.6% (HD dexamethasone).

Median duration of response (IMWG criteria): 32.0 weeks (95% CI: 24.1, NE) in the pomalidomide + LD dexamethasone arm and 28.6 weeks (95% CI: 20.1, 37.1) in the HD dexamethasone arm.

Study CC-4047-MM-002 (Phase I/II)

The Phase II part of the study compared pomalidomide + LD dexamethasone with pomalidomide alone (same pomalidomide dose regimen) so is not directly comparable with the Phase III study. In the Phase II part, a total of 221 subjects were randomised: 113 subjects in the pomalidomide + dexamethasone arm and 108 subjects in the pomalidomide arm. The pomalidomide + LD dexamethasone dosing was as per the Phase III trial, with the reduced 20 mg dexamethasone regimen for those >75. Subjects with PD on the pomalidomide arm could choose to have dexamethasone added to their treatment. The inclusion criteria were similar to Study CC-0407-MM-003.

The primary study endpoint was PFS and secondary efficacy endpoints objective response, time to response, duration of response, OS, overall response (IMWG criteria).

Median PFS times

The median PFS time in the pomalidomide + dexamethasone arm was 16.6 weeks (14.1-21.1 weeks) compared with 12 weeks (CI 8.4-16.1 weeks) for single agent pomalidomide (prior to the addition of dexamethasone). At this time 76% of subjects in the pomalidomide + dexamethasone arm had progressed or died, and 75% in the Pomalidomide overall, and 69.4% in the pomalidomide arm prior to dexamethasone. The requisite number of deaths had not been reached for median OS, and the pre-planned analysis at the cut-off date (1 April 2011) demonstrated no statistically significant differences. Partial responses were observed in 29% of subjects in the pomalidomide + dexamethasone arm and in 9% of subjects in the pomalidomide arm. Objective responses (CR + PR) were observed in 30% of subjects in pomalidomide + dexamethasone arm and 9% of subjects in the pomalidomide arm. Addition of dexamethasone to pomalidomide (for subjects in the pomalidomide arm) did not change the overall best response rate for subjects in this treatment arm.

> *Comment: The Delegate is in agreement with the clinical evaluator that the PFS time difference of 4 weeks found in the study is of doubtful clinical significance, and there is no quality of life data in support. Although the difference in PFS is stated in the Clinical Safety Report to be significant, the 95% confidence intervals overlap, and the upper limit of the HR is 0.99 [0.54-0.99]. The p value was shown as 0.019 in Table 20 of Clinical Safety Report and 0.037 in Figure 2 of the Clinical Safety Report. The statistical analysis plan (SAP) for the study (16 January 2009) based the sample size on an expected value of 10 months PFS in the pomalidomide + dexamethasone arm and 6 months in the pomalidomide arm. At the time of this analysis, the number of events, 167, (progression and death) had exceeded the requirement of the SAP (139 events).*
>
> *Although there was no control non-pomalidomide treatment arm, this study supports pomalidomide being effective in treating relapsed and refractory MM. The addition of LD dexamethasone increased the PFS compared with pomalidomide alone, but the increase was of marginal clinical significance. Although the response rate to the combination was greater than with pomalidomide alone, added dexamethasone did not increase OS.*

Study IFM-2009-02

This Phase II study was multicentre, randomised, open label, compared the efficacy of daily pomalidomide for 21 days versus 28 days, (each with dexamethasone) in MM patients who had relapsed and who had refractory disease which was progressive, and who had achieved at least a partial response to bortezomib and lenalidomide.

A total of 84 patients were randomised (1:1) to receive either 4 mg/day pomalidomide on Days 1 to 21, plus dexamethasone 40 mg on Days 1, 8, 15, and 22 of each 28 day cycle (Arm A) OR 4 mg/day pomalidomide on Days 1 to 28 plus dexamethasone 40 mg on Days 1, 8, 15, and 22 of each 28 day cycle (Arm B). The primary endpoint was the response rate (PR+CR) to pomalidomide and dexamethasone using IMWG response criteria. Secondary endpoints included PFS and OS. The study was non-comparative and the response rate assessed separately for each arm.

The median age was 60 (range 42-83), with 68% male patients, ECOG PS values of 0/1/2/3 were reported in 39/41/19/1% of patients, overall. Patients had received a median of 5 prior lines of treatment, with 23% of patients having received more than 6 prior lines. All patients had received prior treatment with bortezomib and with lenalidomide.

> *Comment: similar to Phase III patients, that is, bortezomib used no other proteasome inhibitor.*

Response rate, PFS, OS

Based on assessment by the IRC, the overall response rate (CR, VGPR, PR) in the ITT population was 35% (95% CI: 25-46%); no significant difference was observed between response rates in either arm. There was no difference in PFS or OS between the arms.

> *Comment: The Delegate is in agreement with the clinical evaluator that the study was underpowered to compare the differences between the regimens, and the width of the CI for all endpoints indicates high patient variability in response. It is supportive of pomalidomide with dexamethasone being active in producing responses in this group of heavily pre-treated patients.*

Comparison of efficacy results of pivotal and supportive trials

The efficacy results of the three trials are shown Table 8. Note that the results for the pivotal study were based on the updated data (1 March 2013) and not the primary analysis in the application.

Table 8: Summary of Key Efficacy Endpoints (based on Best Response Assessment using EBMT/IMWG Criteria; ITT population).

		CC-4047-MM-002		IFM-2009-02		CC-4047-MM-003[c]	
Efficacy endpoint	Statistic	4 mg Pom (21/28 day) (N = 108)	Pom + Dex (21/28) (N = 113)	Pom + Dex (21/28) (N = 43)	Pom + Dex (28/28 day) (N = 41)	Pom + Dex (21/28) (N = 302)	HD-Dex (N = 153)
Progression Free Survival (weeks)[a]	Median (95% CI)	10.7 (8.3, 16.1)	16.6[b] (14.1, 21.1)	25.1 (16.3, 41.7)	25.1 (13.3, 36.0)	16.0 (13.0, 19.6)	8.1 (7.1, 9.4)
Overall Survival (weeks)	Median (95% CI)	59.3 (41.6, NE)	62.6 (53.6, NE)	58.4 (38.7, 60.6)	66.4 (39.9, NE)	55.4 (45.3, 67.3)	35.1 (29.9, 47.1)
Overall Response Rate	N (%)	10 (9.3)	34 (30.1)	15 (34.9)	14 (34.1)	71 (23.5)	6 (3.9)
Duration of Response (>PR) (weeks)	Median (95% CI)	NE (NE, NE)	32.1 (22.1, 39.9)	45.7 (15.1, 54.7)	31.6 (16.1, NE)	35.1 (28.4, 52.9)	28.1 (20.1, 37.1)

CI = confidence interval; Dex = dexamethasone; EBMT = European Group for Blood and Marrow Transplantation; IMWG = International Myeloma Working Group; ITT = intent-to-treat; NE = not estimable; Pom = pomalidomide; PR = partial response.

[a] Values according to EBMT and IMWG criteria are identical for Study CC-4047-MM-002 (Summary of Clinical Efficacy, in-text Table 28).

[b] Fisher Exact Test $p < 0.001$ Pom + Dex vs pomalidomide.

[c] Data shown are from the analysis using a data cutoff date of 01 Mar 2013.

Cutoff date: 01 Apr 2011 (CC-4047-MM-002); 01 Mar 2011 (IFM-2009-02), 01 Mar 2013 (CC-4047-MM-003).

PFS

PFS was similar between Studies MM-002 and MM-003. PFS was longer in Arm A of study IFM-2009-02 (25.1 weeks) although the study population was smaller and differed from those in Studies CC-4047-MM-002 and CC-4047-MM-003 in terms of baseline disease characteristics. Note that the PFS given in Table 8 for the MM-002 was for patients treated in the pomalidomide arm who had had pomalidomide alone and those who had added dexamethasone on request. The PFS for those who had pomalidomide alone was a median of 12 weeks (CI 8.4-16.1).

> *Comment: The baseline disease characteristics of subjects in IFM-2009-02 differed from those in the pivotal Study CC-4407-MM-003. The finding of a longer PFS in the former trial is at odds with the higher rates of poor prognostic factors in trial subjects (more patients had high (≥5.5 mg/L) β-2 microglobulin levels (50% cf 33%), and low albumin (<3.5g/L) (50% versus 36%). The Delegate is in agreement with the Clinical Evaluator that the better PFS and RR outcomes for the IFM trial are difficult to interpret. To assess the effect of adding dexamethasone to pomalidomide treatment, the figures to compare are 12 weeks and 16.6weeks. From these figures, the clinical benefit to the patient of 4.6 weeks is small. The p value of 0.019 was calculated from a comparison of 10.7 and 16.6 weeks, not 12 and 16.6 weeks, so the statistical significance applies to the two treatments used in the study, both with dexamethasone, and not to the effect of adding dexamethasone to pomalidomide treatment.*

Overall Survival (OS)

While there is a lower OS for patients treated with pomalidomide + LD dexamethasone in the pivotal Phase III trial compared with the Phase II studies, this is still better at 55.4 weeks (95% CI: 45.3, 67.3) compared with 35.1 weeks (95% CI: 29.9, 47.1) with HD dexamethasone, despite cross over from the control arm.

Response Rate (RR)

Similarly the 23.5% RR in Study CC-4047-MM-003, in the pomalidomide + LD dexamethasone arm was lower than that of Study CC-4047-MM-002 and IFM-2009-02, although RR was still significantly higher than that of the HD dexamethasone arm (3.9%).

Efficacy summary

In the pivotal trial, pomalidomide + LD dexamethasone significantly increased both the PFS and OS of patients with MM who had failed at least two prior therapies including lenalidomide and bortezomib. The inclusion criteria for the Phase II and III trials specified bortezomib as the prior treatment, and only 7 patients (0.02%) had received a different proteasome inhibitor (carfilzomib); therefore, the Delegate is in agreement with the clinical evaluator that the proposed indication needs to be modified to state bortezomib rather than 'a proteasome inhibitor'. It is also noted that this modified indication is that approved by the other regulatory agencies mentioned above.

The combination of pomalidomide + LD dexamethasone resulted in a clinically significant improvement of 7.7 weeks in PFS, of more than 12 weeks in OS (20 weeks in the updated analysis), and 12.7% in RR. The positive effects were shown in most subgroups, but one subgroup with an adequate number of subjects was those with poor renal function (CrCl <45ml/min) where there was no significant improvement in PFS or OS, but these patients met the exclusion criteria.

The Delegate agrees with the clinical evaluator that the contribution of LD dexamethasone to the combination of pomalidomide + LD dexamethasone remains uncertain in this population of patients. Only Study CC-4047-MM-002 examined this effect and showed a small clinical benefit of adding dexamethasone with an increase of 4.6 weeks in the PFS in the pomalidomide + dexamethasone arm (16.6 weeks) compared to the pomalidomide arm (12 weeks) before dexamethasone was added to Arm B, and 6.6 weeks after the addition (16.6 weeks compared with 10 weeks PFS). However, the OS was the same in each arm, and the addition of dexamethasone to the pomalidomide treatment in the pomalidomide alone arm did not increase the response rate.

Despite being stated in the protocol, there was no quality of life data included. Given this is a palliative treatment, it is important to establish that there is no loss of quality of life with the treatment. The sponsor has been asked to address this in the pre ACPM response.

Safety

Safety was evaluated from 5 trials in the myeloma development program, and the other non-myeloma trials included in the dossier were checked for additional safety signals but not formally evaluated.

- The classification of the AEs is described.

The total numbers of subjects exposed to pomalidomide in the MM studies providing safety data in this review are shown in Table 9 by pomalidomide dose.

Table 9: Number of subjects exposed in MM studies by pomalidomide starting dose (Safety Population).

MM Subjects	Pomalidomide Dose (mg)						
	1	2	3	4	5	10	Total
Number of subjects [a]	10	19	8	617	26	6	686

[a] Includes studies CC-4047-MM-003, CC-4047-MM-002 Phase 2, IFM 2009-02, CC-4047-MM-001, CC-4047-MM-002 Phase 1

Pivotal Study CC-4047-MM-003

The median duration of treatment in the pomalidomide + LD dexamethasone arm was 12.4 weeks compared with 8 weeks in the HD dexamethasone, and the median number of treatment cycles was 3.0 in the pomalidomide + LD dexamethasone arm (range 1-16 cycles) and 2.0 in the HD dexamethasone arm (min, max: 1, 12 cycles) due to the lower rate of discontinuation from treatment seen in the pomalidomide + LD dexamethasone arm.

In the pomalidomide + LD dexamethasone arm:

- 24% required at least 1 pomalidomide dose reduction
- 16.7% required at least 1 dexamethasone dose reduction compared with 26.2% in the higher dose comparator arm
- 58% of subjects required at least 1 pomalidomide dose interruption, mostly due to neutropenia (45.3% incidence); median number of dose interruptions per subject was 2 (min, max: 1 to 14); median time to the first interruption was 29 days (range: 2-253 days)).
- 37% required a dose interruption for dexamethasone compared with 22.1% in comparator HD arm

  Comment: the higher rates of dexamethasone dose interruption likely reflect the greater toxicity of the combined treatment arm and need to discontinue all treatment to allow recovery rather than dexamethasone toxicity per se.

Study CC-4047-002 Phase II

A total of 27.4 % of all subjects required a dose reduction, with a similar rate in the pomalidomide + dexamethasone arm (23.2%) and the pomalidomide arm (31.2%).

Study IFM-2009-02

Patients remained on treatment for an average of 6 treatment cycles overall, with more dose reductions required in the less intense 21/28 treatment arm (44% compared to 34%).

Adverse events

Pivotal study

More subjects in the pomalidomide + LD dexamethasone arm required discontinuation (9.7% compared with 5.4%), dose reductions (23.7% compared with 16%) and dose interruptions (61.3% compared with 50.3%) than the HD dexamethasone arm.

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

There were predictable increases in AEs based on the mechanism of action of pomalidomide and the differing doses of dexamethasone. In the pomalidomide + LD dexamethasone arm, these included Grade 3/4 neutropenia (41.7% versus 14.8%); Grade 3/4 febrile neutropenia (6.7% versus 0%); Grade 3/4 bone pain (6.3% versus 2.7%); neutrophil count decreased (4.0% versus 0.7%).

Events that occurred more frequently in the HD dexamethasone arm included hyperglycemia (6.7% versus 3.0%), asthenia (6.0% versus 3.3%) and myopathy (3.4% versus 0.0%).

AEs of special interest

TEAEs potentially associated with pomalidomide: neutropenia and febrile neutropenia; infection; thrombocytopenia; hemorrhage and bleeding; peripheral neuropathy; thromboembolic events; cardiovascular events/dysrhythmia; SPMs; acute renal failure; cataract.

TEAEs associated with dexamethasone: glucose intolerance; fluid retention/edema; muscular weakness; mood alteration.

Neutropenia: Overall, a large majority of neutropenic events were Grade 3/4 events; however, few were severe or complicated by infection and no subject in either treatment arm discontinued due to neutropenia.

Febrile neutropenia occurred only in pomalidomide + LD dexamethasone subjects (6.7%).

> *Comment: the symptoms +/- reporting rates of febrile neutropenia are likely to be lowered by the temperature masking effect of dexamethasone. This merits inclusion in the PI, as there were deaths from infection.*

Infection rates were higher in the pomalidomide + LD dexamethasone arm, 55% compared with 48.3%; but the Grade 3/4 infection rates were similar in the 2 treatment arms, 24% and 22.8%. Deaths due to infections occurred more frequently in the HD dexamethasone arm (7.4%) than in the pomalidomide + LD dexamethasone arm (2.7%), largely due to higher frequencies of death due to septic shock and sepsis in this arm. Among subjects with Grade 3+ infections, the majority of subjects in each treatment arm had no concurrent neutropenia.

> *Comment: MM patients are prone to infection due to the underlying disease related immunosuppression, independent of the immunosuppressive effect of any treatment.*

Thrombocytopenia occurred in approximately 30% of subjects in each treatment arm. Most of these events were Grade 3/4 events; however, few resulted in treatment discontinuation in either arm.

Haemorrhage and bleeding (particularly epistaxis or haematoma) occurred in 16.3% of pomalidomide + LD dexamethasone subjects and 21.5% of HD dexamethasone subjects. Serious hemorrhage occurred in 2.7% of pomalidomide + LD dexamethasone subjects and 2.7% of HD dexamethasone subjects, and was the cause of death in 2 pomalidomide + LD dexamethasone subjects (1 subarachnoid hemorrhage with no concurrent thrombocytopenia; and 1 subdural hematoma with concurrent thrombocytopenia); and 1 HD dexamethasone subject (gastrointestinal hemorrhage with concurrent thrombocytopenia).

A total 42.9% of pomalidomide + LD dexamethasone subjects and 31.3% HD dexamethasone subjects had thrombocytopenia concurrently with the hemorrhage.

> *Comment: Two subjects, one in each treatment group, died of haemorrhage and concurrent thrombocytopenia. The Delegate is in agreement with the clinical evaluator that the thrombocytopenia is attributable mostly to the disease process. However, the use of aspirin as the stipulated DVT prophylaxis agent, in combination with the*

dexamethasone will also contributed to the risk of haemorrhage, particularly GI. In the PI, aspirin is the recommended agent and it should be added that consideration be given to GI ulcer prophylaxis.

Thromboembolic Events: All subjects in the pomalidomide + LD dexamethasone arm as well as subjects in the HD dexamethasone arm who had a prior history of DVT or PE were to receive VTE prophylaxis. Serious VTEs occurred in 1.7% of pomalidomide + LD dexamethasone subjects and in no HD dexamethasone subjects, but did not lead to death or discontinuation. ATEs occurred in 1.0% of pomalidomide + LD dexamethasone subjects and 0.7% HD dexamethasone subjects, but no deaths resulted.

Peripheral Neuropathy: Those with a pre-existing peripheral neuropathy Grade ≥2 were excluded from the pivotal study. Neuropathy occurred in similar proportions of subjects in the 2 treatment arms, 12.3% and 10.7%. Few occurrences in either arm were Grade 3/4.

Glucose intolerance, hyperglycemia and new onset diabetes: TEAEs related to glucose intolerance, hyperglycemia, and new onset diabetes occurred in 16.0% of subjects in the pomalidomide + LD dexamethasone arm and in 22.1% of subjects in the HD dexamethasone arm. Grade 3/4 hyperglycemia and new onset diabetes mellitus occurred in 5.3% of pomalidomide + LD dexamethasone subjects and 8.1% of HD dexamethasone subjects.

Muscular Weakness: Muscular weakness occurred more frequently in the HD dexamethasone arm (10.7%) than in the pomalidomide + LD dexamethasone arm (2.7%). No subject in the pomalidomide + LD dexamethasone arm and 2 subjects in the HD dexamethasone arm (1.3%) had TEAEs of muscular weakness that were serious.

Acute renal failure: Acute renal failure occurred with similar frequency in the 2 treatment arms (13.0% in the pomalidomide + LD dexamethasone arm and 13.4% in the HD dexamethasone arm). Grade 3/4 acute renal failure occurred in 7.0% of pomalidomide + LD dexamethasone subjects and 5.4% of HD dexamethasone subjects. Serious acute renal failure occurred in 6.7% of subjects in each treatment arm. Renal failure and acute renal failure were the cause of death in 1.0% of pomalidomide + LD dexamethasone subjects and in no HD dexamethasone subjects.

TEAEs (adverse drug reactions)

Pivotal study

TEAEs considered by the investigator to be related to pomalidomide treatment that occurred in ≥ 5% of subjects in the pomalidomide + LD dexamethasone are presented in Table 10. Severe TEAEs related to pomalidomide are presented below in Table 11. The most frequently occurring TEAEs considered by the investigator to be related to pomalidomide included neutropenia (38.7%), anaemia (22.7%), thrombocytopenia (18.7%), and fatigue (17.7%).

Table 10: TEAEs considered related to pomalidomide by the investigator in at least 5% of subjects 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: CSR CC-4047-MM-003 in-text Table 32.
Cutoff date: 07 Sep 2012

Table 11: TEAEs with CTCAE Grade 3 or 4 considered by the investigator related to pomalidomide in at least 2% of subjects 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 Grade 3/4 TEAE related to pomalidomide	170 (56.7)
Blood and lymphatic system disorders	**136 (45.3)**
Neutropenia	107 (35.7)
Thrombocytopenia	41 (13.7)
Anaemia	39 (13.0)
Leukopenia	22 (7.3)
Febrile neutropenia	14 (4.7)
Lymphopenia	10 (3.3)
Infections and infestations	**27 (9.0)**
Pneumonia	10 (3.3)
General disorders and administration site conditions	**18 (6.0)**
Fatigue	9 (3.0)
Asthenia	6 (2.0)
Investigations	**17 (5.7)**
Neutrophil count decreased	11 (3.7)

[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: CSR CC-4047-MM-003 in-text Table 36.
Cutoff date: 07 Sep 2012

Severe TEAEs considered to be treatment related: 56.7% of subjects in the pomalidomide + LD dexamethasone arm had at least one Grade 3/4 TEAE considered by the investigator to be related to pomalidomide. The most frequently occurring of these TEAEs included neutropenia (35.7%), thrombocytopenia (13.7%) and anaemia (13.0%).

Other studies

Study CC-4047-MM-02 Phase II

Pomalidomide related adverse events occurred in 89.3% of subjects in the pomalidomide + dexamethasone arm and 88.8% of subjects in the pomalidomide alone arm. While the pattern of AEs occurring in ≥10% of subjects was the same as for the pivotal trial, there were higher rates in the pomalidomide + LD dexamethasone subjects in this trial as follows: neutropenia (45.5% versus 37.7) fatigue (38.4% and 17.7), Infections and Infestations (SOC) (23.2% <5%), anaemia (25% and 22.7) and thrombocytopenia (20.5% versus 18.7%). This did not translate into significantly higher rates of severe events (Grade 3/ 4) between the Phase II and III trials.

Recovery rates from neutropenia and thrombocytopenia were faster in the pomalidomide + dexamethasone arm compared with HD dexamethasone.

> *Comment: there are higher rates of AEs, particularly for neutropenia, fatigue and infection rates in the Phase II trial, which may be attributable to the longer median treatment time in this group. A Quality of Life assessment would have helped determine the impact and importance of some of these factors especially fatigue. The sponsor has been requested to provide the outcome of these assessments for the Phase III study protocol but analysis were not included in the submission (see Questions for sponsor).*

Study IFM-2009-02

A total 94% experienced at least one drug related TEAE, and the pattern of the TEAEs and severe drug related TEAEs related to pomalidomide was similar to the other trials. Neutropenia rates were much higher (62.8%) than in patients treated similarly (21/28) in Study CC-4047-MM-02 (45.5%) and in the pivotal trial (38.7%). One case (2.3%) of drug related acute renal failure occurred in the 21/28 day group. Although renal failure was

reported in 16 patients (19%), these were primarily considered to be unrelated to study treatment.

Deaths and other SAEs

Deaths

At the pivotal study cut-off (September 2012), 25% of subjects in the pomalidomide + LD dexamethasone arm had died compared to 37.6% in the HD dexamethasone arm, most commonly from MM. Grade 5 AEs (death related to an AE on or within 28 days of discontinuation): 12.3% in the pomalidomide + LD dexamethasone arm and 14.8% in the HD dexamethasone arm died due to an AE while on treatment. Notable differences between the arms were more deaths from infections in the HD dexamethasone group (7.4% compared to 2.3%), and from renal failure in the pomalidomide + LD dexamethasone arm (1% compared to 0%). Deaths from other TEAEs occurred in 1 or 2 subjects in each treatment arm.

In the Phase II M-002 study, 8% of total deaths were suspected to be related to pomalidomide, due to staphylococcal sepsis, pneumonia, MM progression, respiratory failure, and sepsis.

In IFM Study IFM-2009-02, 95% of deaths were considered due to MM. Two deaths on treatment occurred: one with respiratory disease (considered treatment related), and the second with pneumonia and neutropenia (not considered drug related) although both the clinical evaluator and the Delegate consider treatment could potentially be related as the patient developed pneumonia and was neutropenic at the time of death.

> *Comment: the clinical evaluator and Delegate are uncertain why MM progression is included as a Grade 5 AE.*

Other SAEs

In the pivotal study, SAEs (≥ 2% subjects) occurred in approximately half of all patients, most commonly pneumonia and general physical deterioration. The only notable difference between the arms were that febrile neutropenia only occurred in the pomalidomide + LD dexamethasone arm, and septic shock occurred more often in HD dexamethasone (4% versus 1%).

In the Phase II Study MM-002, total SAEs were more frequent in the pomalidomide + dexamethasone arm (61.6%) than in the pomalidomide alone arm before dexamethasone (46.7%). Pneumonia occurred twice the frequency in the pomalidomide + dexamethasone arm (18.8% versus 9.3%), and notably, acute renal failure occurred more commonly than in the pivotal study. Pneumonia and neutropenia were the most common SAEs suspected by the investigator to be related to pomalidomide.

The most serious AE attributable to pomalidomide treatment is febrile neutropenic and the results from all the studies suggest renal failure may be an issue.

> *Comment: 3 SAEs appear to be prominent: infection, neutropenia, and renal failure.*

Discontinuation due to adverse events

Pivotal study

In the pivotal study, pomalidomide was discontinued in 8.0% in the pomalidomide + LD dexamethasone arm mostly due to infections (2%) and renal disorders (1.3%). In the Phase II study (MM-002), 10% discontinued pomalidomide in the pomalidomide + LD dexamethasone, and 12.1% in the pomalidomide alone arm. The main reasons were renal failure (acute in a total of 1.4% and rise in creatinine in 0.9%) and thrombocytopenia, and fatigue, each in 0.9%.

Dexamethasone was discontinued in 8.3% in the pomalidomide + LD dexamethasone arm and 5.4% in the HD dexamethasone arm, and the only notable cause of discontinuation was pneumonia.

Study IFM-2009-02 and the Phase I studies' safety assessments did not show any new patterns of adverse events not seen in the larger Phase II and III studies.

Laboratory tests

Liver function

There did not appear to be any significant changes in liver function tests with the study treatment in any of the trials.

Kidney function

Baseline serum creatinine concentration was normal in the pomalidomide + LD dexamethasone arm was 65% and in the HD dexamethasone arm 60.8%, while a change to Grade 3/4 abnormalities occurred in 1.2% and 2.8%, respectively. CrCl measurements were normal at baseline in 60.2% in the pomalidomide + LD dexamethasone and 53.3% of subjects in the HD dexamethasone arms, worsening to Grade 3/4 abnormalities in 4.6% and 11.6% respectively.

In the Phase II study (MM-002) change to a Grade 3 serum creatinine abnormality occurred in 2.0% from Grade 1, and 2.5% from Grade 2.

The results from Study CC-IFM-2029-002 were difficult to interpret due to differing baseline creatinine levels in the arms. But during the course of the study, equal numbers (5%) had a Grade 3-4 elevated serum creatinine.

> *Comment: there were a significant proportion of patients with renal impairment at baseline, and it is difficult to determine whether the rise in serum creatinine and decrease in CrCl is due to the underlying disease progressing, concomitant medications or related to the study drug.*

Other clinical chemistry

Pivotal study

In the pivotal study, serum glucose levels rose predictably with dexamethasone, but there were no other biochemical abnormalities that could be predictably attributable to the different treatments received.

Haematology

In the pivotal study, many more patients in the pomalidomide + LD dexamethasone arm than in the HD dexamethasone arm experienced Grade 3 or 4 leukocyte levels (44.6% versus 12.4%). Haemoglobin levels were similar across the arms.

Neutropenia and thrombocytopenia have already been described.

Electrocardiograph

Pivotal study CC-4047-MM-003

Mean and median changes from baseline in QT intervals (corrected) were all under 30 msec. Two subjects in the pomalidomide + LD dexamethasone arm (0.7%) and no subject in the HD dexamethasone arm had a TEAE of QT prolonged. One event was Grade 2 and one was Grade 3; both events resolved, and neither recurred despite continued treatment. One subject in the pomalidomide + LD dexamethasone arm (0.3%) and no subject in the HD dexamethasone arm had a TEAE of ST segment depression. No other ECG related TEAEs were reported.

Comment: while there does not appear to be a safety signal to date, a study of QT/QTc in healthy subjects has been done and this should be submitted as a condition of registration.

Safety in special populations

Overall, the safety profile of pomalidomide + LD dexamethasone remained was unaffected by age (> 65 or ≤ 65 years old), gender, ECOG performance status, disease population, or baseline renal function.

Safety related to drug-drug interactions and other interactions

The sponsor has included warnings in the PI about administration of the pomalidomide with strong inhibitors of CYPs 3A4 and 1A2. The top line data for this has been requested for safety reasons, and the sponsor has indicated this study will be submitted post registration, and is a condition of registration.

Use in pregnancy and lactation

Pomalidomide is a thalidomide analogue, and was teratogenic in rats and rabbits. It is not known if pomalidomide is excreted in human milk, but was detected in the milk of lactating rats following administration to the mother.

Appropriate warnings based on the above are important in the Product Information and CMI documents.

Second Primary Malignancies (SPMs)

A total of 32 subjects have experienced a total of 40 SPMs across all programs. This represents a current reporting rate of approximately 1% among the approximately 3000 subjects exposed to pomalidomide in all contexts against an age expected background of for those ≥ 65 years of 2.1/100 patient years. Calculation of an overall SPM incidence rate was not possible due to incomplete data on duration of exposure outside of the Celgene sponsored studies.

AML cases have been reported in the myelofibrosis patients treated with pomalidomide, most likely related to the underlying condition, and were also identified in a monkey in the nonclinical studies. No cases were identified in the MM population but the numbers are small and this is an important area for pharmacovigilance.

Safety summary

Overall, the most frequently occurring severe TEAEs related to pomalidomide included neutropenia (35.7%), thrombocytopenia (13.7%) and anaemia (13.0%). Febrile neutropenia occurred in 4.7% of subjects.

Neutropenia was the most significant treatment related effect and the increasing rates of adverse events with longer treatment duration (up to 62% of such subjects) raise the question of a cumulative effect of pomalidomide treatment, particularly myelosuppression, rather than just a longer duration of treatment leading to increased reporting rates. A potential cumulative effect would not be captured by the reporting system as AEs were only recorded once for a given individual, regardless of how often they occurred.

Although there were high rates of neutropenia, these were generally manageable as indicated by the low discontinuation rates, and few deaths with concurrent neutropenia. The advice in the PI differs from the information regarding neutropenia rates and management and needs to be addressed (see PI section).

The main AEs seen can be attributed to the disease itself (or its progression) which makes it difficult to determine whether there is a contribution from pomalidomide usage to the observed bone marrow failure, renal impairment, fatigue and general deterioration.

There was a relatively high rate of baseline impairment in renal function, but there were also episodes of acute renal failure in all trials, including as a cause of death. While renal abnormalities (both TEAEs and severe TEAEs) were less frequent in the pomalidomide + LD dexamethasone group of subjects than in those receiving HD dexamethasone, there were cases reported in the Phase II studies. It was also the second most common TEAE leading to treatment discontinuation, after infections. It is difficult to determine whether acute or worsening renal failure is a pomalidomide effect, secondary to other adverse events such as sepsis, or due to the disease itself (including progression). There are sufficient cases of emergent renal failure for this risk to be included in the RMP, and in the PI until it is clearer, and for the study on pomalidomide in renally impaired subjects which may provide clearer prescribing instructions to be submitted as a condition of registration. It is noted, despite being an exclusion criterion, subjects with CrCl<45 ml/min were included in the Phase III trial, with no apparent improvement in PFS and OS (see PI section).

The proposed PI includes a risk of delayed pomalidomide metabolism with co-administration with strong inhibitors of CYP3A4 and CYP1A2. The sponsor has indicated that submission of the trial that contained this data is planned for submission post-registration. A brief summary pertaining to the positive findings regarding these particular drug-drug interactions is requested in the pre ACPM response, with submission of the study for full evaluation as a Category 1 application as a condition of registration.

While no specific safety signals have been detected in the populations in the clinical trials, overall the total numbers are relatively small and the submission of the studies in hepatically impaired subjects and the QT/QTc studies are important in establishing the safety profile of a new chemical entity. These should be submitted upon completion as Category 1 applications as they become available.

Risk management plan

The OPR has accepted the EU-RMP Version 6.0 (dated 5 June 2013; DLP 24 May 2013) and ASA Version 1.0 (dated 11 September 2013; no DLP given); the implementation of this and any future updates (where TGA approved) as a condition of registration.

The sponsor should form a registry of patients treated with pomalidomide for the proposed usage to monitor, characterise and determine the incidence of adverse reactions and to monitor compliance with the RMP and off-label use (supported by the Advisory Committee for the Safety of Medicines).

It is considered that the sponsor's response to the TGA's request for further information has adequately addressed all of the issues identified in the RMP evaluation report, with the exception of the outstanding issues below.

Parts of the sponsor's response to the TGA's request with regard to the *i-access* program are not entirely satisfactory. The Delegate is in agreement with the RMP evaluator that given the potential teratogenic effect of pomalidomide in humans:

- The sponsor should specify that the pregnancy test should be a β Human Chorionic Gonadotropin (HCG) blood test.
- Additional to the actions described by the sponsor in their response with regard to a positive pregnancy test, the sponsor should follow-up a continuing pregnancy.

The OPR recommended a range of PI changes in the RMP report but the details of these are beyond the scope of this AusPAR.

Risk-benefit analysis

Delegate's considerations

The Delegate believes that efficacy has been satisfactorily demonstrated and that the safety studies indicate that overall, the safety of pomalidomide is satisfactory (but this will be further established by the specified studies being submitted for evaluation as per the Conditions of Registration), for the following modified indication:

> *Pomalidomide in combination with dexamethasone is indicated in the treatment of 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 Delegate does not believe that it is necessary to restrict the indication to adults as although rare in those under 18 years of age, there is no reason to assume that there would be any difference in efficacy and safety for MM in this age group, and this would be a valid palliative treatment option in an incurable setting.

Data deficiencies

The studies listed in the condition of registration are important in establishing the safety for the proposed usage.

Questions for the sponsor

1. The sponsor is requested to provide dates of completion for the studies listed below, and timeframes for submission following completion.
2. The sponsor is requested to provide a summary of the quality of life outcomes undertaken as per the study protocol, including the proportion of patients who completed these assessments fully (with a denominator of all evaluable patients) as part of Study CC-4047-MM-003 in the pre ACPM response.
3. In the PI, the rate of febrile neutropenia was said to be 6.7% (4% "serious"), yet the dose interruptions were only 3.7% and dose reductions only occurred in 1.3%. This statement and the data underpinning it require explanation please as this is inconsistent with the recommendations for dose modification in the PI. Was granulocyte colony stimulating factor (GCSF) used? Did the febrile neutropenia occur during the week off of the 4 week cycle?
4. There is information about the co-administration of fluvoxamine of CYP1A2 in presence of ketoconazole increasing the levels and potential effects of pomalidomide. It is noted that the sponsor plans to submit the relevant drug-drug study after registration. In the meantime, the sponsor is requested to provide top line data to support this finding (that is, not the whole study as this will need to be evaluated) as this should be included in the PI now as it pertains to safety (subsequent PI modifications may be required following a formal submission and evaluation of this study post registration).

Conditions of registration

The following are proposed as conditions of registration:

- Submission of the following studies:
  - Safety study in patients with MM with renal impairment as a Category 1 submission upon completion (Study CC-4047-MM-008).

  - Drug-drug interaction study from which PI information regarding CYP3A4 and 1A2 derived (interim information has been requested) as a Category 1 submission within 3 months of registration.
  - Safety study in hepatically impaired males as Category 1 submission
  - QT/QTc study in healthy volunteers as a Category 1 submission
- Implementation of the EU-RMP Version 6.0 (dated 5 June 2013; DLP 24 May 2013) and ASA Version 1.0 (dated 11 September 2013; no DLP given), and any future updates (where TGA approved)
- The sponsor should form a registry of patients treated with pomalidomide for the proposed usage to monitor, characterise and determine the incidence of adverse reactions and to monitor compliance with the RMP and off-label use.

Summary of issues

Efficacy has been satisfactorily demonstrated for pomalidomide in relapsed and refractory MM, although the benefit of including dexamethasone in the regimen is not clear.

Safety has been adequately demonstrated, with the majority of adverse events being manageable.

No quality of life data were submitted, despite being described in the protocol for the Phase III study.

There are some PK studies which have not been submitted that would inform the prescriber about the safe use of pomalidomide. Submission of these has been included in the conditions of registration.

Proposed action

The Delegate has no reason to say, at this time, that the application for pomalidomide should not be approved for registration for the following modified indication:

> *Pomalidomide, in combination with dexamethasone, is indicated in the treatment of 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.*

Request for ACPM advice

The committee is requested to provide advice on the following specific issues:

- Whether efficacy and safety have been adequately demonstrated.

The committee is (also) requested to provide advice on any other issues that it thinks may be relevant to a decision on whether or not to approve this application.

Response from sponsor

In this Category 1 (New Chemical Entity) submission, the sponsor proposed for the following indication:

> *Pomalyst in combination with dexamethasone is indicated for the treatment of patients with multiple myeloma who have failed at least two prior therapies including lenalidomide and a proteasome inhibitor.*

In the Delegate's preliminary assessment, a modified indication is suggested:

The Delegate has no reason to say, at this time, that the application for pomalidomide should not be approved for registration for the following **modified indication**:

> *Pomalidomide, in combination with dexamethasone, is indicated in the treatment of 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 issues raised in the Delegate's overview are addressed in the following pages.

Delegate's comment #1

- Renal study: A dedicated study in MM patients with renal impairment is underway (Phase I, dose escalation pharmacokinetic and safety study CC-4047-MM-008) … The sponsor is requested to indicate a likely completion date for this study in the pre ACPM response.

Response

The pharmacokinetic and safety study of MM subjects with renal impairment (CC-4047-MM-008) is currently ongoing and the sponsor anticipates to have the study report finalised in 1Q 2016.

Delegate's comment #2

- *Drug-drug interaction study - The Summary of Clinical Pharmacology states that a trial is completed and under analysis (CC-4047-CP-008) … The sponsor is requested to provide the immediately relevant information to support these findings and submit the study for full clinical evaluation within 3 months of registration.*

Response

The report for Study CC-4047-CP-008 was completed after the pre-submission stage for the pomalidomide Category 1 application. However, key clinical observations from this study were included in the PI at the time of pre-submission. A copy of the study synopsis is provided in the attachment and the conclusions from the study report are listed below.

- Co-administration of a strong CYP3A4/P-glycoprotein inhibitor (ketoconazole) or CYP3A4 inducer (carbamazepine) with pomalidomide had no clinically relevant effect on mean exposure to pomalidomide.
- Co-administration of a strong CYP1A2 inhibitor (fluvoxamine) with pomalidomide in the presence of a strong CYP3A4 inhibitor approximately doubled the mean exposure to pomalidomide.
- The majority of TEAEs in this study were judged by the investigator as not suspected of being related to pomalidomide. With the exception of 1 subject with low glomerular filtration rate and a mild TEAE of increased blood creatinine, there were no remarkable findings or changes in laboratory assessments, vital sign measurements, ECGs, or physical examinations.
- Single doses of pomalidomide were generally well tolerated by healthy subjects when administered as single 4 mg oral doses with multiple oral doses of ketoconazole, fluvoxamine, and/or carbamazepine.

The effect of inducing the CYP1A2 isozyme will be assessed from the comparative exposures to pomalidomide in smokers and non-smokers in the Study CC-4047-CP-011. The sponsor anticipates the Clinical Safety Report to be finalised in the fourth quarter of 2015.

Delegate's comment #3

- Hepatic impairment ... A clinical trial evaluating pharmacokinetics in MM patients otherwise healthy subjects but with hepatic impairment is in progress (CC-4047-CP-009). Again, given the age at median diagnosis and likelihood of co-morbidities, this trial should be submitted to the TGA upon completion and the PI updated accordingly.

Response

Study CC-4047-CP-009 is ongoing and consists of two parts: Part 1 in MM subjects with severe hepatic impairment and Part 2 in MM subjects with mild/moderate hepatic impairment. The sponsor anticipates the Clinical Safety Report to be finalised in the first quarter of 2016.

Delegate's comment #4

- *Thorough QT/QTc... A formal thorough QT/QTc study in healthy subjects is planned with a target start date of 3Q 2013. The sponsor is requested to indicate the likely completion date in the pre ACPM response, and it should be submitted upon completion as a condition of registration.*

Response

The report for the QT/QTc study in healthy subjects (CC-4047-CP-010) is anticipated to be finalised in first quarter of 2015.

Delegate's comment #5

- *Patients with CrCL <45ml/min were ineligible and the Sponsor did not address the clinical evaluator's question about the inclusion of these 48 patients, nor how their CrCL was measured (Cockcroft-Gault versus 24 h urine CrCl) ... Significant uncertainty remains about any benefit of the study treatment in this group with impaired renal function and this needs to be reflected in the PI under Special Populations/Precautions.*

Response

As noted by the clinical evaluator, there were no protocol violations recorded in the CC-4047-MM-003 study as the sub-group of subjects described above met all of the inclusion/exclusion criteria. The CrCL for these 48 subjects was within the inclusion criteria of > 45ml/min at the screening stage (measured by the Cockcroft-Gault method as per the protocol), however fell below 45 ml/min (measured by Cockcroft-Gault method) at the last assessment prior to the study treatment (used as the baseline for the study). As per the protocol, only the subjects who had a creatinine clearance <45 mL/min measured by Cockcroft-Gault method at screening and/or on the first day of treatment would have a 24 h urine sample measurement. Although a subgroup analysis of these 48 patients was conducted, the results are non-conclusive and no firm conclusions can be made as the patient numbers are low and the study was not powered to measure the efficacy outcomes in such a small group. As requested by the RMP evaluator, the sponsor has added a new Renal Impairment heading in the 'Dosage and Administration' section of the PI on treatment of patients with renal impairment. The sponsor believes this is sufficient to inform prescribers and advise them to monitor patients with renal impairment.

Delegate's comment #6

- *Despite being stated in the protocol, there was no quality of life data included. Given this is a palliative treatment, it is important to establish that there is no loss of quality of life with the treatment. The sponsor has been asked to address this in the pre ACPM response.*

Response

An updated study report for the pivotal Study CC-4047-MM-003 with data cut-off 1 March 2013 was completed during the evaluation of the current application. Health related quality of life (HRQoL) outcomes are included in this updated study report. The relevant

section from the updated Clinical Safety Report and an abstract from a publication summarising the outcomes were included with this response.

In heavily pre-treated RRMM patients who have exhausted lenalidomide and bortezomib treatment, in addition to providing survival benefits and a manageable safety profile:

- Pomalidomide + LD dexamethasone consistently resulted in favourable HRQoL versus points treated with HD dexamethasone in cross-sectional and mixed model analyses.
- Time to first worsening analyses confirmed that patients randomised to pomalidomide + LD dexamethasone maintain HRQoL for an extended period of time versus HD dexamethasone.
- Pomalidomide + LD dexamethasone should be considered a standard of care in RRMM points, as it confers survival advantages as well as HRQoL benefits.

Delegate's comment #7

- *The symptoms +/- reporting rates of febrile neutropenia are likely to be lowered by the temperature masking effect of dexamethasone. This merits inclusion in the PI, as there were deaths from infection.*

Response

The proposed PI already includes a warning statement advising prescribers to monitor and manage cases of febrile neutropenia. Additionally, treatment is restricted to specialist haematologists who are experienced regarding the potential for febrile neutropenia and treatment effects of dexamethasone. As monitoring of such events is standard medical management of patients with late stage myeloma, the sponsor does not consider that additional warnings on the effects of dexamethasone are warranted. Adverse effects that may occur during treatment with corticosteroids would be managed under general patient care.

Delegate's comment #8

- *The use of aspirin as the stipulated DVT prophylaxis agent, in combination with the dexamethasone will also contribute to the risk of haemorrhage, particularly Gl. In the PI, aspirin is the recommended agent and it should be added that consideration be given to GI ulcer prophylaxis.*

Response

The sponsor wishes to clarify that numerous agents are recommended in the PI for DVT prophylaxis in addition to aspirin, including warfarin, heparin, or clopidogrel. The potential for haemorrhage is a known outcome from aspirin treatment and is managed by the specialist under general patient care. The sponsor therefore does not consider it appropriate to add additional warnings to the PI on potential side effects of aspirin. Furthermore, the sponsor believes that the current VTE warning in the PI stating '*A decision to take prophylactic measures should be made carefully after an assessment of an individual patient's underlying risk factors*' addresses the Delegate's concerns.

Delegate's comment #9

- *The clinical evaluator and Delegate are uncertain why MM progression is included as a Grade 5AE.*

Response

The sponsor wishes to clarify that it is the sponsor's policy to never remove a Grade 5 AE (that is, death event reported on study) from an analysis for completeness sake; as a consequence disease progression is included as a Grade 5 AE, which usually means that disease progression eventually led to the death of the patient.

Delegate's comment #10

- The sponsor should form a registry of patients treated with pomalidomide for the proposed usage to monitor, characterise and determine the incidence of adverse reactions and to monitor compliance with the RMP and off-label use.

Response

The sponsor does not consider that a separate patient registry is warranted in Australia as:

- sufficient controls already exist that cover the use of pomalidomide,
- small numbers of local patients with significant confounding co-morbidities are unlikely to provide meaningful data, and
- access to larger global registries will be more informative regarding the potential risks associated with treatment.

Existing controls

The sponsor does not believe that a registry is required to manage off-label use in Australia because access to pomalidomide is highly controlled. Every patient who will receive pomalidomide must be enrolled in the *i-access* RMP. The treatment indication for every patient is recorded prior to his or her acceptance into the *i-access* program. For an unapproved indication, the sponsor only authorises supply after a valid Special Access Scheme (SAS) notification has been submitted to the TGA. Therefore, no supply occurs until the correct TGA authority is available, and the sponsor has the capacity to monitor the small number of patients who may access pomalidomide treatment outside of the TGA approved indication. Furthermore, it is the sponsor's experience that use outside of Pharmaceutical Benefits Scheme reimbursed indications is minimal due to the personal cost of treatment. Therefore, the sponsor believes that no further measures are required to inform about off-label use.

Under the *i-access* program, every monthly dispense of pomalidomide to each patient must be authorised by the sponsor and assigned a unique verification number before the product is supplied to the patient. This is a closed loop process where supply to pharmacy is reconciled with patient's verifications to ensure compliance with the restrictions specified in the *i-access* program. Under this highly developed and controlled system, the sponsor can determine when patients commence, interrupt dose, adjust dose and complete pomalidomide treatment. Pharmacovigilance practices conducted by the local Celgene Drug Safety department ensure all AE reports received are followed up with the reporter and data are fed back into the consolidated, global Celgene patient safety database for analysis. A combination of *i-access* controlled supply and pharmacovigilance activities ensures that the sponsor is well informed about the use of pomalidomide.

The potential and identified risks associated with pomalidomide are already addressed with warnings, precautions and advice to the prescriber in the PI. These treatment effects are typically consistent with those seen with thalidomide and lenalidomide, treatments that the patient will have already received. Management of patients is restricted to specialist haematologists who are vigilant and experienced in managing risks that are typical of this class of compound. As the potential and identified risks are predictable, preventable and manageable based on the information already included in the PI, Celgene does not believe that establishing a local registry is warranted.

Meaningful outcomes

Outcomes from events detected in an Australian patient registry are not expected to be meaningful due to the anticipated modest number of pomalidomide patients treated at any one time (not expected to exceed a few hundred patients). This is because treatment will be limited to the forth or later line of treatment for the following reasons: the

restriction in the proposed pomalidomide indication requires prior treatment with lenalidomide and bortezomib; and reimbursement restrictions in Australia dictate that a patient must have been treated with thalidomide prior to qualifying for reimbursed lenalidomide treatment.

This ensures a patient will receive a minimum of 3 prior treatments. Consequently patients typically present themselves with advanced disease and significant co-morbidities. This combined with the expected small number of patients will confound outcomes from an Australia registry, making meaningful conclusions unlikely. A more robust dataset can be accessed from global use which includes sufficient patient numbers to be meaningful.

In Europe, there is not an equivalent unified *i-access* program for all EU Member States that collects the level of data available from Australian patients. Consequently, Europe has established a patient registry to monitor and manage the use of pomalidomide. Cases from Australia cannot be included in the European registry. Given the similarities in patient populations and indications in the two regions, findings from the EU registry that are applicable to Australia will be adopted as part of a broader ongoing management of the safe use of pomalidomide. In addition, global post marketing surveillance and the analyses presented in the PSURs ensures that the use of pomalidomide and outcomes are closely tracked and tightly managed.

Local registry not warranted

Patients accessing pomalidomide typically present with advanced disease, significant comorbidities and a poor prognosis with few treatment options. Consequently, they are closely managed by the treating specialist haematologist who will be vigilant to emerging AEs as part of the standard level of care. Therefore, the sponsor contends that an Australian registry is not required due to the high level of control already present in the *i-access* program, poor quality of data expected from a small number of patients who typically have significant comorbidities, and utilisation of more meaningful datasets from global exposure.

Delegate's comment #11

- *The sponsor should specify that the pregnancy test should be a β HCG blood test.*

Response

Within the Pomalyst PI and as a core component of the *i-access* RMP, the sponsor mandates that a medically supervised pregnancy test that has a minimum sensitivity of 25 mIU/mL is conducted. The majority of the pregnancy tests are blood tests. Under certain circumstances and at the discretion of the trained healthcare professional, the pregnancy test may also be conducted on urine samples. A negative pregnancy test result **must** be recorded before the sponsor will approve the supply of pomalidomide to the patient. It is the responsibility of the medically trained professional to ensure the pregnancy test is conducted appropriately and meets the minimum sensitivity requirements of 25 mIU/mL. This test may be from either a blood or a urine sample, at the discretion of the healthcare professional, and would fulfil the *i-access* program requirements. It is also noteworthy that the *i-access* program has been effective in Australia for controlling lenalidomide since 2008 with no recorded incidence of a positive pregnancy. The sponsor proposes to keep the minimum sensitivity of 25 mIU/ml and the method of blood or urine testing at the medical discretion of the healthcare professional due to the points mentioned above.

- *Additional to the actions described by the sponsor in their response with regard to a positive pregnancy test, the sponsor should follow-up a continuing pregnancy*

Response

The sponsor confirms that in addition to the action items outlined in an event of a positive pregnancy test, Celgene Drug Safety procedures on pregnancy reporting include assessing the root cause failure of the *i-access* program for a confirmed pregnancy in a patient or female partner of a male patient who is exposed to pomalidomide, and follow-up on pregnancies reported.

Delegate's comment #12

- *The PI states that DVT prophylaxis was mandatory for all patients in the studies whereas it was stated elsewhere that this was for patients with previous venous or arterial thromboembolic events. The sponsor is requested to clarify this.*

Response

The sponsor wishes to clarify that DVT prophylaxis was mandatory for all patients treated with pomalidomide. The subjects who had a prior history of DVT or pulmonary embolism during the study, regardless of the treatment arm assigned, were also given DVT prophylaxis. As DVT prophylaxis was mandatory for all pomalidomide patients, the second requirement mainly applies to the subjects assigned to the comparator arm.

Delegate's comment #13: Secondary primary malignancies

- *This needs to state that a case of AML was observed (in) nonclinical studies and to state what second cancers were observed in the clinical studies. Any such cases need to be presented under a separate heading, "Description of selected adverse events."*

Response

Despite a small number of SPMs having been reported in patients receiving pomalidomide, the sponsor believes that the clinical significance of these observations is inconclusive, especially against an expected higher background incidence of SPMs in this patient population. The proposed PI already includes a warning in the Precautions section for prescribers to be vigilant for the occurrence of SPMs, and as such inclusion of further detail in the PI is not presently warranted. The sponsor will continue to monitor the occurrence of SPMs and will update the PI should new data be received.

Delegate's comment #14: Rate of febrile neutropenia

- *the rate of febrile neutropenia was said to be 6.7% (4% "serious"), yet the dose interruptions were only 3.7% and dose reductions only occurred in 1.3%. This statement and the data underpinning it require explanation….*

Response

Per protocol (Protocol CC-4047-MM-003 Amendment 4), GCSF was allowed anytime during the study. The sponsor has not conducted an analysis to determine how many subjects with febrile neutropenia were treated with GCSF or to determine when the febrile neutropenia episodes occurred. The dose modifications in the PI are recommended by the sponsor's in-house haematology medical team on evaluation of available clinical data.

Advisory committee considerations

The submission seeks to register a new chemical entity.

The ACPM, taking into account the submitted evidence of efficacy, safety and quality, agreed with the Delegate and considered Pomalyst capsule containing 1 mg, 2 mg, 3 mg and 4 mg of pomalidomide to have an overall positive benefit-risk profile for the Delegate's amended indication:

> *Pomalidomide, in combination with dexamethasone, is indicated in the treatment of 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.

Proposed conditions of registration

The ACPM agreed with the Delegate on the proposed conditions of registration, particularly the submission of the ongoing and proposed trials to clarify important missing information.

Proposed Product Information (PI)/Consumer Medicine Information (CMI) amendments

The ACPM agreed with the Delegate to the proposed amendments to the PI and CMI and specifically advised on the inclusion of the following:

- In the 'Adverse Events' section the table comparing pomalidomide with LD dexamethasone and HD dexamethasone glucose intolerance, hyperglycaemia, and new onset diabetes rates should be included.
- A statement in the 'Adverse Events' section on arterial thrombotic events should be included.

Specific advice

The ACPM advised the following in response to the specific Delegate's questions on this submission:

- Whether efficacy and safety have been adequately demonstrated.

The ACPM advised that efficacy had been clearly demonstrated in a heavily pre-treated population with significant comorbidities. There may be some exceptions in patient subgroups where efficacy has not yet been established; but these are populations with small numbers. There were no unexpected safety issues reported in the trial populations and the ACPM noted that when considering adverse events it is difficult to differentiate treatment from disease. Nonetheless, there remains some concern with the issue of the cumulative effect of pomalidomide exposure on myelosuppression and also concern with the impact on renal function. The ACPM noted the study in renally impaired subjects is not yet completed.

The ACPM further advised that it considered the request by the RMP evaluator to specify that pregnancy test be a blood test is reasonable in the circumstances.

The ACPM advised that the implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided would support the safe and effective use of this product.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Pomalyst capsules containing pomalidomide 1 mg, 2 mg, 3 mg and 4 mg for indicated for:

Pomalidomide, in combination with dexamethasone, is indicated for the treatment of 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.

Specific conditions of registration applying to these goods

- The Pomalyst EU Risk Management Plan (EU-RMP), version 6.0, dated 5 June 2013; DLP 24 May 2013 and ASA Version 1.0 dated 11 September 2013; no DLP given, included with submission PM-2013-02037-1-4, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

Attachment 1. Product Information

The Product Information approved for Pomalyst at the time this AusPAR was published is at Attachment 1. For the most recent PI, please refer to the TGA website at <http://www.tga.gov.au/hp/information-medicines-pi.htm>.

Attachment 2. Extract from the Clinical Evaluation Report

Therapeutic Goods Administration

PO Box 100 Woden ACT 2606 Australia
Email: info@tga.gov.au Phone: 1800 020 653 Fax: 02 6232 8605
http://www.tga.gov.au