PRODUCT MONOGRAPH

Pr POMALYST®

pomalidomide

1 mg, 2 mg, 3 mg and 4 mg Capsules

Antineoplastic Agent
Immunomodulatory Agent

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Date of Revision:
August 21, 2019

Submission Control No: 229243

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[Pr]POMALYST®

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
oral	Capsule, 1 mg, 2 mg, 3 mg, 4 mg	Capsule shells contain gelatin Mannitol *For a complete listing see Dosage Forms, Composition and Packaging section.*

INDICATIONS AND CLINICAL USE

- POMALYST® (pomalidomide) in combination with dexamethasone (dex) and bortezomib is indicated in the treatment of adult patients with multiple myeloma (MM) who have received at least one prior treatment regimen that included lenalidomide.
- POMALYST® in combination with dexamethasone is indicated for patients with multiple myeloma 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.

Distribution restrictions

POMALYST® is only available through a controlled distribution program called RevAid®. Under this program, only prescribers and pharmacists registered with the program are able to prescribe and dispense the product. In addition, POMALYST® can only be dispensed to patients who are registered and meet all the conditions of the RevAid® program. Please call 1-888-RevAid1 (1-888-738-2431) or log onto www.RevAid.ca.

Geriatrics (> 65 years of age):

No dosage adjustment is required for POMALYST® based on age.

The concomitant administration of dexamethasone may increase the risk of infection, particularly pneumonia, in patients > 65 years of age treated with POMALYST®. Dexamethasone dosing may need to be reduced or interrupted in these patients in case of infection.

There is limited information on the safety of POMALYST® in combination with dexamethasone in patients > 75 years of age (see **CLINICAL TRIALS**). The concomitant dexamethasone dose should be reduced by half in patients > 75 years of age (see **DOSAGE AND ADMINISTRATION**).

Pediatrics (< 18 years of age):

The safety and effectiveness of POMALYST® in children and adolescents have not been established.

CONTRAINDICATIONS

- POMALYST® (pomalidomide) is contraindicated in patients who are hypersensitive to it or to thalidomide, lenalidomide or to any ingredient in the formulation or component of the container. For a complete listing, see **DOSAGE FORMS, COMPOSITION AND PACKAGING**.
- POMALYST® is contraindicated in pregnant women and women at risk of becoming pregnant (see **WARNINGS AND PRECAUTIONS**). Pomalidomide is structurally related to thalidomide, a known human teratogen that causes severe and life-threatening birth defects. Pomalidomide induced malformations in rats and rabbits similar to those described with thalidomide. If POMALYST® is taken during pregnancy, it may cause severe birth defects or death to the fetus (see **WARNINGS AND PRECAUTIONS**). Females of Child-Bearing Potential may be treated with POMALYST® provided that adequate contraception, with two simultaneous effective methods of contraception, is used to prevent fetal exposure to the drug. The choice of the two simultaneously effective contraceptive methods will necessitate a risk/benefit discussion between the patient and a qualified physician experienced in the use of contraceptive methods. (See **Serious Warnings and Precautions Box**).
- Breast feeding women.

Male patients unable to follow or comply with the required contraceptive measures (see **WARNINGS AND PRECAUTIONS, Special Populations – Male Patients**).

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

POMALYST® (pomalidomide) should be administered under the supervision of a qualified physician experienced in the use of cancer chemotherapeutic agents.

- Potential for human birth defects, stillbirths, and spontaneous abortions (see **WARNINGS AND PRECAUTIONS**, **Special Populations: Females of Child-Bearing Potential** and **Male patients**).
- Neutropenia and Thrombocytopenia (see **WARNINGS AND PRECAUTIONS**, **Hematologic** and **ADVERSE REACTIONS** and **DOSAGE AND ADMINISTRATION**).
- Infections, including fatal cases (see **WARNINGS AND PRECAUTIONS, Infections**)
- Deep Vein Thrombosis (DVT) and Pulmonary Embolism (PE) (see **WARNINGS AND PRECAUTIONS**, **Cardiovascular**).
- Hepatotoxicity, including fatal cases (see **WARNINGS AND PRECAUTIONS, Hepatic**).
- Anaphylaxis (see **WARNINGS AND PRECAUTIONS, Immune**).
- Reactivation of hepatitis B, including fatal cases, has been reported rarely in patients receiving POMALYST® in combination with dexamethasone who have previously been infected with the hepatitis B virus (HBV) (see **WARNINGS AND PRECAUTIONS, Infection**).
- Severe dermatologic reactions including Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN), and drug reaction with eosinophilia and systemic symptoms (DRESS), including fatal cases (see **WARNINGS AND PRECAUTIONS, Skin**).
- Tumor lysis syndrome (TLS), including fatal cases (see **WARNINGS AND PRECAUTIONS, Tumor Lysis Syndrome**).
- Available only under a controlled distribution program called RevAid®.

General

Patients should be informed to not give blood while taking POMALYST® and for at least 4 weeks after stopping POMALYST®. If a woman who is pregnant received their donated blood, her baby may be exposed to POMALYST® and may be born with birth defects.

Patients should be instructed never to give this medication to another person and to return any unused capsules to RevAid® at the end of treatment.

Consult the Product Monograph for bortezomib when given in combination with POMALYST® and dexamethasone, prior to initiating treatment.

Increased mortality was observed in clinical trials in patients with multiple myeloma when pembrolizumab was added to dexamethasone and a thalidomide analogue.

Cardiovascular

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

Atrial fibrillation has been reported, mainly in patients with pre-existing cardiac disease or cardiac risk factors.

Thromboembolic Events: The use of POMALYST® in combination with dexamethasone ± bortezomib for the treatment of MM results in an increased risk of venous thromboembolic events (VTE), such as deep vein thrombosis (DVT) and pulmonary embolism (PE) (see **ADVERSE REACTIONS, Clinical Trial Adverse Reactions**).

Previous history of thromboembolic events or concomitant administration of erythropoietic agents or other agents such as hormone replacement therapy, may also increase thrombotic risk. Therefore, these agents should be used with caution in MM patients receiving POMALYST® in combination with dexamethasone ± bortezomib. The use of hormonal contraceptives is associated with an increased risk of thromboembolic disorders. Hormonal contraceptives are not recommended (see **Special Populations**, **Females of Child-Bearing Potential**).

Prophylactic antithrombotic medications, such as low dose aspirin, low molecular weight heparins or warfarin, should be recommended.

Carcinogenesis and Mutagenesis

Studies examining the carcinogenic potential of pomalidomide in mice and rats have not been conducted. One of twelve monkeys dosed with 1 mg/kg of pomalidomide (an exposure approximately 15-fold of the exposure in patients at the recommended dose of 4 mg/per day) developed acute myeloid leukemia in a 9-month repeat-dose toxicology study.

Pomalidomide was not mutagenic or clastogenic in a battery of tests, including a bacteria reverse mutation assay (Ames test), an *in vitro* cytogenetic assay using human peripheral blood lymphocytes and a micronucleus test in rats orally treated with doses up to 2000 mg/kg/day (see **TOXICOLOGY**).

Second Primary Malignancies: Second primary malignancies (SPM), including non-melanoma skin cancer, have been reported in patients receiving pomalidomide. The clinical significance of these observations is unclear. Physicians should carefully evaluate patients before and during treatment using standard cancer screening for occurrence of SPM and institute treatment as indicated.

Hematologic

Decreased blood cell counts, including neutropenia, anemia, or thrombocytopenia, including Grade 3 or 4 occurrences, have been reported in association with the clinical use of POMALYST® in combination with dexamethasone ± bortezomib.

Monitor patients for hematologic toxicities, especially neutropenia and thrombocytopenia. Patients should be advised to report febrile episodes promptly. Monitor complete blood counts weekly for the first 8 weeks and monthly thereafter (see **WARNINGS AND PRECAUTIONS**, **Monitoring and Laboratory Tests)**. Patients may require dose interruption and/or modification. Patients may require use of blood product support and/or growth factors (see **DOSAGE AND ADMINISTRATION**). Patients and physicians are advised to be observant for signs and symptoms of bleeding including epistaxis, especially in case of concomitant medication susceptible to induce bleeding.

Hepatic

Hepatic failure, including serious and fatal cases, and markedly elevated levels of alanine aminotransferase and bilirubin (≥ Grade 3) have been observed in clinical trial patients treated with POMALYST® (see **ADVERSE REACTIONS, Post Market Adverse Drug Reactions**). Cases of hepatitis that resulted in discontinuation of pomalidomide have also been reported. Regular monitoring of liver function in all patients is recommended (see **SERIOUS WARNINGS AND PRECAUTIONS**, and **Monitoring and Laboratory Tests,** and **DRUG INTERACTIONS**).

Immune

The safety of POMALYST® in patients requiring other immunosuppressive treatments (such as for rheumatoid arthritis, multiple sclerosis and lupus) has not been established. The safety of initiating POMALYST® treatment in patients with active hepatitis A, B, or C infection has not been demonstrated. In order to reduce the risk of developing serious infections, treatment of such patients with POMALYST® should be avoided if possible.

Hypersensitivity reactions (e.g., angioedema, anaphylaxis, urticaria) have been reported (see **ADVERSE REACTIONS, Post Market Adverse Drug Reactions**). Some cases were severe and serious, requiring immediate medical intervention and resulting in permanent discontinuation of POMALYST®. Patients with prior history of allergic reactions associated with thalidomide or lenalidomide were excluded from pomalidomide clinical studies, may be at a higher risk of hypersensitivity and are contraindicated to receive POMALYST® (see **CONTRAINDICATIONS**). Pomalidomide interruption or discontinuation should be considered for Grade 2-3 skin rash, and only resumed when the perceived benefit outweighs the potential risk. Pomalidomide must be permanently discontinued for angioedema, anaphylaxis and Grade 4 rash (see **DOSAGE AND ADMINISTRATION, Dose Modification or Interruption**).

Infection

Infections were fatal (Grade 5) in 11 (4.0%) subjects in the POMALYST®, dexamethasone and bortezomib arm and 3 (1.1%) subjects in the dexamethasone and bortezomib arm (the median

overall duration of treatment differed between treatment arms and should be taken into consideration).

Reactivation of hepatitis B, including fatal cases, has been reported rarely in patients receiving POMALYST® in combination with dexamethasone who have previously been infected with the hepatitis B virus (HBV). Some of these cases have progressed to acute hepatic failure, resulting in discontinuation of POMALYST®. Caution should be exercised when POMALYST® in combination with dexamethasone is used in patients previously infected with HBV. These patients should be closely monitored for signs and symptoms of active HBV infection throughout therapy. See **ADVERSE REACTIONS, Post-Market Adverse Drug Reactions**.

Interstitial lung disease (ILD)

Interstitial lung disease (ILD) and related events, including cases of pneumonitis, have been observed in clinical trial patients treated with pomalidomide. Careful assessment of patients with an acute onset or unexplained worsening of pulmonary symptoms should be performed to exclude ILD. Pomalidomide should be interrupted pending investigation of these symptoms and if ILD is confirmed, appropriate treatment should be initiated. Pomalidomide should only be resumed after a thorough evaluation of the benefits and the risks. See **WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests,** and **ADVERSE REACTIONS, Post-Market Adverse Drug Reactions,** and **DOSAGE AND ADMINISTRATION, Dose Modification or Interruption.**

Neurologic

Confusion, fatigue, depressed level of consciousness and dizziness have been reported with the use of POMALYST®. Patients should be advised as to the possible impairment of mental and/or physical abilities required for the performance of hazardous tasks such as driving a car or operating other complex or dangerous machinery.

Patients with ongoing ≥ Grade 2 peripheral neuropathy were excluded from clinical studies with POMALYST®. Appropriate caution should be exercised when considering the treatment of such patients with POMALYST®.

Skin

Severe dermatologic reactions including Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN), and drug reaction with eosinophilia and systemic symptoms (DRESS), including fatal cases, have been reported. DRESS may present with a cutaneous reaction (such as rash or exfoliative dermatitis), eosinophilia, fever, and/or lymphadenopathy with systemic complications such as hepatitis, nephritis, pneumonitis, myocarditis, and/or pericarditis.

If skin rash is exfoliative, purpuric, or bullous or if SJS, TEN or DRESS is suspected, POMALYST® must be permanently discontinued (see **DOSAGE AND ADMINISTRATION, Dose Modification or Interruption)**.

Tumor Lysis Syndrome

Tumor lysis syndrome (TLS) may occur in patients treated with POMALYST®. **Some cases of TLS were fatal.** Patients at risk for TLS are those with high tumor burden prior to treatment. These patients should be monitored closely, and appropriate precautions taken.

Special Populations

1. Females of Child-Bearing Potential:

Females of Child-Bearing Potential are all females who are menstruating, amenorrheic from previous treatments, and/or perimenopausal.

Pomalidomide is an analogue of thalidomide, a known human teratogen that causes severe and life-threatening birth defects. Embryo-fetal development studies in rats and rabbits indicate that pomalidomide produced malformations in the offspring of female rats and rabbits given the drug during pregnancy, similar to birth defects observed in humans following exposure to thalidomide during pregnancy. The teratogenic effect of pomalidomide in humans cannot be ruled out. POMALYST® may cause fetal harm when administered to a pregnant female.

For Females of Child-Bearing Potential, POMALYST® is contraindicated unless **ALL** of the following conditions are met:

- ✓ The patient is capable of understanding and carrying out instructions. (In some cases, the patient will need a competent support person to ensure RevAid® program compliance).
- ✓ The patient is willing and able to comply with the **two** mandatory, simultaneous and effective contraceptive measures or to commit to continually abstaining from heterosexual contact.
- ✓ The patient has a consultation with a health care professional, who has experience with the use of contraceptive methods, to discuss the best and most effective **two** simultaneous contraceptive methods to be used.
- ✓ The patient understands the cumulative risks of DVT, including, but not limited to, POMALYST®, dexamethasone, cancer and hormonal contraception.
- ✓ The patient knows the risk of possible contraceptive failure.
- ✓ The patient is willing and able to comply with the pregnancy testing requirements noted in detail below. This includes two negative pregnancy tests prior to the first dispense and on-going pregnancy tests throughout treatment.
- ✓ The patient is aware of the potential need for emergency contraception.
- ✓ The patient is informed of the risk of teratogenicity should a pregnancy occur.
- ✓ The patient knows and understands the need to consult her physician immediately if there is a risk of pregnancy.
- ✓ The patient acknowledges the importance of compliance with all the conditions of use.

Contraceptive Measures:

- All Females of Child-Bearing Potential (including those who normally do not use contraception due to a history of infertility, and those who have amenorrhea) must use the two simultaneous, effective methods of contraception:
  - For at least 4 weeks before starting POMALYST® treatment.
  - During dose interruptions.

- During POMALYST® treatment.
- For at least 4 weeks following the discontinuation of POMALYST® treatment.

- The patient who chooses to abstain from heterosexual contact as a contraceptive measure, must commit to using two methods of contraception at the same time if abstinence is no longer practiced.
- The use of hormonal contraceptives is associated with an increased risk of thromboembolic disorders. Hormonal contraceptives are not recommended (see **WARNINGS AND PRECAUTIONS, Cardiovascular**).
- Any method of contraception can fail. It is, therefore, critically important that Females of Child-Bearing Potential use two effective methods of contraception simultaneously.
- If pregnancy does occur during treatment, the drug should be immediately discontinued. Under these conditions, the patient should be referred to an obstetrician/gynecologist experienced in reproductive toxicity, for further evaluation and counseling.
- Any suspected embryo-fetal exposure to POMALYST® should be reported immediately by telephone to Celgene at 1-888-RevAid1 (1-888-738-2431).
- Female patients with a previous hysterectomy or bilateral oophorectomy are exempt from contraception use during POMALYST® therapy.

Pregnancy Testing:

- Females of Child-Bearing Potential must not be given POMALYST® until pregnancy is excluded. The patient must have two negative pregnancy tests before starting POMALYST® therapy, as well as subsequent tests throughout the treatment.
- The first pregnancy test should be conducted seven to 14 days prior to the start of therapy.
- The second pregnancy test should be conducted 24 hours prior to dispensing and starting the drug.
- A pregnancy test should be conducted weekly during the first month of treatment, monthly thereafter during treatment (or every 2 weeks if menses are irregular) and 4 weeks after the discontinuation of treatment.
- The pregnancy test should be a blood test performed in a licensed laboratory. The dates and results of pregnancy tests should be documented.
- The pregnancy test should have a serum hCG sensitivity of at least 25 mIU/mL.
- Pregnancy testing and consultation with an obstetrician/gynecologist should also occur if a patient misses her period, or if there is any abnormal menstrual bleeding.

2. Pregnant Women:

- POMALYST® is contraindicated in females who are, or may become, pregnant.
- POMALYST® is contraindicated in Females of Child-Bearing Potential who are not using the two mandatory, simultaneous and effective methods of contraception or who are not continually abstaining from heterosexual sexual contact.

- If pregnancy does occur during treatment, the drug should be immediately discontinued. Under these conditions, the patient should be referred to an obstetrician/gynecologist experienced in reproductive toxicity, for further evaluation and counseling.
- Any suspected embryo-fetal exposure to POMALYST® should be reported immediately by telephone to Celgene at 1-888-RevAid1 (1-888-738-2431).

3. Nursing Women:

POMALYST® should not be used when a patient is breast-feeding (see **CONTRAINDICATIONS**).

The safe use of POMALYST® during lactation has not been established.

4. Male Patients:

Pomalidomide is present in the semen of males who take POMALYST®. (See **ACTION AND CLINICAL PHARMACOLOGY**, **Pharmacokinetics**, **Distribution**). There is a potential risk of birth defects, stillbirths and spontaneous abortions if a developing fetus is exposed to pomalidomide through the semen of male patients (see **WARNINGS AND PRECAUTIONS**, **Females of Child-Bearing Potential**). Therefore, males receiving POMALYST® must always use a condom during any sexual contact with Females of Child-Bearing Potential even if they have undergone a successful vasectomy. The condom should be used:

- While the male patient is taking POMALYST®.
- During interruption of treatment.
- For at least 4 weeks after stopping POMALYST®.

Patients should not donate semen while taking POMALYST® and for at least 4 weeks after stopping POMALYST®.

Male patients must inform their female sexual partners of child-bearing potential that:

- The male patient is taking POMALYST®.
- There is a potential risk of birth defects, stillbirths and spontaneous abortions if a developing fetus is exposed to the semen of the male patient.
- A condom must be used during any sexual contact.

If a pregnancy occurs in a partner of a male patient taking pomalidomide, it is recommended to refer the female partner to a physician specialized or experienced in teratology for evaluation and advice.

5. Patients with Hepatic Impairment:

Pomalidomide is primarily metabolized in the liver. Administration of POMALYST® should be avoided in patients with serum bilirubin greater than 1.5 X the upper limit of normal (ULN) and AST/ALT greater than 3.0 X ULN. Following single dose administration, the AUC of pomalidomide increased 51%, 58%, and 72% in subjects with mild (Child-Pugh class A), moderate (Child-Pugh class B), and severe (Child-Pugh class C) hepatic impairment compared to subjects with normal liver function. Dose adjustment is recommended in patients with hepatic

impairment (see **DOSAGE AND ADMINISTRATION** and **ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions**).

6. Patients with Renal Impairment:

Pomalidomide is extensively metabolized prior to excretion. Pomalidomide and its metabolites are excreted by the kidneys. In patients with severe renal impairment requiring dialysis, the AUC of pomalidomide increased by 35.8% and the rate of SAEs increased relative to patients with normal renal function; therefore, starting dose adjustment is recommended in these patients. For patients with severe renal impairment requiring dialysis, POMALYST® should be administered after the completion of hemodialysis on dialysis days because exposure of pomalidomide could be significantly decreased during dialysis (see **DOSAGE AND ADMINISTRATION, OVERDOSAGE,** and **ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions).**

7. Pediatrics (< 18 years of age):

Safety and effectiveness in pediatric patients below the age of 18 have not been established (see **ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Condition)**.

For **ALL** sexually active Females of Child-Bearing Potential the use of two simultaneous effective methods of contraception is mandatory.

8. Geriatrics (> 65 years of age):

No dosage adjustment is required for POMALYST® based on age.

For patients > 75 years of age the starting dose of dexamethasone should be reduced by half (see **DOSAGE AND ADMINISTRATION**).

The concomitant administration of dexamethasone may increase the risk of infection, particularly pneumonia, in patients > 65 years of age treated with POMALYST®. Dexamethasone dosing may need to be reduced or interrupted in these patients in case of infection.

In the Phase III study evaluating the combination of POMALYST® and dexamethasone (Pd) 45% were > 65 years of age and 8% were > 75 years of age in the Pd arm (n=302). In the Phase III study evaluating the combination of POMALYST®, dexamethasone and bortezomib, 56.2% were > 65 years of age and 16.4 % were > 75 years of age in the POMALYST®, dexamethasone and bortezomib combination arm (n = 281).

<u>Monitoring and Laboratory Tests</u>

Monitor patients for hematologic toxicities, especially neutropenia and thrombocytopenia. Monitor complete blood counts weekly for the first 8 weeks and monthly thereafter. Patients with hematologic toxicities may require dose interruption and/or modification and/or the use of blood support and/or growth factors (see **DOSAGE AND ADMINISTRATION**).

Liver function including blood chemistries involving aspartate aminotransferase (AST), alanine aminotransferase (ALT), direct bilirubin and prothrombin time (INR), as well as renal function i.e., creatinine, and creatinine clearance, should be monitored at baseline and at the beginning of each treatment cycle.

Careful assessment of patients with an acute onset or unexplained worsening of pulmonary symptoms should be performed to exclude interstitial lung disease (ILD). See **WARNINGS AND PRECAUTIONS, Interstitial Lung Disease** and **DOSAGE and ADMINISTRATION**.

ADVERSE REACTIONS

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

POMALYST® in combination with dexamethasone and bortezomib

In the multicentre, randomized, open-label Phase III study, 548 patients with multiple myeloma who had received at least one prior regimen, including lenalidomide, were included in the Safety Population: 278 in the POMALYST®, dexamethasone and bortezomib arm and 270 in the dexamethasone and bortezomib arm. The median overall duration of treatment differed between treatment arms and should be taken into consideration when comparing frequencies of adverse events, as well as rates of deaths during the treatment period across treatment arms. The median duration of treatment was 38.3 weeks (1.1 – 187.3 weeks) in the POMALYST®, dexamethasone and bortezomib arm compared to 21.4 weeks (0.4 – 164.4 weeks) in the control arm.

In the POMALYST®, dexamethasone and bortezomib arm, the most common adverse events leading to dose interruption of POMALYST® were neutropenia (23%), thrombocytopenia (14%), and pneumonia (14%); overall the median time to the first dose interruption of POMALYST® was 32 days. The most common adverse events leading to dose reduction of POMALYST ® were neutropenia (10%), followed by thrombocytopenia (9%); overall the median time to the first dose reduction of POMALYST® was 64.5 weeks. The most common adverse events leading to discontinuation of POMALYST® were fatigue (1%), peripheral sensory neuropathy and pulmonary embolism (1% each). Study treatment discontinuation due to an adverse event occurred in 10.7% of subjects in the POMALYST®, dexamethasone and bortezomib arm, and 17.6% in the dexamethasone and bortezomib arm.

The most commonly reported adverse events in the POMALYST®, dexamethasone and bortezomib arm (≥ 20%, with ≥ 2% [n=6] frequency versus the comparator) were peripheral sensory neuropathy, neutropenia, fatigue, constipation, peripheral edema, diarrhea, upper respiratory infection, cough and dyspnea. The most commonly reported Grade 3 or 4 adverse reactions in the POMALYST®, dexamethasone and bortezomib arm (≥ 5%, with ≥ 1% [n=3] frequency versus the comparator) were neutropenia, thrombocytopenia, pneumonia, hyperglycemia, fatigue, peripheral sensory neuropathy, diarrhea and hypokalemia. The most commonly reported serious adverse reactions in the POMALYST®, dexamethasone and bortezomib arm (≥ 1%, with ≥ 1% frequency versus the comparator) was pneumonia (9%), pyrexia (4%), influenza, lower respiratory tract infection, atrial fibrillation (3% each), septic shock, respiratory tract infection, sepsis (2% each), dyspnea and death (1% each).

The treatment emergent adverse events observed in the POMALYST®, dexamethasone and bortezomib arm are listed in Table 1. All adverse events observed in ≥ 5% patients and Grade 3 or 4 adverse events observed in ≥ 1% patients are included (≥ 2% frequency for all grade adverse events and a ≥ 1% frequency for Grade 3-4 adverse reactions versus the comparator is applied).

Table 1: Adverse Events with POMALYST®, dexamethasone and bortezomib combination from the Phase III trial (safety population)

System Organ Class/ Preferred term	POMALYST® + dex + bortezomib (N=278)		dex + bortezomib (N=270)	
	All grade n (%)	Grade 3-4 n (%)	All grade n (%)	Grade 3−4 n (%)
Blood and lymphatic system disorders	**187 (67)**	**154 (55)**	**143 (53)**	**112 (42)**
Neutropenia	130 (47)	116 (42)	29 (11)	23(9)
Thrombocytopenia[a]	102 (37)	76 (27)	103 (38)	79 (29)
Anemia[a]	79 (28)	39 (14)	73 (27)	38 (14)
Leukopenia	32 (12)	15 (5)	9 (3)	5 (2)
Lymphopenia	12 (4)	12 (4)	9 (3)	8 (3)
Febrile Neutropenia	9 (3)	9 (3)	0	0
Cardiac Disorders	**63 (23)**	**22 (8)**	**37 (14)**	**12 (4)**
Atrial Fibrillation	26 (9)	9 (3)	5 (2)	2(0.7)
Eye Disorders	**59 (21)**	**8 (3)**	**46 (17)**	**1 (0.4)**
Cataract	10 (4)	3 (1)	0	0
Gastrointestinal disorders	**195 (70)**	**36 (13)**	**168 (62)**	**19 (7)**
Constipation	102 (37)	7 (3)	65 (24)	1 (0.4)
Diarrhea	94 (34)	20 (7)	81 (30)	9 (3)
Nauseaa	49 (18)	1 (0.4)	54 (20)	1 (0.4)
Vomitinga	32 (12)	3 (1)	27 (10)	1 (0.4)
Abdominal pain	27 (10)	4 (1)	18 (7)	4 (2)
Abdominal pain upper	22 (8)	1 (0.4)	15 (6)	0
Stomatitis	17 (6)	1 (0.4)	1 (0.4)	0
Dry mouth	16 (6)	0	10 (4)	0
Abdominal distension	15 (5)	1 (0.4)	6 (2)	0
General disorders and administration site conditions	**213 (77)**	**50 (18)**	**172 (64)**	**31 (12)**
Fatigue	103 (37)	23 (8)	71 (26)	10 (4)
Edema peripheral	94(34)	5 (2)	54 (20)	2 (0.7)
Pyrexia	64 (23)	6 (2.2)	32 (12)	2 (0.7)
Non-cardiac chest pain	14 (5)	4 (1)	13 (5)	1 (0.4)
Edema	10 (4)	4 (1)	1 (0.4)	0

Table 1: Adverse Events with POMALYST®, dexamethasone and bortezomib combination from the Phase III trial (safety population) (continued)

System Organ Class/ Preferred term	POMALYST® + dex + bortezomib (N=278)		dex + bortezomib (N=270)	
	All grade n (%)	Grade 3-4 n (%)	All grade n (%)	Grade 3−4 n (%)
Injury, poisoning and procedural complications	**85 (31)**	**8 (3)**	**56 (21)**	**5 (2)**
Accidental Overdose	23 (8)	7 (3)	5 (2)	3 (1)
Fall	17 (6)	1 (0.4)	10 (4)	0
Infections and infestations	**223 (80)**	**86 (31)**	**175 (65)**	**48 (18)**
Upper respiratory tract infection	58 (21)	3 (1)	48 (18)	3 (1)
Pneumonia	53 (19)	32 (12)	37 (14)	17 (6)
Bronchitis	39 (14)	4 (1)	19 (7)	3 (1)
Viral upper respiratory tract infection	31 (11)	0	14 (5)	0
Influenza	27 (10)	7 (3)	15 (6)	4 (2)
Urinary tract infection	27 (10)	4 (1)	25 (10)	1 (0.4)
Respiratory tract infection	23 (8)	4 (1)	12 (4)	0
Lower respiratory tract infection	22 (8)	4 (1)	7 (3)	2 (0.7)
Sepsis	6 (2)	6 (2)	1 (0.4)	1 (0.4)
Septic shock	6 (2)	4 (1)	0	0
Clostridium difficile colitis	4 (1)	3 (1)	1 (0.4)	0
Lung infection	4 (1)	3 (1)	3 (1)	0
Bronchiolitis	4 (1)	3 (1)	0	0
Investigations	**70 (25)**	**20 (7)**	**67 (25)**	**17 (6)**
Weight decreased	16 (6)	3 (1)	17 (6)	0
Metabolism and nutrition disorders	**144 (52)**	**71 (26)**	**113 (42)**	**49 (18)**
Hypokalemia	43 (16)	17 (6)	30 (11)	11 (4)
Hyperglycemia	40 (14)	25 (9)	30 (11)	14 (5)
Hypomagnesemia	19 (7)	5 (2)	7 (3)	2 (0.7)
Hypocalcemia	18 (7)	5 (2)	9 (3)	1 (0.4)
Hypophosphatemia	16 (6)	11 (4)	8 (3)	5 (2)
Hyperkalemia	11 (4)	7 (3)	6 (2)	2 (0.7)
Hypercalcemia	11 (4)	4 (1)	4 (2)	1 (0.4)

Table 1: Adverse Events with POMALYST®, dexamethasone and bortezomib combination from the Phase III trial (safety population) (continued)

System Organ Class/ Preferred term	POMALYST® + dex + bortezomib (N=278)		dex + bortezomib (N=270)	
	All grade n (%)	Grade 3-4 n (%)	All grade n (%)	Grade 3−4 n (%)
Musculoskeletal and connective tissue disorders	**171 (62)**	**17 (6)**	**119 (44)**	**14 (5)**
Back Pain	52 (19)	3 (1)	36 (13)	4 (2)
Muscular weakness	38 (14)	3 (1)	13 (5)	1 (0.4)
Muscle spasms	26 (9)	0	14 (5)	0
Bone pain	22 (8)	1 (0.4)	15 (6)	3 (1.1)
Nervous system disorders	**205 (74)**	**57 (21)**	**163 (60)**	**32 (12)**
Peripheral sensory neuropathy	133 (48)	23 (8)	100 (37)	12 (4)
Dizziness	48 (17)	1 (0.4)	28 (10)	1 (0.4)
Tremor	30 (11)	1 (0.4)	8 (3)	0
Dysgeusia	18 (7)	0	8 (3)	0
Syncope	17 (6)	14 (5)	11 (4)	6 (2)
Peripheral sensorimotor neuropathy	16 (6)	5 (2)	12 (4)	1 (0.4)
Paresthesia	16 (6)	0	5 (2)	0
Psychiatric disorders	**95 (34)**	**13 (5)**	**86 (32)**	**5 (2)**
Insomnia	45 (16)	5 (2)	53 (20)	2 (0.7)
Depression	15 (5)	3 (1)	7 (3)	0
Renal and urinary disorders	**52 (19)**	**19 (7)**	**28 (10)**	**6 (2)**
Acute kidney injury	15 (5)	9 (3)	10 (4)	4 (2)
Chronic kidney disease	6 (2)	3 (1)	0	0
Urinary retention	4 (1)	3 (1)	0	0
Respiratory, thoracic and mediastinal disorders	**141 (51)**	**24 (9)**	**107 (40)**	**13 (5)**
Cough	57 (21)	0	40 (15)	0
Dyspnea	56 (20)	8 (3)	33 (12)	3 (1)
Pulmonary embolism	11 (4)	11 (4)	1 (0.4)	1 (0.4)
Skin and subcutaneous tissue disorders	**91 (33)**	**9 (4)**	**59 (22)**	**0**
Rash	26 (9)	6 (2)	8 (3)	0
Vascular disorder	**79 (28)**	**17 (6)**	**52 (19)**	**8 (3)**
Hypotension	24 (9)	5 (2)	14 (5)	1 (0.4)

Table 1: Adverse Events with POMALYST®, dexamethasone and bortezomib combination from the Phase III trial (safety population) (continued)

System Organ Class/ Preferred term	POMALYST® + dex + bortezomib (N=278)		dex + bortezomib (N=270)	
	All grade n (%)	Grade 3-4 n (%)	All grade n (%)	Grade 3−4 n (%)
Hypertension	18 (7)	8 (3)	17 (6)	4 (2)
Deep vein thrombosis	14 (5)	2 (0.7)	5 (2)	1 (0.4)

[a] Additional adverse events that did not meet the criteria for inclusion but were included based on their frequency, clinical relevance and seen as adverse reactions in other POMALYST® studies and /or post marketing surveillance.
Data cut-off date: 26 Oct 2017

Less Common Clinical Trial Adverse Drug Reactions (≥ 1% to < 5%)

Treatment emergent adverse events reported in ≥ 1% to <5% of patients in the POMALYST®, dexamethasone and bortezomib with ≥ 1% frequency versus the comparator, not described elsewhere are:

Ear and labyrinth disorders: tinnitus, deafness

Eye disorders: ocular hyperemia

Cardiac disorders: cardiac failure, bradycardia

Gastrointestinal disorders: abdominal discomfort, flatulence, gastritis

General disorders and administration site conditions: influenza like illness, dysphagia, toothache, gastritis

Infections and infestations: oral candidiasis, pharyngitis, herpes zoster, sinusitis, rhinitis, eye infection, respiratory syncytial virus infection

Injury, poisoning and procedural complications: rib fracture, wound, infusion related reaction

Investigations: weight increased, alanine aminotransferase increased, aspartate aminotransferase increased, blood cholesterol increased, blood creatinine phosphokinase increased

Metabolism and nutrition disorders: decreased appetite, diabetes mellitus, hyperphosphatemia, hyponatremia, dehydration

Musculoskeletal and connective tissue disorders: myalgia, spinal pain, musculoskeletal chest pain, osteonecrosis of jaw, limb discomfort, pathological fracture

Neoplasms benign, malignant and unspecified (including cysts and polyps): Basal cell carcinoma (included as is likely related to POMALYST®)

Nervous system disorders: neuropathy peripheral, ageusia, balance disorder, head discomfort,

Psychiatric disorders: mood altered, anxiety, agitation, delirium

Renal and urinary disorders: hematuria, dysuria, pollakiuria, anuria

Reproductive system and breast disorders: pelvic pain

Respiratory, thoracic and mediastinal disorders: rhinorrhea, hiccups

Skin and subcutaneous tissue disorders: hyperhidrosis, swelling face, night sweats, blister, rash macular

Vascular disorders: embolism venous

Abnormal Hematologic and Clinical Chemistry Findings

A summary of the proportion of patients who had shifts from baseline to a worse Grade 3 or 4 value on study based on CTCAE are summarized in Table 2 for both hematology and chemistry parameters. A > 1% (n=3) difference in frequency between the two arms is applied.

Table 2: Shifts from Baseline to Worst Grade 3 or 4 Value on Study by Common Terminology Criteria (CTC) Grade

Laboratory Parameter	POMALYST®+dex+bortezomib	dex+bortezomib
	Grade 3 or 4 n (%)	Grade 3 or 4 n/ [a](%)
Abnormal Hematology	**N = 267**	**N = 267**
Lymphocytes	142 (51.4)	97 (36.5)[a]
Neutrophils	120 (43.5)	22 (8.3)[a]
Leukocytes	91 (33)	22 (8.2)
Platelets	72 (26.1)	80 (30)
Hemoglobin	36 (13)	29 (11)
Abnormal Clinical Chemistry	**N = 267**	**N = 266**
Phosphate	60 (21.7)	46 (17.3)
Glucose	45 (16.2)	38 (14.3)
Potassium	32 (11.6)	22 (8.3)
Calcium	15 (5.4)	4 (1.5)
Calcium, corrected	14 (5.1)	4 (1.5)
Creatinine	10 (3.6)	5 (1.9)

[a] N = 266
Data cut-off date: 26 Oct 2017

POMALYST® in combination with dexamethasone

In the multicentre, randomized, open-label Phase III study, 449 patients with relapsed and refractory multiple myeloma were included in the Safety Population: 300 in the pomalidomide plus low-dose dexamethasone arm and 149 in the high-dose dexamethasone arm.

Approximately 24% of subjects in the POMALYST®+dexamethasone arm had pomalidomide dose reductions, most of which were due to blood disorders, including 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%); pneumonia (4%); febrile neutropenia, general physical health deterioration, and pyrexia (3.7% each); fatigue (2.3%); and anemia (2%).

The most commonly reported adverse reactions in patients receiving POMALYST®+ dexamethasone were related to blood and lymphatic system disorders (anemia, neutropenia and thrombocytopenia); general disorders and administration site conditions (fatigue, pyrexia and edema peripheral); and infections and infestations (pneumonia). The most commonly reported Grade 3 or 4 adverse reactions were neutropenia, anemia, thrombocytopenia, pneumonia, fatigue, pyrexia, and edema peripheral. The most commonly reported serious adverse reactions were pneumonia and febrile neutropenia. Other serious adverse reactions of interest included neutropenia, thrombocytopenia, and venous thromboembolic events.

Adverse reactions tended to occur more frequently within the first two cycles of treatment with POMALYST®.

The treatment emergent adverse events observed in patients treated with POMALYST®+ dexamethasone are listed in Table 3 below by system organ class and frequency for all adverse events ≥ 5% and for Grade 3 or 4 adverse events ≥ 1%.

Table 3: **Adverse Events with POMALYST®+dexamethasone (Safety Population) from the Phase III trial**

System Organ Class/ Preferred term[a]	POMALYST®+dex (N=300)		HD-dex (N=149)	
	All grade n (%)	Grade 3-4 n (%)	All grade n (%)	Grade 3−4 n (%)
Blood and lymphatic system disorders[c]				
Anemia	137 (46)	81 (27)	63 (42)	43 (29)
Neutropenia	136 (45)	125 (42)	29 (20)	22 (15)
Thrombocytopenia	81 (27)	62 (21)	40 (27)	36 (24)
Leukopenia	37 (12)	26 (9)	8 (5)	5 (3)
Febrile neutropenia	20 (7)	20 (7)	0 (0)	0 (0)
Lymphopenia	13 (4)	11 (4)	8 (5)	6 (4)
Cardiac disorders				
Atrial fibrillation	10 (3)	4 (1)	2 (1)	1 (<1)
Ear and labyrinth disorders				
Vertigo	9 (3)	3 (1)	0 (0)	0 (0)
Gastrointestinal disorders				
Constipation	58 (19)	5 (2)	18 (12)	0 (0)
Diarrhea	55 (18)	3 (1)	24 (16)	2 (1)
Nausea	35 (12)	2 (1)	13 (9)	2 (1)
Vomiting	23 (8)	4 (1)	6 (4)	0 (0)
General disorders and administration site conditions				
Fatigue	85 (28)	14 (5)	36 (24)	7 (5)
Pyrexia	63 (21)	9 (3)	29 (20)	4 (3)
Asthenia	41 (14)	10 (3)	24 (16)	9 (6)

Table 3: **Adverse Events with POMALYST®+dexamethasone (Safety Population) from the Phase III trial (continued)**

System Organ Class/ Preferred term[a]	POMALYST®+dex (N=300)		HD-dex (N=149)	
	All grade n (%)	Grade 3-4 n (%)	All grade n (%)	Grade 3−4 n (%)
Edema peripheral	39 (13)	4 (1)	16 (11)	3 (2)
General physical health deterioration	27 (9)	16 (5)	14 (9)	10 (7)
Pain	7 (2)	3 (1)	4 (3)	1 (<1)
Infections and infestations[d]				
Pneumonia	32 (11)	27 (9)	14 (9)	11 (7)
Upper respiratory tract infection	28 (9)	3 (1)	9 (6)	2 (1)
Bronchitis	24 (8)	1 (<1)	6 (4)	0 (0)
Nasopharyngitis	19 (6)	0 (0)	1 (<1)	0 (0)
Respiratory tract infection	17 (6)	3 (1)	5 (3)	0 (0)
Urinary tract infection	14 (5)	2 (1)	8 (5)	3 (2)
Bronchopneumonia	9 (3)	5 (2)	2 (1)	1 (< 1)
Lower respiratory tract infection	8 (3)	5 (2)	7 (5)	3 (2)
Infection	8 (3)	3 (1)	3 (2)	1 (<1)
Sepsis	7 (2)	6 (2)	4 (3)	3 (2)
Lung infection	7 (2)	3 (1)	3 (2)	1 (<1)
Septic shock	4 (1)	4 (1)	6 (4)	1 (<1)
Cellulitis	4 (1)	3 (1)	2 (1)	1 (<1)
Neutropenic sepsis	3 (1)	3 (1)	0 (0)	0 (0)
Metabolism and nutrition disorder[c]				
Decreased appetite	30 (10)	2 (1)	11 (7)	2 (1)
Hypokalemia	20 (7)	9 (3)	10 (7)	4 (3)
Hypercalcemia	19 (6)	11 (4)	16 (11)	8 (5)
Hyperglycemia	15 (5)	9 (3)	12 (8)	10 (7)
Dehydration	13 (4)	3 (1)	9 (6)	2 (1)
Hyperkalemia	8 (3)	5 (2)	0 (0)	0 (0)
Hyperuricemia	8 (3)	3 (1)	6 (4)	3 (2)
Hyponatremia	7 (2)	6 (2)	3 (2)	3 (2)
Musculoskeletal and connective tissue disorders				
Back pain	44 (15)	11 (4)	20 (13)	5 (3)

Table 3: **Adverse Events with POMALYST®+dexamethasone (Safety Population) from the Phase III trial (continued)**

System Organ Class/ Preferred term[a]	POMALYST®+dex (N=300)		HD-dex (N=149)	
	All grade n (%)	Grade 3-4 n (%)	All grade n (%)	Grade 3−4 n (%)
Bone pain	44 (15)	19 (6)	15 (10)	4 (3)
Muscle spasms	30 (10)	1 (<1)	9 (6)	1 (1)
Arthralgia	14 (5)	1 (<1)	6 (4)	1 (1)
Pain in extremity	12 (4)	4 (1)	8 (5)	1 (<1)
Muscular weakness	8 (3)	3 (1)	16 (11)	4 (3)
Musculoskeletal chest pain	9 (3)	3 (1)	2 (1)	1 (<1)
Nervous system disorders				
Peripheral neuropathy[b]	34 (11)	3 (1)	14 (9)	2 (1)
Dizziness	27 (9)	2 (1)	9 (6)	1 (1)
Headache	15 (5)	0	7 (5)	0
Tremor	15 (5)	2 (1)	2 (1)	0 (0)
Syncope	7 (2)	3 (1)	1 (<1)	1 (<1)
Depressed level of consciousness	4 (1)	3 (1)	0 (0)	0 (0)
Psychiatric disorders				
Insomnia	24 (8)	1 (<1)	31 (21)	4 (3)
Confusional state	11 (4)	7 (2)	8 (5)	2 (1)
Renal and urinary disorders				
Renal failure	12 (4)	9 (3)	3 (2)	2 (1)
Renal failure acute	11 (4)	9 (3)	7 (5)	4 (3)
Reproductive system and breast disorders				
Pelvic pain	5 (2)	4 (1)	3 (2)	0 (0)
Respiratory, thoracic and mediastinal disorders				
Dyspnea	50 (17)	14 (5)	17 (11)	7 (5)
Cough	45 (15)	1 (<1)	12 (8)	0 (0)
Epistaxis	27 (9)	2 (<1)	14 (9)	3 (2)
Pulmonary embolism	3 (1)	2 (1)	0 (0)	0 (0)
Skin and subcutaneous tissue disorders				
Pruritus	21 (7)	0 (0)	4 (3)	0 (0)
Rash	20 (7)	3 (1)	1 (1)	0 (0)

[a] System organ classes and preferred terms are coded using the MedDRA dictionary version 14.0. System organ classes are listed alphabetically and preferred terms are listed in descending order of frequency of POMALYST®+dex group. A patient with multiple occurrences of an ADR is counted only once in the AE

category. The severity of the toxicities is graded according to the National Cancer Institute Common Toxicity Criteria for Adverse Events version 4.

[b] Peripheral neuropathy is a composite term including: paresthesia, neuropathy peripheral, gait disturbance, polyneuropathy, hypoesthesia, dysesthesia, burning sensation, neuralgia, peripheral motor neuropathy, sensory loss.

[c] Laboratory abnormalities within the Blood and Lymphatic and Metabolism and Nutrition system organ classes are considered to be adverse events only if the abnormality: resulted in discontinuation from the study; required treatment, dose modification/interruption, or any other therapeutic intervention; or was judged to be of significant clinical importance

[d] All Preferred Terms under SOC of Infections and Infestations (including bacterial, viral and fungal infections) except for rare infections of Public Health interest will be considered listed.

Note: The adverse events reported in Table 3 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.

Less Common Clinical Trial Adverse Drug Reactions (≥ 1% to < 5%)

Treatment emergent adverse events reported in ≥ 1% to <5% of patients in the POMALYST®, dexamethasone and bortezomib arm are:

Blood and lymphatic system disorders: lymphadenopathy

Cardiac disorders: palpitations, cardiac failure, tachycardia, extrasystoles

Eye disorders: vision blurred, cataract, conjunctivitis

Gastrointestinal disorders: abdominal pain, dyspepsia, dry mouth, abdominal distension, stomatitis, abdominal pain upper, flatulence, toothache

General disorders and administration site conditions: chills, malaise, chest pain, mucosal inflammation, non-cardiac chest pain, gait disturbance, edema

Hepatobiliary disorders: hepatotoxicity (<1%), hyperbilirubinemia (<1%)

Immune system disorders: drug hypersensitivity

Infections and infestations: sinusitis, oral candidiasis, rhinitis, cystitis, ear infection, gastroenteritis, herpes simplex, herpes zoster, neutropenic sepsis, oral herpes, pharyngitis

Investigations: blood creatinine increased, weight decreased, c-reactive protein increased, hematocrit decreased, aspartate aminotransferase increased, blood bicarbonate decreased, lymphocyte count decreased, red blood cell count decreased, weight increased

Metabolism and nutrition disorders: hypocalcemia, hypoalbuminemia, hyperphosphatemia, hypomagnesemia

Musculoskeletal and connective tissue disorders: musculoskeletal pain, myalgia, groin pain, neck pain, pain in jaw, pathological fracture

Nervous system disorders: paraesthesia, neuropathy peripheral, lethargy, dysgeusia, hypoesthesia, balance disorder, polyneuropathy, somnolence

Psychiatric disorders: depression, agitation, mood altered, anxiety, sleep disorder, disorientation, restlessness

Renal and urinary disorders: pollakiuria, dysuria, renal impairment, urinary retention, hematuria, urinary incontinence

Respiratory, thoracic and mediastinal disorders: dyspnea exertional, dysphonia, oropharyngeal pain, productive cough, hiccups, pleural effusion, nasal congestion, pulmonary embolism, wheezing, pneumonitis (<1%)

Skin and subcutaneous tissue disorders: night sweats, hyperhidrosis, erythema, rash generalized, alopecia, decubitus ulcer, dry skin

Vascular disorders: hypotension, hypertension, hematoma, flushing, deep vein thrombosis

Abnormal Hematologic and Clinical Chemistry Findings

Hematological abnormalities occur frequently in patients with advanced multiple myeloma. In study MM-003, substantially higher percentages of subjects in the POMALYST®+dexamethasone arm than in the HD-dex arm experienced Grade 3 or 4 leukocytes (44.6% vs. 12.4%) and neutrophils (55.1% vs. 16.3%). Neutropenia occurred most frequently during the first 3 cycles. The percentages of subjects who experienced Grade 3 or 4 hemoglobin, lymphocytes, and platelets were similar in the POMALYST® + dexamethasone and HD-dex treatment arms. For most clinical chemistry parameters, the percentages of subjects with Grade 3 or 4 values were relatively low and similar in the 2 treatment arms, and no substantial differences were noted between treatment arms. No substantial differences were noted regarding serum electrolyte parameters.

A summary of the proportion of patients who had shifts from baseline to a worse Grade 3 or 4 value on study based on CTCAE are summarized in Table 4 for both hematology and chemistry parameters.

Table 4: Shifts from Baseline to Worst Grade 3 or 4 Value on Study by Common Terminology Criteria (CTC) Grade

Laboratory Parameter	POMALYST®+dex	HD-dex
	Grade 3 or 4 n/N [a](%)	Grade 3 or 4n/N [a](%)
Abnormal Hematology		
Hemoglobin	67/293 (23%)*	37/142 (26%)*
Leukocytes	128/287 (45%)	17/137 (12%)
Lymphocytes	150/293 (51%)	66/140 (47%)
Neutrophils	158/287 (55%)	22/135 (16%)
Platelets	82/290 (28%)	37/140 (26%)
Abnormal Clinical Chemistry		
Alanine Aminotransferase	3/258 (1.2%)*	0
Alkaline Phosphatase	3/247 (1.2%)*	0
Bilirubin	2/259 (0.8%)*	0
Calcium, corrected	6/258 (2.3%)	4/120 (3.3%)
Creatinine	3/259 (1.1%)	4/120 (3.3%)
Gamma Glutamyl Transferase	8/249 (3.2%)	9/120 (7.5%)
Glucose	1/233 (0.4%)	0
Creatinine Clearance	12/259 (4.6%)	9/120 (7.5%)
Phosphate	18/175 (10.3%)*	6/72 (8.3%)*
Potassium	16/259 (6.2%)	3/119 (2.5%)*
Protein Albumin	5/258 (1.9%)*	6/120 (5%)*
Protein Urine	36/268 (13.4%)*	27/125 (21.6%)*

Table 4: Shifts from Baseline to Worst Grade 3 or 4 Value on Study by Common Terminology Criteria (CTC) Grade (continued)

Laboratory Parameter	POMALYST®+dex	HD-dex
	Grade 3 or 4 n/N [a](%)	Grade 3 or 4n/N [a](%)
Sodium	7/259 (2.7%)*	7/120 (5.8%)*
Urate	72/238 (30.2%)	40/115 (34.8%)

[a] N = Number of subjects with baseline and post-baseline measurements. This number is used as the denominator for calculation of percentage.
n = Number of subjects who had shifts from baseline to a worse Grade 3 or 4 value. This number is used as the numerator for calculation of percentage.
*No Grade 4 toxicity was observed

The worst (highest) CTC Grade is used if subject has more than one lab value from post-baseline.

Post-Market Adverse Drug Reactions

The following adverse drug reactions have been identified from the worldwide post-marketing experience with POMALYST® and are not listed under **Clinical Trial Adverse Drug Reactions.** Because these reactions are reported voluntarily from a population of uncertain size it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Blood and Lymphatic System Disorders: pancytopenia

Endocrine Disorders: Hypothyroidism

Gastrointestinal Disorders: gastrointestinal hemorrhage

Hepatobiliary Disorders: hepatic failure, hepatitis, cytolytic hepatitis, acute liver injury, hepatic steatosis

Immune System Disorders: hypersensitivity, e.g., angioedema, anaphylaxis, urticaria

Infections and Infestations: hepatitis B virus reactivation

Investigations: increased liver function tests, prothrombin time (PT) prolonged

Metabolism and Nutrition Disorders: tumor lysis syndrome

Neoplasms benign, malignant and unspecified (incl. cysts and polyps): basal cell carcinoma, squamous cell carcinoma of the skin

Respiratory, Thoracic and Mediastinal Disorders: pneumonitis, interstitial lung disease, pulmonary fibrosis

Skin and Subcutaneous Tissue Disorders: Stevens-Johnson Syndrome, toxic epidermal necrolysis, drug reaction with eosinophilia and systemic symptoms (DRESS)

DRUG INTERACTIONS

Overview

Pomalidomide is a substrate of P-glycoprotein (Pg-p) and is partly metabolised by CYP1A2 and CYP3A4. The use of POMALYST® with concomitant strong CYP1A2 inhibitors should be

avoided. If concomitant use of strong inhibitors of CYP1A2 with POMALYST® cannot be avoided due to medical necessity and are co-administered with POMALYST®, reduce the POMALYST® dose by 50%. There is no clinical safety and efficacy data in multiple myeloma patients supporting the concomitant use of POMALYST® and strong CYP1A2 inhibitors. Co-administration of POMALYST® with a strong CYP3A4 inhibitor, ketoconazole, had no clinically relevant effect on exposure to POMALYST®. See **DOSAGE AND ADMINSTRATION**. The risk of thromboembolic events may be increased with the simultaneous use of POMALYST® with erythropoietic agents, hormone replacement therapy or hormonal contraceptives. Cigarette smoking may reduce the efficacy of POMALYST®. Interactions with other drugs have not been established. POMALYST® may possibly impair mental and/or physical abilities required for the performance of hazardous tasks, such as driving a car or operating other complex or dangerous machinery.

Drug-Drug Interactions

Table 5: Established or Potential Drug-Drug Interactions

Proper name	Ref	Effect	Clinical comment
CYP1A2 Inhibitors	CT	Co-administration of the strong CYP1A2 inhibitor fluvoxamine with pomalidomide in the presence of ketoconazole, increased mean exposure (AUC inf) to pomalidomide by 107% with a 90 % confidence interval [91% to 124%] compared with pomalidomide plus ketoconazole. In a second study to evaluate the contribution of a CYP1A2 inhibitor alone to metabolism changes, co-administration of fluvoxamine alone with pomalidomide increased mean exposure (AUC inf) to pomalidomide by 125% with a 90% confidence interval [98% to 157%] compared to pomalidomide alone.	The use of POMALYST® with concomitant strong CYP1A2 inhibitors should be avoided. If concomitant use of strong inhibitors of CYP1A2 with POMALYST® cannot be avoided due to medical necessity and are co-administered with POMALYST®, reduce the POMALYST® dose by 50%. See **DOSAGE AND ADMINISTRATION.**
CYP3A4 Inhibitors	CT	Co-administration of the CYP3A4 inhibitor ketoconazole with pomalidomide increased mean exposure (AUC inf) to pomalidomide by 19% with a 90% confidence interval [10% to 28%]	Co-administration of POMALYST® with a strong CYP3A4 inhibitor, ketoconazole, had no clinically relevant effect on exposure to POMALYST®. See **DETAILED PHARMACOLOGY, Human Pharmacology-Effect of Other Medicinal Products on POMALYST®**

CT = Clinical Trial

The risk of DVT and PE may potentially be increased with the simultaneous use of erythropoietic agents or hormone replacement therapy in menopause.

Hormonal contraceptives are not recommended due to the increased risk of venous thromboembolic disease.

Drug-Food Interactions

POMALYST® can be administered without regard to food intake.

Drug-Laboratory Interactions

Interactions with laboratory tests have not been established.

Drug-Lifestyle Interactions

Confusion, fatigue, depressed level of consciousness and dizziness have been reported with the use of POMALYST®. Therefore, patients are advised to be cautious when operating machinery, or when driving.

Smoking: In 14 healthy male subjects who smoked 25 cigarettes per day for a total of 10 days, after single oral dose of 4 mg POMALYST, C_{max} of pomalidomide increased 14.4% while AUC of pomalidomide decreased 32.3%, compared to that in 13 healthy male volunteers who were non-smokers. Patients should be advised that smoking may reduce the efficacy of POMALYST® due to CYP1A2 induction.

DOSAGE AND ADMINISTRATION

Dosing Considerations

- POMALYST® (pomalidomide) capsules should be taken orally as a single dose, at about the same time each day.
- The capsules should not be opened, broken or chewed.
- POMALYST® capsules should be swallowed whole, preferably with water, either with or without food.
- Patients should be instructed to not extensively handle the capsules.
- Capsules should be kept in the blister package until it is time to take them unless it is determined by the pharmacist that it is not safe to do so.
- No dosage adjustment is required for POMALYST® based on age.
- The recommended starting dose of dexamethasone in patients >75 years of age should be reduced by half.
- Prophylactic antithrombotic medications should be recommended.

Recommended Dose and Dosage Adjustment

Recommended Dose:

The recommended starting dose of POMALYST® is:4 mg orally once daily. The starting dosage regimen for POMALYST® with dexamethasone and/or bortezomib is summarized in Table 6 .

Table 6: Dosage Regimen for Patients Treated with POMALYST® for Multiple Myeloma

Drug	Dose	Regimen
POMALYST® in combination with bortezomib and dexamethasone		
POMALYST®	4 mg orally once daily (No dosage adjustment required based on age)	Days 1-14 for each 21-day cycle until disease progression
dexamethasone	20 mg orally once daily (in patients > 75 years of age reduce dose to 10 mg)	Cycles 1-8: Days 1, 2, 4, 5, 8, 9, 11, and 12 of a 21-day cycle Cycle 9 onwards: Days 1, 2, 8, and 9 of a 21-day cycle until disease progression
bortezomib	1.3 mg/m^2 intravenous or subcutaneous (Consult the bortezomib product monograph prior to use)	Cycles 1-8: Days 1, 4, 8 and 11 of a 21-day cycle Cycle 9 onwards: Days 1 and 8 of 21-day cycle until disease progression
POMALYST® in combination dexamethasone alone		
POMALYST®	4 mg orally once daily (No dosage adjustment required based on age)	Days 1-21 of repeated 28-day cycles until disease progression
dexamethasone	40 mg orally once daily (in patients > 75 years of age reduce dose to 20 mg)	Days 1, 8, 15 and 22 of repeated 28-day cycles until disease progression

There is no indication for the use of POMALYST® in the pediatric population. The safety and effectiveness of POMALYST® has not been established (see **ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions**).

Recommended Dosage Adjustment:

Recommended Starting Dose Adjustment for POMALYST® due to Drug Interactions
The use of POMALYST® with concomitant strong CYP1A2 inhibitors should be avoided. If concomitant use of strong inhibitors of CYP1A2 (e.g. fluvoxamine, ciprofloxacin) with POMALYST cannot be avoided due to medical necessity and are co-administered with POMALYST®, reduce the POMALYST® dose by 50% and monitor closely for the occurrence of side effects. See **DRUG INTERACTIONS**.

Recommended Starting Dose Adjustment for POMALYST® in Renal Impairment:
For patients with severe renal impairment (CrCl < 30 mL/min) requiring dialysis, the recommended starting dose of POMALYST® is 3 mg daily (25% dose reduction). On hemodialysis days, patients should take POMALYST® following hemodialysis. See **WARNINGS AND PRECAUTIONS, Special Populations, OVERDOSAGE,** and **ACTION AND CLINICAL PHARMACOLOGY**, **Special Populations and Conditions**.

Recommended Starting Dose Adjustment for POMALYST® in Hepatic Impairment:
For patients with mild or moderate hepatic impairment (Child-Pugh classes A or B), the recommended starting dose of POMALYST® is 3 mg daily (25% dose reduction). For patients

with severe hepatic impairment (Child-Pugh class C), the recommended dose of POMALYST® is 2 mg (50% dose reduction) (see **WARNINGS AND PRECAUTIONS, Special Populations** and **ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions**).

Before initiating POMALYST® treatment, the neutrophil count must be ≥ 1000/μL and the platelet count must be ≥ 50,000/μL.

Dosing is continued or modified based upon clinical and laboratory findings.

Dose Modification or Interruption:

Instructions for dose interruptions and reductions for POMALYST® related to hematologic adverse reactions are outlined in the table below:

Table 7: Dose modification instructions for hematologic toxicities

Toxicity	Dose Modifications
Neutropenia • ANC* < 500/μL or Febrile neutropenia (fever ≥38.5°C and ANC <1,000/μL)	Interrupt POMALYST® treatment, follow CBC** weekly. Consider treatment with G-CSF*** if clinically indicated. When ANC returns to ≥ 1000/μL, resume POMALYST® treatment at 3 mg daily.
• For each subsequent drop < 500/μL	Interrupt POMALYST® treatment. When ANC returns to ≥ 1000/μL, resume POMALYST® treatment at 1 mg less than the previous dose.
Thrombocytopenia • Platelet Count <25,000/μL	Interrupt POMALYST® treatment, follow CBC** weekly. When platelet count returns to ≥ 50,000/μL, resume POMALYST® treatment at 3 mg daily.
• For each subsequent drop <25,000/μL	Interrupt POMALYST® treatment. When platelet count returns to ≥ 50,000/μL, resume POMALYST® treatment at 1 mg less than the previous dose.

*ANC – Absolute Neutrophil Count; **CBC – Complete Blood Count; ***G-CSF – Granulocyte- Colony Stimulating Factor

To initiate a new cycle of POMALYST®, the neutrophil count must be ≥ 1000/μL, the platelet count must be ≥ 50,000/μL.

For other Grade 3 or 4 adverse reactions judged to be related to POMALYST®, stop treatment. The treatment can be restarted at 1 mg less than the previous dose when these adverse reactions have resolved to ≤ Grade 2, at the physician's discretion. If Grade 3 or 4 adverse reactions occur after dose reductions to 1 mg, then the medicinal product should be discontinued.

Pomalidomide interruption or discontinuation should be considered for Grade 2-3 skin rash, only resumed when the perceived benefit outweighs the potential risk. Pomalidomide must be

permanently discontinued for angioedema, anaphylaxis and Grade 4 rash. If skin rash is exfoliative, purpuric or bullous, or if Stevens-Johnson syndrome, toxic epidermal necrolysis or drug rash with eosinophilia and systemic symptoms is suspected, POMALYST® must be permanently discontinued (see **WARNINGS AND PRECAUTIONS, Immune**).

POMALYST® should be interrupted pending investigation of signs and symptoms of ILD. POMALYST® should only be resumed after a thorough evaluation of the benefits and risks. See **WARNINGS AND PRECAUTIONS, Interstitial Lung Disease**.

For dosage adjustments due to toxicity with bortezomib, refer to the bortezomib Product Monograph.

Missed Dose

If less than 12 hours has elapsed since missing a dose, the patient can take the dose. If more than 12 hours has elapsed since missing a dose at the normal time, the patient should not take the dose, but take the next dose at the normal time on the following day. Patients should not take two doses at the same time.

OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

Information on overdosage of POMALYST® (pomalidomide) is limited. No cases of overdose have been reported during the clinical studies. POMALYST® doses as high as 50 mg as a single dose in healthy volunteers and 10 mg as once-daily multiple doses in multiple myeloma patients have been studied without reported serious adverse events related to overdose. No specific information is available on the treatment of overdose with POMALYST®. Pomalidomide was removed by hemodialysis.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Pomalidomide, an analogue of thalidomide, is an immunomodulatory agent with antineoplastic activity. In *in vitro* cellular assays, pomalidomide inhibited proliferation and induced apoptosis of hematopoietic tumor cells. Additionally, pomalidomide inhibited the proliferation of lenalidomide-resistant multiple myeloma cell lines and synergized with dexamethasone in both lenalidomide-sensitive and lenalidomide-resistant cell lines to induce tumor cell apoptosis. Pomalidomide enhanced T cell- and natural killer (NK) cell-mediated immunity and inhibited production of pro-inflammatory cytokines (e.g., tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6)) by monocytes. Pomalidomide demonstrated anti-angiogenic activity in a mouse tumor model and in the *in vitro* umbilical cord model.

Pomalidomide binds directly to the protein cereblon (CRBN), which is part of an E3 ligase complex that includes deoxyribonucleic acid (DNA) damage-binding protein 1(DDB1), cullin 4 (CUL4), and Roc1, and can inhibit the auto-ubiquitination of CRBN within the complex. E3

ubiquitin ligases are responsible for the poly-ubiquitination of a variety of substrate proteins, and may partially explain the pleiotropic cellular effects observed with pomalidomide treatment.

In the presence of pomalidomide *in vitro*, substrate proteins Aiolos and Ikaros are targeted for ubiquitination and subsequent degradation leading to direct cytotoxic and immunomodulatory effects. *In vivo*, pomalidomide therapy led to reduction in the levels of Ikaros in patients with relapsed lenalidomide-refractory multiple myeloma.

Cardiac Electrophysiology

A thorough QT/QTc study was conducted to evaluate the effects of pomalidomide on QT interval at single doses of 4 mg and 20 mg. A single dose of pomalidomide up to 20 mg was not associated with prolongation of the QT interval in healthy male subjects. Pomalidomide is not expected to result in clinically significant prolongation of the QT interval in patients at the approved therapeutic doses.

Pharmacokinetics

Table 8: Summary of Mean Pharmacokinetic Parameters of Single Dose Pomalidomide in Multiple Myeloma Patients

	C_{max} (ng/mL)	$t_{½}$ (h)	AUC_{0-8} (ng·h/mL)	Clearance (L/h)	Volume of distribution (L)
4 mg	78.8	7.5†	411	8.31*	73.78*

† mean apparent terminal elimination half-life in MM patients was similar across dose levels and dosing days, 1 mg qd, 2 mg qd, 10 mg qd and 5 mg qod
*in healthy male subjects
AUC_{0-8} = area under the plasma concentration time curve from time zero to the last quantifiable concentration which was 8 hours post-dose

Absorption: Pomalidomide is absorbed with a C_{max} occurring between 2 and 3 hours and is at least 73% absorbed following administration of a single oral dose. The systemic exposure (AUC) of pomalidomide increases in an approximately dose-proportional and linear manner. Accumulation is minimal or not observed. These preceding data are based on healthy subjects. Exposure in multiple myeloma patients is similar to that observed in healthy male subjects. There is minimal accumulation following multiple doses in MM patients (27-33%). There is moderate inter-subject variability (%CV) for the AUC and C_{max} in MM patients varying between 11-55%.

Pomalidomide is a substrate of P-glycoprotein *in vitro*, but this did not appear to limit its absorption in humans, where at least 73% of the drug was absorbed. Co-administration of pomalidomide with the P-gp inhibitor ketoconazole had no clinically relevant effect on exposure to pomalidomide, therefore clinically relevant drug-drug interactions are not anticipated when pomalidomide is co-administered with inhibitors of P-glycoprotein.

Coadministration with a high-fat and high-calorie meal slows the rate of absorption, decreasing plasma C_{max} by ~25%, but has minimal effect on the overall extent of absorption with an 8% decrease in AUC. Therefore, pomalidomide can be administered without regard to food intake.

Distribution: Pomalidomide has a mean apparent volume of distribution (Vd/F) between 62 and 138 L at steady state. Pomalidomide is distributed in semen of healthy subjects at a concentration of approximately 67% of plasma level at 4 hours post-dose (~T_{max}) after 4 days of once daily dosing at 4 mg. *In vitro* binding of pomalidomide enantiomers to proteins in human plasma ranges from 12% to 44% and is not concentration dependent. It is not known if pomalidomide or its metabolites are present in human milk. Pomalidomide was detected in milk of lactating rats following administration to the mother. Because of the potential for adverse reactions in nursing infants from pomalidomide, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Metabolism: Pomalidomide is the major circulating component (approximately 70% of plasma radioactivity) *in vivo* in healthy subjects who received a single oral dose of [^{14}C]- pomalidomide (2 mg). No metabolites were present at >10% relative to parent or total radioactivity in plasma.

Pomalidomide is extensively metabolized prior to excretion in humans via multiple pathways including CYP-mediated metabolism and non-CYP dependent hydrolysis. The predominant metabolic pathways of excreted radioactivity are hydroxylation with subsequent glucuronidation, or hydrolysis. *In vitro*, CYP1A2 and CYP3A4 were identified as the primary enzymes involved in the CYP-mediated hydroxylation of pomalidomide, with additional minor contributions from CYP2C19 and CYP2D6.

Administration of pomalidomide in smokers, with smoking tobacco known to induce the CYP1A2 isoform, increased exposure to pomalidomide compared to that exposure to pomalidomide observed in non-smokers. In 14 healthy male subjects who smoked 25 cigarettes per day for a total of 10 days, after single oral dose of 4 mg POMALYST, C_{max} of pomalidomide increased 14.4% while AUC of pomalidomide decreased 32.3%, compared to that in 13 healthy male volunteers who were non-smokers.

Co-administration of pomalidomide with the strong CYP3A4/5 inhibitor ketoconazole, or the strong CYP3A4/5 inducer carbamazepine, had no clinically relevant effect on exposure to pomalidomide. Co-administration of the strong CYP1A2 inhibitor fluvoxamine with pomalidomide in the presence of ketoconazole, increased mean exposure (AUC inf) to pomalidomide by 107% with a 90 % confidence interval [91% to 124%] compared to pomalidomide plus ketoconazole. In a second study to evaluate the contribution of a CYP1A2 inhibitor alone to metabolism changes of pomalidomide, a single dose of pomalidomide was given on day 5 of fluvoxamine dosing (steady state). Co-administration of fluvoxamine alone with pomalidomide increased mean exposure (AUC inf) to pomalidomide by 125% with a 90% confidence interval [98% to 157%] compared to pomalidomide alone and increased the half-life of pomalidomide from 5.97 hours (pomalidomide alone) to 13.09 hours (pomalidomide plus fluvoxamine). The use of POMALYST® with concomitant strong CYP1A2 inhibitors should be avoided. If concomitant use of strong inhibitors of CYP1A2 (e.g. fluvoxamine, ciprofloxacin with POMALYST cannot be avoided due to medical necessity and are co-administered with

POMALYST®, reduce the POMALYST® dose by 50%. See **DRUG INTERACTIONS** and **DOSAGE AND ADMINISTRATION**.

Excretion: Pomalidomide is eliminated with a median plasma half-life of approximately 9.5 hours in healthy subjects and approximately 7.5 hours in subjects with multiple myeloma. Pomalidomide has a mean total body clearance (CL/F) of 7-10 L/hr.

Following a single oral administration of [^{14}C]-pomalidomide (2 mg) to healthy subjects, approximately 73% and 15% of the radioactive dose was eliminated in urine and feces, respectively, with approximately 2% and 8% of the dosed radiocarbon eliminated as pomalidomide in urine and feces. The three predominant metabolites in urine (formed via hydrolysis or hydroxylation with subsequent glucuronidation) accounted for approximately 23%, 17%, and 12%, respectively, of the dose in the urine.

CYP dependent metabolites account for approximately 43% of the total excreted radioactivity, while non-CYP dependent hydrolytic metabolites account for 25%, and excretion of unchanged pomalidomide accounted for 10%.

Special Populations and Conditions

Pediatrics: No pharmacokinetic data are available in patients under 18 years of age. POMALYST® was evaluated in an open-label, Phase 1 dose-finding study conducted in 26 pediatric patients (range: 5 to 17 years of age) with recurrent, progressive, or refractory central nervous system (CNS) tumours. The majority of patients experienced disease progression within two months of the first dose. The safety and effectiveness of POMALYST® in this pediatric population has not been established.

Geriatrics: Pharmacokinetic studies have not been carried out in the geriatric population.

Gender: The effects of gender on the pharmacokinetics of pomalidomide have not been studied.

Race: Pharmacokinetic differences due to race have not been studied.

Hepatic Insufficiency: Patients with serum total bilirubin > 2.0 mg/dL were excluded from clinical studies. Administration of POMALYST® should be avoided in patients with serum bilirubin greater than 1.5 X ULN and AST/ALT greater than 3.0 X ULN. In a dedicated study, the pharmacokinetic parameters were changed in hepatically impaired patients (defined by Child-Pugh criteria, n=8 per group) compared to healthy patients. Mean exposure to pomalidomide increased by 51% (90% CI 9%-110%) in mildly hepatically impaired patients (Child-Pugh A) compared to healthy patients. Mean exposure to pomalidomide increased by 58% (90% CI 13%-119%) in moderately hepatically impaired patients (Child-Pugh B) compared to healthy patients. Mean exposure to pomalidomide increased by 72% (90% CI 24%-138%) in severely hepatically impaired patients (Child-Pugh C) compared to healthy patients. Dose adjustment is recommended in patients with hepatic impairment (see **DOSAGE AND ADMINSTRATION**).

Renal Insufficiency: Population pharmacokinetic analyses showed that the pomalidomide pharmacokinetic parameters were not remarkably affected in patients with moderate or severe renal impairment (defined by creatinine clearance or estimated glomerular filtration rate [eGFR]) compared to patients with normal renal function (CrCl ≥60 mL/minute). Mean normalized AUC

exposure to pomalidomide was 98.2% (90% CI 77.4%-120.6%) in moderate renal impairment patients (eGFR ≥30 to ≤45mL/minute/1.73 m^2) compared to patients with normal renal function. Mean normalized AUC exposure to pomalidomide was 100.2% (90% CI 79.7%-127.0%) in severe renal impairment patients not requiring dialysis (CrCl <30 or eGFR <30 mL/minute/1.73 m^2) compared to patients with normal renal function.
Mean normalized AUC exposure to pomalidomide increased by 35.8% (90% CI 7.5%-70.0%) in severe renal impairment patients requiring dialysis (CrCl <30mL/ minute requiring dialysis) compared to patients with normal renal function. In patients with severe renal impairment requiring dialysis, the estimated dialysis clearance is approximately 12 L/h which is higher than pomalidomide total body clearance, indicating hemodialysis will remove pomalidomide from the blood circulation.

Dosage adjustment is recommended for patients with severe renal impairment requiring dialysis (see **DOSAGE AND ADMINISTRATION**).

STORAGE AND STABILITY

Store at 15-30ºC. Keep out of the reach of children.

SPECIAL HANDLING INSTRUCTIONS

Currently, no published data are available regarding the cutaneous absorption of pomalidomide. Most health care institutions recommend that latex gloves be worn while handling chemotherapeutic agents. Health care providers may consider wearing gloves when directly handling POMALYST® (pomalidomide) capsules, along with standard hand washing. Females who could become pregnant, or who plan to become pregnant can handle POMALYST® capsules if they are using latex gloves.

Patients should be instructed to not extensively handle or open the capsules and to maintain storage of capsules in blister packs until ingestion wherever possible. If there is contact with non-intact POMALYST® capsules or the powder contents, the exposed area should be washed with soap and water.

Repackaging of POMALYST® must only be done on exceptional circumstances. This should only be done by pharmacists.

DOSAGE FORMS, COMPOSITION AND PACKAGING

POMALYST® (pomalidomide) capsules are packaged in blister packs with aluminum push through foil.

Each capsule contains pomalidomide, mannitol, pregelatinized starch, and sodium stearyl fumarate.

The additional composition of the different capsule shells is provided in the table below.

Table 9: **Strengths and Description of POMALYST® Capsules**

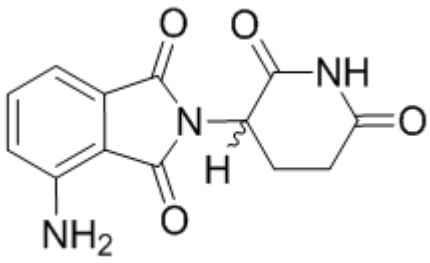
Strength	Markings	Non-medicinal Composition	Colour	Package size
1 mg	POML† 1 mg*	Gelatin, titanium dioxide, FD&C blue 2, yellow iron oxide	Dark blue opaque and yellow opaque	21count blisters
2 mg	POML 2 mg†	Gelatin, titanium dioxide, FD&C blue 2, yellow iron oxide, FD&C red 3	Dark blue opaque and orange opaque	21count blisters
3 mg	POML 3 mg†	Gelatin, titanium dioxide, FD&C blue 2, yellow iron oxide	Dark blue opaque and green opaque	21count blisters
4 mg	POML 4 mg†	Gelatin, titanium dioxide, FD&C blue 1, FD&C blue 2	Dark blue opaque and blue opaque	21count blisters

*Imprint is in white and black ink; †Imprint is in white ink

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper name:	Pomalidomide
Chemical name:	(RS)-4-Amino-2-(2,6-dioxo-piperidin-3-yl)-isoindoline-1,3-dione CAS: 4-amino-2-(2,6-dioxo-3-piperidinyl)-1H-Isoindole-1,3(2H)-dione
Molecular formula and molecular mass:	$C_{13}H_{11}N_3O_4$, 273.24 g/mol
Structural formula:	
Physicochemical properties:	Pomalidomide is a yellow powder. It is very slightly soluble in organic solvents and practically insoluble in water. Pomalidomide is non-hygroscopic and has an onset of melting at approximately 319°C. The pH of pomalidomide in aqueous solution is 6.1. It has one asymmetric carbon atom and is produced as a racemic mixture.

CLINICAL TRIALS

The efficacy and safety of POMALYST® in the treatment of patients with multiple myeloma has been evaluated in open-label, active-controlled Phase 3 studies as described in Table 10.

Table 10: Summary of Pivotal Clinical Trials in Multiple Myeloma Patients

Study and Trial Design	Dosage, route of administration and duration	Study patients
CC-4047-MM-007 (OPTIMISMM) Phase III, multi-centre, randomised, open-label study comparing treatment with POMALYST® in combination with dexamethasone and bortezomib to treatment with dexamethasone and bortezomib in previously treated adult patients with relapsed or refractory multiple myeloma, who had received at least one prior regimen, including lenalidomide.	Patients were randomized in a 1:1 ratio to 1 of 2 treatment arms and treated to progression or intolerable adverse events. POMALYST® 4 mg on Days 1 to 14 of each 21-day cycle. Bortezomib 1.3 mg/m^2/dose in both study arms on Days 1, 4, 8 and 11 of a 21-day cycle for Cycles 1 to 8; and on Days 1 and 8 of a 21-day cycle for Cycles 9 and onwards. Dexamethasone 20 mg/day (≤ 75 years old) or 10 mg/day (> 75 years old) in both study arms on Days 1, 2, 4, 5, 8, 9, 11 and 12 of a 14-day cycle for Cycles 1 to 8; and on Days 1, 2, 8 and 9 of each subsequent 21-day cycle from Cycles 9 onwards.	N = 559 POMALYST®, dexamethasone and bortezomib = 281 dexamethasone and bortezomib = 278
CC-4047-MM-003 Phase III multi-center, randomized, open-label study. comparing POMALYST® in combination with dexamethasone with HD-dex in previously treated adult patients with relapsed and refractory multiple myeloma, who had received at least two prior treatment regimens, had failed both lenalidomide and bortezomib, and had demonstrated disease progression on the last therapy.	Patients were randomized in a 2:1 ratio to 1 of following 2 treatment arms: POMALYST®+-dexamethasone (POMALYST 4 mg/day on Days 1-21 and dexamethasone 40 mg on Days 1, 8, 15, and 22 of a 28-day cycle) (Patients > 75 years of age received dexamethasone 20 mg.) or; HD-dex (40 mg on Days 1 through 4, 9 through 12, and 17 through 20 of a 28-day cycle. (Patients > 75 years of age received dexamethasone 20 mg.)	N = 455 POMALYST®, dexamethasone = 302 HD-dex = 155

POMALYST® in Combination with Dexamethasone and Bortezomib in Patients with Previously Treated Multiple Myeloma

Study demographics and trial design

The efficacy and safety of POMALYST® in combination with bortezomib and dexamethasone was compared with bortezomib and dexamethasone in study CC-4047-MM-007. Key eligibility criteria included patients with multiple myeloma who had received 1-3 prior antimyeloma regimens and demonstrated disease progression on or after the last therapy. Patients were also required to receive prior treatment with a lenalidomide containing regimen. Patients that received bortezomib-containing prior antimyeloma therapy were eligible, provided they did not progress during therapy or within 60 days of the last dose of bortezomib containing therapy under the 1.3 mg/m^2/dose twice weekly dosing schedule. Approximately 70% of patients were refractory to lenalidomide (71.2% in POMALYST®, dexamethasone and bortezomib arm and, 68.7 % in dexamethasone and bortezomib arm). Refractory is defined as nonresponsive (at least minimal response not achieved or progression within 60 days of last dose) to the medication the last time it was received by the patient. Approximately, 40% of patients were in 1st relapse and approximately 73% of patients received bortezomib as prior treatment. Patients were stratified at randomization by age (≤ 75 versus > 75), number of prior anti myeloma regimens (1 versus >1), and β_2M at screening (< 3.5 mg/L versus ≥ 3.5 mg/L - ≤ 5.5 mg/L versus > 5.5 mg/L).

The baseline patient and disease-related characteristics of the patients were generally consistent among the 2 arms (see Table 11).

The primary efficacy endpoint was progression-free survival (PFS), defined as the time between the randomisation and disease progression, or death, whichever is earlier. Response was assessed by an Independent Response Adjudication Committee (IRAC) according to the IMWG criteria using the intent to treat (ITT) population as the primary analysis. Other important efficacy endpoints were objective response rate (ORR), duration of response (DoR), and overall survival (OS).

Table 11: Summary of Patient Demographics and Baseline Disease Characteristics

	POMALYST®+ dex+ bortezomib (N=281)	**dex+ bortezomib (N=278)**
Age (years)		
Median (min, max)	67 (29, 87)	68 (27, 89)
Age Distribution, n (%)		
≤ 65 years	123 (43.8)	120 (43.2)
> 65 years	158 (56.2)	158 (56.8)
> 75 years	46 (16.4)	47 (16.9)
Sex, n (%)		
Male	155 (55.2)	147 (52.9)
Female	126 (44.8)	131 (47.1)

Table 11: Summary of Patient Demographics and Baseline Disease Characteristics (continued)

	POMALYST®+ dex+ bortezomib (N=281)	dex+ bortezomib (N=278)
ISS Stage at Study Entry, n (%)[a]		
I	149 (53.0)	138 (49.6)
II	85 (30.2)	90 (32.4)
III	47 (16.7)	50 (18)
Cytogenetic Abnormality, n (%)		
High risk[b]	61 (21.7)	49 (17.6)
Not high risk	137 (48.8)	132 (47.5)
Distribution of Prior Anti-Myeloma Lines[c] , n (%)		
1	111 (39.5)	117 (41.4)
≥ 2	170 (60.5)	163 (58.6)
Exposure to Prior Anti-Myeloma Therapies, n (%)		
Immunomodulatory Agents	**281 (100)**	**278 (100)**
Lenalidomide	281 (100)	278 (100)
Proteasome Inhibitors	**212 (75.4)**	**213 (76.6)**
Bortezomib	201 (71.5)	203 (73)
Refractory to Common PriorAnti-Myeloma Drugs, n (%)		
Immunomodulatory agents	**202 (71.9)**	**193 (69.4)**
lenalidomide	200 (71.2)	191 (68.7)
Proteasome inhibitors	**37 (13.2)**	**37 (13.3)**
Bortezomib[d]	24 (8.5)	32 (11.5)
Refractory to Last Anti-Myeloma Therapy, n (%)	**196 (69.8)**	**184 (66.2)**
ECOG Performance Status, n (%)		
0	149 (53.0)	137 (49.3)
1	121 (43.1)	119 (42.8)
2	11 (3.9)	22 (7.9)
CrCl at Diagnosis, n (%)		
<30 mL/min	11 (3.9)	10 (3.6)
30 - <45 mL/min	26 (9.3)	28 (10.1)

Table 11: Summary of Patient Demographics and Baseline Disease Characteristics (continued)

	POMALYST®+ dex+ bortezomib (N=281)	dex+ bortezomib (N=278)
45 - <60 mL/min	54 (19.2)	38 (13.7)
60 - <80 mL/min	71 (25.3)	80 (28.8)
≥80 mL/min	119 (42.3)	122 (43.9)

[a] International Staging System is calculated using baseline values of Albumin and Beta-2-microglobulin.
[b] High-risk is defined as presence of cytogenetic abnormality in at least one or more of the following cytogenetic abnormalities: Del(17p), t(4;14), t(14;16).
[c] A therapeutic line is defined by subject's progression status. Only a regimen after disease progression is counted as a new line.
[d] Bortezomib-refractory subjects were eligible provided they did not have PD during therapy or within 60 days of the last dose of bortezomib containing therapy under the 1.3 mg/m^2/dose twice weekly dosing schedule.
Data cut-off date: 26 Oct 2017

Study results

The median duration of treatment was 8.8 months (12 treatment cycles) in the POMALYST®, dexamethasone and bortezomib arm and 4.9 months (7 treatment cycles) in the dexamethasone and bortezomib arm.

The efficacy results are summarized in Table 12 below. The final analysis of PFS, the primary endpoint with 26 Oct 2017 data cutoff, was conducted on 316 events (57% of the ITT population). The PFS was significantly longer in the POMALYST®, dexamethasone, bortezomib arm than in dexamethasone, bortezomib arm: HR 0.61 (95% CI: 0.49, 0.77), p-value <0.0001. Kaplan-Meier curve for PFS for the ITT population is provided in Figure 1 .

As per the pre-defined interim analysis for OS (26 Oct 2017 data cutoff), after a median follow-up period of 15.9 months, the difference in OS between treatment arms (HR = 0.98, 95% CI: 0.73, 1.32; p = 0.894) did not cross the prespecified superiority boundary. With the overall event rate of 31.5%, the OS data are not considered mature.

Table 12: Summary of overall efficacy data (ITT population)

	POMALYST®+dex+ bortezomib (N = 281)	dex+ bortezomib (N = 278)
PFS IRAC (months)		
Median[a] time (95% CI) [b]	11.20 (9.66, 13.73)	7.10 (5.88, 8.48)
HR [c] (95% CI), p-value[d]	0.61 (0.49, 0.77), <0.0001	
Censored, n (%)	127 (45.2)	116 (41.7)
Progressed/Died, n (%)	154 (54.8)	162 (58.3)
ORR IRAC, n (%)	82.2 %	50.0%

Table 12: Summary of overall efficacy data (ITT population) (Continued)

	POMALYST®+dex+ bortezomib (N = 281)	dex+ bortezomib (N = 278)
sCR	9 (3.2)	2 (0.7)
CR	35 (12.5)	9 (3.2)
VGPR	104 (37.0)	40 (14.4)
PR	83 (29.5)	88 (31.7)
SD	32 (11.4)	106 (38.1)
PD	11 (3.9)	16 (5.8)
OR (95% CI) [e], p-value[f]	5.02 (3.35, 7.52), <0.001	
DoR IRAC (months)		
Median[a] time (95% CI) [b]	13.7 (10.94, 18.10)	10.94 (8.11, 14.78)
HR[c] (95% CI)	0.76 (0.56, 1.02)	
OS (months)		
Median[a] time (95% CI) [b]	NE (28.48, NE)	31.24 (27.01, NE)
HR[c] (95% CI)	0.98 (0.73, 1.32)	
Died	87 (31.0)	89.(32.0)

CI = Confidence interval; CR = Complete response; DoR = Duration of response; HR = Hazard Ratio; OR = Odds ratio; ORR = Overall response rate; OS = Overall Survival, PD = Progressive Disease, PFS = Progression free survival; PR = Partial Response; sCR = Stringent complete response, SD = Stable Disease, VGPR = Very good partial response

[a] The median is based on the Kaplan-Meier estimate.

[b] 95% CI about the median.

[c] Based on Cox proportional hazards model.

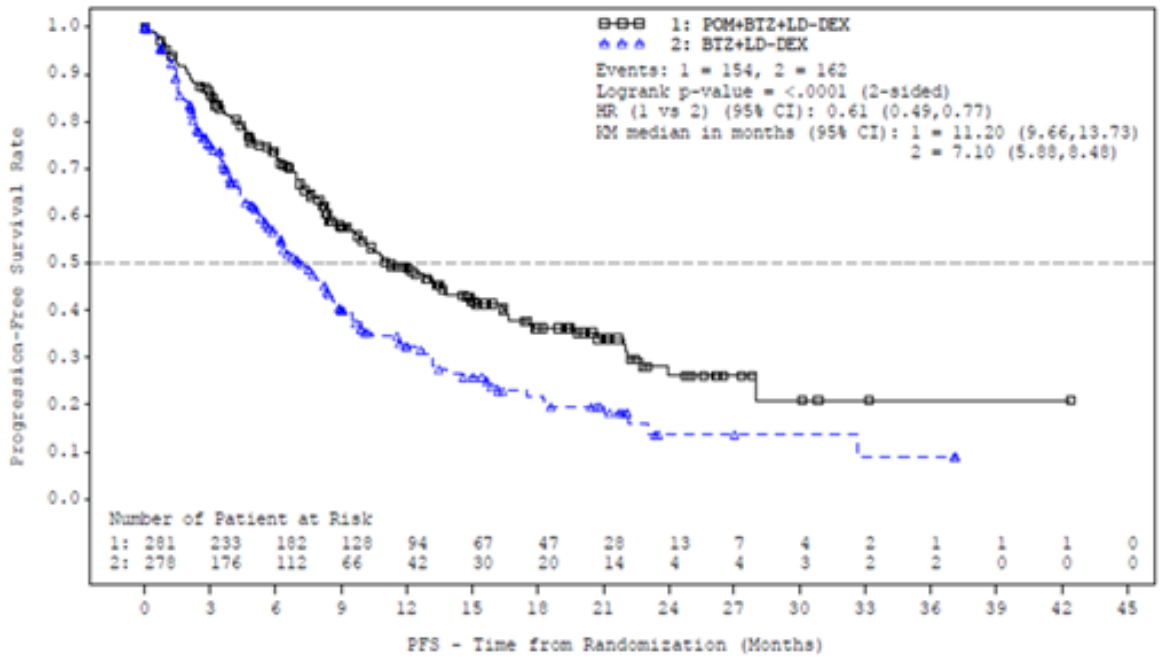
[d] The p-value is based on a stratified log-rank test.

[e] Odds ratio is for POMALYST®+dexamethasone+ bortezomib: dexamethasone+bortezomib

[f] The p-value is based on a CMH test, stratified by age (<=75 vs >75), Prior number of antimyeloma regimens (1 vs >1), and Beta-2 microglobulin at screening (< 3.5 mg/L versus ≥ 3.5 mg/l, ≤ 5.5 mg/l versus > 5.5 mg/l).

Data cut-off date: 26 Oct 2017

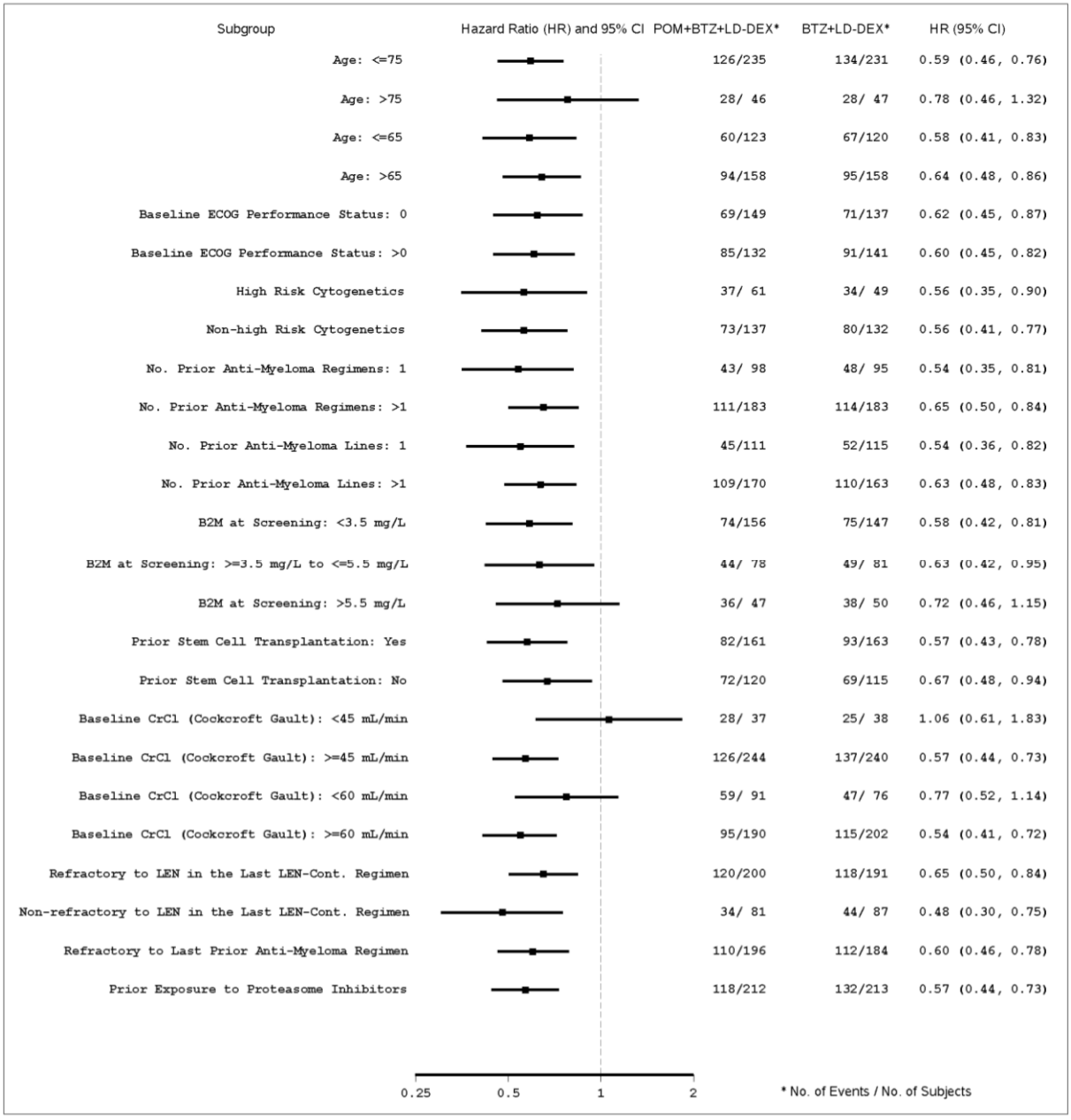
Figure 1: Progression Free Survival Based on IRAC Review of Response by IMWG Criteria (Stratified Log Rank Test) (ITT Population)



Data cut-off date: 26 Oct 2017

Subgroup analyses based on PFS hazard ratio were generally consistent across the pre-specified subgroups.

Figure 2: Forest Plot for PFS (Stratified Log Rank Test) (ITT Population)



In subjects who received only one prior line of therapy, the median PFS time was 20.73 months (95% CI: 15.11, 27.99) in the POMALYST®, dexamethasone and bortezomib arm and 11.63 months (95% CI: 7.52, 15.74) in the dexamethasone and bortezomib arm.

POMALYST®in Combination with Dexamethasone Alone for the Treatment of Patients with Relapsed and Refractory Multiple Myeloma

Study demographics and trial design

The efficacy and safety of POMALYST® (pomalidomide) in combination with dex was compared with HD-dex. Induction therapy followed by autologous stem cell transplant and consolidation/maintenance was considered as one line of therapy. Patients must have received adequate prior alkylator therapy in one of the following ways: as part of a stem cell transplant, or a minimum of 6 consecutive cycles of an alkylator-based therapy, or progression on treatment with an alkylator; provided that the patient received at least 2 cycles of an alkylator-containing therapy.

The majority of patients were male (59%) and white (79%); the median age for the overall population was 64 years (min, max: 35, 87 years). Patients with ongoing ≥ Grade 2 peripheral neuropathy or significant cardiac dysfunction (congestive heart failure [NY Heart Association Class III or IV]; myocardial infarction within 12 months of starting study; unstable or poorly controlled angina pectoris); serum total bilirubin > 2.0 mg/dL; moderate or severe renal impairment (creatinine clearance < 45 mL/min) were excluded from the study. The demographics of the study population and the baseline disease characteristics are summarized in Table 13 .

Patients assigned to the POMALYST®+dexamethasone treatment arm received low-dose aspirin, low molecular weight heparin, or other equivalent antithrombotic or anti-coagulant, as did those who had a prior history of DVT or PE, regardless of treatment arm assignment.

The primary study endpoint was progression-free survival (PFS) by International Myeloma Working Group (IMWG) criteria. The study was also powered to show an advantage in overall survival (OS), one of the secondary study endpoints.

Treatment continued until patients had disease progression. Patients who did not progress, who were intolerant to treatment, or no longer wished to receive study treatment remained in the PFS follow-up period of the treatment phase. Patients on the HD-dex arm following disease progression had the option to receive POMALYST® alone or with dexamethasone in a companion study.

Table 13: Summary of Patient Demographics and Baseline Disease Characteristics

	POMALYST®+dex (N=302)	**HD-dex (N=153)**	**Overall (N=455)**
Age (years)			
Mean (SD)	63.6 (9.33)	63.7 (9.56)	63.6 (9.40)
Median (min, max)	64.0 (35.0, 84.0)	65.0 (35.0, 87.0)	64.0 (35.0, 87.0)
Age Distribution, n (%)			
≤ 65 years	167 (55.3)	81 (52.9)	248 (54.5)
> 65 years	135 (44.7)	72 (47.1)	207 (45.5)
≤ 75 years	278 (92.1)	141 (92.2)	419 (92.1)

Table 13: Summary of Patient Demographics and Baseline Disease Characteristics (Continued)

	POMALYST®+dex (N=302)	HD-dex (N=153)	Overall (N=455)
> 75 years	24 (7.9)	12 (7.8)	36 (7.9)
Sex, n (%)			
Male	181 (59.9)	87 (56.9)	268 (58.9)
Female	121 (40.1)	66 (43.1)	187 (41.1)
Multiple Myeloma Stage before Study Entry, n (%)			
I	21 (7.0)	12 (7.8)	33 (7.3)
II	95 (31.5)	37 (24.2)	132 (29.0)
III	177 (58.6)	103 (67.3)	280 (61.5)
Missing	9 (3.0)	1 (0.7)	10 (2.2)
Time from First Pathologic Diagnosis (years)			
Mean (SD)	6.2 (4.02)	6.5 (3.63)	6.3 (3.89)
Median (min, max)	5.3 (0.6, 30.0)	6.1 (0.9, 21.1)	5.6 (0.6, 30.0)
Number of Prior Anti-Myeloma Therapies			
Mean (SD)	5.1 (2.07)	5.2 (2.25)	5.1 (2.13)
Median (min, max)	5.0 (1.0, 14.0)	5.0 (2.0, 17.0)	5.0 (1.0, 17.0)
Prior Anti-Myeloma Therapies, n (%)			
Stem Cell Transplant	214 (70.9)	106 (69.3)	320 (70.3)
Radiation Therapies	108 (35.8)	48 (31.4)	156 (34.3)
Cancer Surgeries	25 (8.3)	17 (11.1)	42 (9.2)
Refractory to Last Anti-Myeloma Therapy, n (%)			
	288 (95.4)	147 (96.1)	435 (95.6)
ECOG Performance Status, n (%)			
0	110 (36.4)	36 (23.5)	146 (32.1)
1	138 (45.7)	86 (56.2)	224 (49.2)
2	52 (17.2)	24 (16.3)	77 (16.9)
3	0 (0)	3 (2.0)	3 (0.7)
Missing	2 (0.7)	3 (2.0)	5 (1.1)

SD=standard deviation

Table 14: Exposure to Prior Anti-Myeloma Therapy in > 1 Subject in Either Treatment Arm by Class and Preferred Term (ITT Population)

Class/Preferred Term[a]	POMALYST®+dex (N=302)	HD-Dex (N=153)	Overall (N=455)
Subjects with at least one prior Anti-MM Drug	**302 (100.0)**	**153 (100.0)**	**455 (100.0)**
Corticosteroids	**302 (100.0)**	**153 (100.0)**	**455 (100.0)**
Dexamethasone	294 (97.4)	152 (99.3)	446 (98.0)
Prednisolone	150 (49.7)	83 (54.2)	233 (51.2)
Methylprednisolone	12 (4.0)	13 (8.5)	25 (5.5)
Betamethasone	3 (1.0)	0 (0.0)	3 (0.7)
Immunomodulatory Agents	**301 (99.7)**	**152 (99.3)**	**453 (99.6)**
Lenalidomide	301 (99.7)	152 (99.3)	453 (99.6)
Thalidomide	173 (57.3)	93 (60.8)	266 (58.5)
Proteasome Inhibitors	**301 (99.7)**	**153 (100.0)**	**454 (99.8)**
Bortezomib	301 (99.7)	153 (100.0)	454 (99.8)
Carfilzomib	4 (1.3)	3 (2.0)	7 (1.5)
Alkylators	**299 (99.0)**	**150 (98.0)**	**449 (98.7)**
ASCT	214 (70.9)	106 (69.3)	320 (70.3)
Cyclophosphamide	214 (70.9)	110 (71.9)	324 (71.2)
Melphalan	146 (48.3)	71 (46.4)	217 (47.7)
Ifosfamide	10 (3.3)	7 (4.6)	17 (3.7)
Anthracyclines	**172 (57.0)**	**101 (66.0)**	**273 (60.0)**
Doxorubicin	143 (47.4)	83 (54.2)	226 (49.7)
Pegylated Liposomal Doxorubicin Hydrochloride	25 (8.3)	6 (3.9)	31 (6.8)
Idarubicin	11 (3.6)	14 (9.2)	25 (5.5)
Epirubicin	10 (3.3)	7 (4.6)	17 (3.7)
Liposomal Doxorubicin Hydrochloride	7 (2.3)	6 (3.9)	13 (2.9)
Alkaloids	**139 (46.0)**	**82 (53.6)**	**221 (48.6)**
Vincristine	109 (36.1)	70 (45.8)	179 (39.3)
Etoposide	51 (16.9)	22 (14.4)	73 (16.0)
Vindesine	0 (0.0)	3 (2.0)	3 (0.7)

Table 14: Exposure to Prior Anti-Myeloma Therapy in > 1 Subject in Either Treatment Arm by Class and Preferred Term (ITT Population) (Continued)

Class/Preferred Term[a]	POMALYST®+dex (N=302)	HD-Dex (N=153)	Overall (N=455)
Nitrosureas	**86 (28.5)**	**42 (27.5)**	**128 (28.1)**
Bendamustine	71 (23.5)	33 (21.6)	104 (22.9)
Carmustine	19 (6.3)	11 (7.2)	30 (6.6)
Lomustine	2 (0.7)	3 (2.0)	5 (1.1)
Other Investigational Products[b]	**59 (19.5)**	**32 (20.9)**	**91 (20.0)**
Platinum	**35 (11.6)**	**14 (9.2)**	**49 (10.8)**
Cisplatin	33 (10.9)	14 (9.2)	47 (10.3)

ASCT = Autologous stem cell transplant;
[a] Preferred terms are based on World Health Organization Drug Dictionary March 2011 and listed in descending order of frequency of POMALYST®+dex Group.
Preferred terms with the same main component are combined. Only 9 classes are included in this table. ASCT is included in the alkylator class.
[b] This category includes products not approved for MM
Data cutoff: 07 Sep 2012

Study results

Progression Free Survival (PFS)

PFS by Independent Response Adjudication Committee (IRAC) review based on IMWG criteria in the intent-to-treat (ITT) population is presented in Table 15. Kaplan-Meier curve of PFS time for the ITT population based on IRAC review by IMWG criteria is provided in Figure 3 .

Identical results were obtained by IRAC review based on European Group for Blood and Marrow Transplantation (EBMT) criteria in the ITT population.

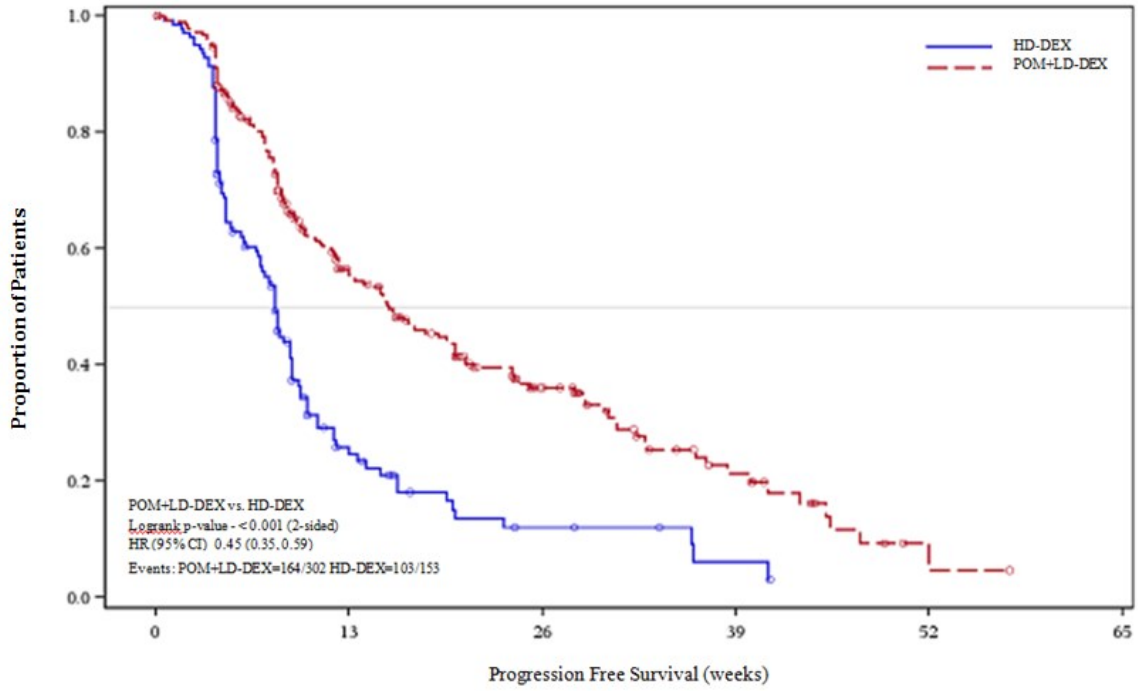
PFS was evaluated in several relevant subgroups: gender, age. ECOG performance status, cytogenetic risk, creatinine clearance, baseline albumin levels, and microglobulin. Regardless of the subgroup evaluated, PFS was generally consistent with that observed in the ITT population for both treatment groups.

Table 15: PFS Time by IRAC Review Based on IMWG Criteria (ITT Population)

	POMALYST®+dex (N=302)	HD-dex (N=153)
PFS		
Censored, n (%)	138 (45.7)	50 (32.7)
Progressed/Died, n (%)	164 (54.3)	103 (67.3)
PFS Time (weeks)		
Median[a]	15.7	8.0
Two sided 95% CI[b]	[13.0, 20.1]	[7.0, 9.0]
Hazard Ratio (POMALYST®+dex:HD-dex) 2-Sided 95% CI[c]	0.45 [0.35, 0.59]	
Log-Rank Test Two sided P-Value[d]	< 0.001	

[a] The median is based on Kaplan-Meier estimate.
[b] 95% confidence interval about the median PFS time.
[c] Based on Cox proportional hazards model comparing the hazard functions associated with treatment groups, stratified by age(≤75 vs >75), diseases population (refractory to both lenalidomide and bortezomib vs not refractory to both drugs), and prior number of anti myeloma therapy (=2 vs >2).
[d] The p-value is based on a stratified log-rank test with the same stratification factors as the above Cox model.
Note: CI=Confidence interval
Data cutoff: 07 Sep 2012

Figure 3: PFS Based on IRAC Review of Response by IMWG Criteria (ITT Population)



Data cutoff: 07 Sep 2012

Time to Progression (TTP)

TTP, defined as the time from randomization to disease progression, was performed as a sensitivity analysis for PFS. Median TTP by IRAC review based on IMWG criteria in the ITT population was 20.1 weeks (95% CI: 16.1, 28.1) in the POMALYST®+dexamethasone group compared with 8.3 weeks (95% CI: 7.7, 9.6) in the HD-dex group. The hazard ratio was 0.42 (95% CI: 0.31, 0.56, $p < 0.001$).

Overall Survival

Overall survival was a key secondary study endpoint, and is summarized in Table 16 for the ITT population. Median overall survival time from the interim analysis for the POMALYST®+dexamethasone group was 55 weeks. Median OS time for the HD-dex arm was 35 weeks; however, approximately 29% of subjects in this treatment arm received POMALYST® after progression on HD-dex. The 1-year event free rate was 51% (± 3%) for the POMALYST®+dexamethasone group and 39% (± 4%) for the HD-dex group.

Kaplan-Meier curve for overall survival for the ITT population is provided in Figure 4. Overall survival was evaluated in several relevant subgroups: gender, age. ECOG performance status, cytogenetic risk, creatinine clearance, baseline albumin levels, and microglobulin. For most of the subgroups evaluated, overall survival was generally consistent with that observed in the ITT population for both treatment groups.

Table 16: Overall Survival (ITT Population)

	POMALYST®+dex (N=302)	**HD-dex (N=153)**
Censored, n (%)	157 (52.0)	71 (46.4)
Died, n (%)	145 (48.0)	82 (53.6)
Median[a] Survival Time (weeks)	55.4	35.1
Two sided 95% CI[b]	[45.3, 67.3]	[29.9, 47.1]
Hazard Ratio [Two sided 95% CI[c]]	0.74 [0.56, 0.97]	
Log-Rank Test Two sided P-Value[d]	0.028	

[a] The median is based on Kaplan-Meier estimate.

[b] 95% confidence interval about the median progression free survival time.

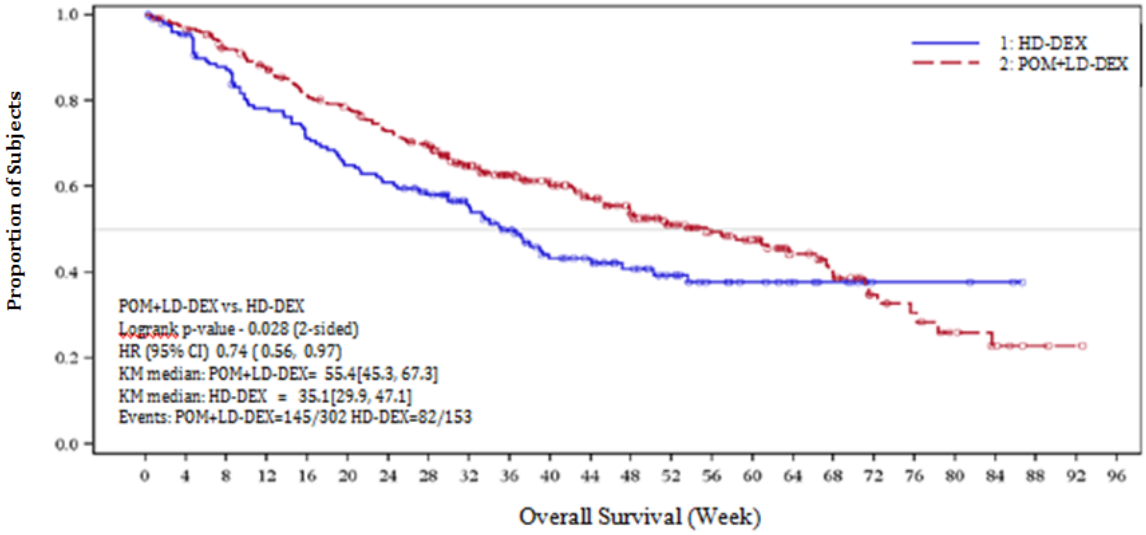
[c] Based on Cox proportional hazards model comparing the hazard functions associated with treatment groups.

[d] The p-value is based on an unstratified log-rank test.

CI=Confidence interval.

Data cutoff: 01 March 2013

Figure 4: Kaplan-Meier Curve of Overall Survival (ITT Population)



Data cutoff: 01 March 2013

Response Rate

Response rates by IRAC review based on IMWG criteria are summarized in Table 17 for the ITT population. Consistent results were observed in response rates by IRAC review based on EBMT criteria.

Table 17: Myeloma Response Rates by IRAC (Based on Best Response Assessment Using IMWG Criteria) (ITT Population)

Statistics	**POMALYST®+dex (N=302)**	**HD-dex (N=153)**
CR or VGPR or PR	50 (16.6)	6 (3.9)
Stable disease or PD or NE[a]	252 (83.4)	147 (96.1)
p-value[b]	< 0.001	
Odds ratio (95% CI)[c]	4.86 [2.03, 11.61]	
p-value[d]	< 0.001	

SCR = stringent complete response; CR = complete response; VGPR = very good partial response; PR = partial response; PD= progressive disease; NE = response not evaluable

[a] Including patients who did not have any response assessment data, or whose only assessment was response not evaluable.

[b] Probability from Fisher Exact test.

[c] Odds ratio is for POMALYST®+dex:HD-dex. CI=Confidence Interval.

[d] p-value is based on a Cox proportional hazards model test stratified by age (≤75 vs >75), diseases population (refractory to both lenalidomide and bortezomib vs not refractory to both drugs), and prior number of anti-myeloma therapy (=2 vs >2).

Data cutoff:07 Sep 2012

DETAILED PHARMACOLOGY

Pomalidomide has multiple modes of action, including tumoricidal, immunomodulatory, and anti-inflammatory effects. The tumoricidal activity of pomalidomide has been tested in a number of MM cell lines and demonstrates a wide range of activities. Pomalidomide was active at inhibiting proliferation of MM cell lines selected for resistance to dexamethasone, melphalan, doxorubicin, or mitoxantrone.

In a series of *in vitro* studies, pomalidomide exhibited potent inhibition of tumor necrosis factor-alpha (TNF-α) activity and other pro-inflammatory cytokines and chemokines in lipopolysaccharide-stimulated human peripheral blood mononuclear cells (PBMCs). A number of observations link TNF-α function in the bone marrow microenvironment in promoting MM. TNF-α triggers survival, proliferation, MAPK and NF-kB activation, BCL3 and adhesion molecule expression, and migration by MM cells. Multiple myeloma cells produce TNF-α in vivo, and TNF-α levels are elevated in MM patient bone marrow and serum. TNF-α gene polymorphisms are significantly associated with an increased risk of MM. Bone marrow stromal cells and mesenchymal progenitor cells derived from MM patients produce significantly more TNF-α than cells from normal controls. TNF-α contributes to osteoclast formation, and TNF-α levels in the bone marrow are significantly higher in MM patients with osteolytic bone lesions than in those without the disease. Pomalidomide's anti-TNF-α activity observed in vitro could be potentially linked to pomalidomide's mechanism of action in vivo via modulation of cytokine release from pro-tumorigenic microenvironmental cells.

In vivo, as a single agent, pomalidomide inhibited tumor growth of MM1S tumors and the addition of bortezomib, dexamethasone, or the combination of both further increased the tumor growth inhibition. In CD4 T cells costimulated with anti-CD3 monoclonal antibodies, pomalidomide enhanced proliferation, and increased production of interferon-gamma (IFN-γ) and interleukin-2 (IL-2). Pomalidomide also augmented the activity of natural killer (NK) cells and enhanced antibody-dependent cell-mediated cytotoxicity of targeted tumor cells in combination with therapeutic antibodies to tumor-specific surface antigens, and has been demonstrated to boost expansion of NK T cells in MM patients. These studies, using immune cells from healthy human volunteers, have been confirmed using both PBMCs and bone marrow mononuclear cells (BMMC) from patients with MM. Pomalidomide has also been shown to be an inhibitor of angiogenesis in in vitro and in vivo tumor models. Studies also demonstrate that pomalidomide is cytotoxic in cell lines that have been made resistant to lenalidomide. The combination of pomalidomide plus dexamethasone is synergistic at inhibiting cell proliferation and inducing apoptosis in both lenalidomide-sensitive and lenalidomide-resistant cell lines. Synergy between pomalidomide and dexamethasone was also noted in vivo in a lenalidomide-refractory H929 human plasma cell myeloma xenograft model.

Human Pharmacology

Potential for POMALYST® to Affect Other Drugs:

Pomalidomide does not inhibit CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1 or CYP3A4/5 *in vitro*. In addition, pomalidomide does not induce CYP1A2, CYP2B6, CYP2C9, CYP2C19 or CYP3A4/5 *in vitro*.

Pomalidomide is not an inhibitor of P-glycoprotein, and had little to no inhibitory effect on breast cancer resistant protein (BCRP), organic anion transporter protein (OATP)1B1, OATP1B3, organic anion transporters OAT1 and OAT3 and organic cation transporter OCT2 based on *in vitro* studies.

Pomalidomide is not anticipated to cause clinically relevant pharmacokinetic drug-drug interactions due to enzyme inhibition or induction or transporter inhibition when co-administered with substrates of these enzymes or transporters. The potential for such drug-drug interactions, including the potential impact of pomalidomide on exposure of oral contraceptives, has not been evaluated clinically.

Effect of Other Medicinal Products on POMALYST®:

Pomalidomide is partly metabolised by CYP1A2 and CYP3A4. It is also a substrate for P-glycoprotein. Co-administration of pomalidomide with the strong CYP3A4/5 and P-glycoprotein inhibitor ketoconazole, or the strong CYP3A4/5 inducer carbamazepine, had no clinically relevant effect on exposure to pomalidomide. Co-administration of pomalidomide with the strong CYP1A2 inhibitor fluvoxamine increased pomalidomide exposure. POMALYST® dose should be reduced by 50% if co-administered with a strong inhibitor of CYP1A2.

Co-administration of multiple doses of up to 4 mg pomalidomide with 20 mg to 40 mg dexamethasone (a weak to moderate inducer of several CYP enzymes including CYP3A) to patients with multiple myeloma had no effect on the pharmacokinetics of pomalidomide compared with pomalidomide administered alone.

TOXICOLOGY

Study Title	**Findings**
General Toxicology A 6-Month Toxicity Study of Pomalidomide Administered by Oral Gavage to Rats with a 1-Month Recovery Period	In rats, chronic administration of pomalidomide at doses of 50, 250, and 1000 mg/kg/day for 6 months was well tolerated. No adverse findings were noted up to 1000 mg/kg/day (175-fold exposure ratio relative to a 4-mg clinical dose).
General Toxicology A 9-month Oral Toxicity Study of Pomalidomide Administered by Nasogastric Gavage to Cynomolgus Monkeys, with an 8-Week Recovery Period	In monkeys, pomalidomide was evaluated in repeat-dose studies of up to 9 months in duration. In these studies, monkeys exhibited greater sensitivity to pomalidomide effects than rats. The primary toxicities observed in monkeys were associated with the hematopoietic/lymphoreticular systems. In the 9-month study in monkeys with doses of 0.05, 0.1, and 1 mg/kg/day, morbidity and early euthanasia of 6 animals were observed at the dose of 1 mg/kg/day and were attributed to immunosuppressive effects (staphylococcal infection, decreased peripheral blood lymphocytes, chronic inflammation of the large intestine, lymphoid depletion of lymphoid tissues, and lymphoid hypocellularity of bone marrow) at high exposures of pomalidomide (15-fold exposure ratio relative to a 4 mg clinical dose). These

	immunosuppressive effects resulted in early euthanasia of 4 monkeys due to poor health condition (watery stool, inappetence, reduced food intake, and weight loss); histopathologic evaluation of these animals showed chronic inflammation of the large intestine and villous atrophy of the small intestine. Staphylococcal infection was observed in 4 monkeys; 3 of these animals responded to antibiotic treatment and 1 died without treatment. In addition, findings consistent with acute myelogenous leukemia led to euthanasia of 1 monkey; clinical observations and clinical pathology and/or bone marrow alterations observed in this animal were consistent with immunosuppression. Minimal or mild bile duct proliferation with associated increases in ALP and GGT were also observed at 1 mg/kg/day. Evaluation of recovery animals indicated that all treatment-related findings were reversible after 8 weeks of dosing cessation, except for proliferation of intrahepatic bile ducts observed in 1 animal in the 1 mg/kg/day group. The NOAEL was 0.1 mg/kg/day (0.5-fold exposure ratio relative to a 4 mg clinical dose). Generally, similar findings were seen in shorter duration studies in monkeys that included higher dose level/exposures and also resulted in decreased peripheral blood neutrophil counts and sometimes lower red blood cell parameters.
Reproductive Toxicology A Fertility and Early Embryonic Development Study in Rats Administered Pomalidomide Orally	In a fertility and early embryonic development study in rats, pomalidomide was administered to males and female rats at doses of 25, 250, and 1000 mg/kg/day before, during, and after mating with animals at the same dose level. Uterine examination on Gestation Day 13 showed a decrease in mean number of viable embryos and an increase in postimplantation loss at all dose levels. Therefore, the No Observed Adverse Effect Level (NOAEL) for these effects was <25 mg/kg/day (AUC 24h was 39960 ng•h/mL) at this lowest dose tested, and the exposure ratio was 99-fold relative to a 4 mg clinical dose). When treated males on this study were mated with untreated females, all uterine parameters were comparable to the controls. Based on these results, the observed effects were attributed to the treatment of females.
Developmental Toxicology An Embryo-Fetal Development Study in Rats Administered Pomalidomide Orally	Pomalidomide was teratogenic in rats when administered during the period of major organogenesis. In the rat embryofoetal developmental toxicity study, malformations of absence of urinary bladder, absence of thyroid gland, and fusion and misalignment of lumbar and thoracic vertebral elements (central and/or neural arches) sometimes associated with discontinuous and misshapen ribs were observed at all dosage levels (25, 250, and 1000 mg/kg/day). There was no maternal toxicity observed in this study. Therefore, the maternal NOAEL was 1000 mg/kg/day, and the NOAEL for developmental toxicity was <25 mg/kg/day (AUC24h was 34340

	ng•h/mL on Gestation Day 17 at this lowest dose tested, and the exposure ratio was 85-fold relative to a 4 mg clinical dose).
Developmental Toxicology Oral (Stomach Tube) Developmental Toxicity Study of Pomalidomide in Rabbits	Pomalidomide was teratogenic in rabbits when administered during the period of major organogenesis. In rabbits, pomalidomide at doses ranging from 10 to 250 mg/kg produced embryo-foetal developmental malformations and variations. Increased cardiac anomalies (such as interventricular septal defect) and skeletal malformations (caudal vertebral) were seen at all dose levels. At 100 and 250 mg/kg/day, there were slight increases in post-implantation loss and slight decreases in fetal body weights. At 100 and/or 250 mg/kg/day, fetal malformations also included limb anomalies (flexed and/or rotated fore- and/or hindlimbs, unattached or absent digit) and associated skeletal malformations (not ossified metacarpal, misaligned phalanx and metacarpal, not ossified phalanx, and short not ossified or bent tibia); moderate dilation of the lateral ventricle in the brain; abnormal placement of the right subclavian artery; absent intermediate lobe in the lungs; low-set kidney; altered liver morphology; incompletely or not ossified pelvis; an increased average for supernumerary thoracic ribs and a reduced average for ossified tarsals. Slight reduction in maternal body weight gain, significant reduction in triglycerides, and significant decrease in absolute and relative spleen weights were observed at 100 and 250 mg/kg/day. The maternal NOAEL was 10 mg/kg/day, and the developmental NOAEL was <10 mg/kg/day. AUC24h was 418 ng•h/mL on Gestation Day 19 at this lowest dose tested, which was similar to that obtained from a 4 mg clinical dose. Thalidomide was used as a positive control in the study and elicited many of the same findings as pomalidomide.
Carcinogenicity	One of twelve monkeys dosed with 1 mg/kg of pomalidomide (an exposure approximately 15-fold of the exposure in patients at the recommended dose of 4 mg/per day) developed acute myeloid leukemia in a 9-month repeat-dose toxicology study.
Mutagenicity/Genotoxicity Evaluation of Pomalidomide in the Bacterial Reverse Mutation with a Confirmatory Assay Evaluation of Pomalidomide in the Chromosomal Aberrations Assay in Cultured Human Peripheral Blood Lymphocytes	Pomalidomide was not mutagenic in bacterial and mammalian mutation Ames assays, and did not induce chromosomal aberrations in human peripheral blood lymphocytes in vitro or micronuclei formation in polychromatic erythrocytes in bone marrow of rats administered doses up to 2000 mg/kg/day.

Evaluation of Pomalidomide in the *In Vivo* Rat Bone Marrow Micronucleus Assay	
Immunotoxicity A 28-Day Immunotoxicity Study of Pomalidomide Administered by Nasogastric Gavage to Cynomolgus Monkeys Followed By a 30-Day Recovery Period	Oral administration of pomalidomide at 2 mg/kg/day for 28 days impaired primary and secondary humoral immune responses (attenuated anti-KLH IgM and IgG antibody production) and resulted in mild to moderate decreases in circulating peripheral lymphocytes (CD20+ B-lymphocytes, CD3+ T-lymphocytes, CD3+/CD4+ T-helper lymphocytes, and CD3+/CD8+ T-cytotoxic lymphocytes, CD3-/CD16+ NK cells, and CD3-/CD14+ monocytes), correlating with mild to moderate bone marrow lymphocyte hypocellularity as well as marked lymphoid depletion of the thymus, spleen (including lympholysis and/or increased red pulp cellularity), and the mandibular and mesenteric lymph nodes. There were no effects on granulocyte, monocyte, and NK cell function. One male was euthanized in poor clinical condition. Clinical and anatomic pathology findings were reversible.

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PART III: CONSUMER INFORMATION

Pr POMALYST®
pomalidomide

This leaflet is part III of a three-part "Product Monograph" published when POMALYST® was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about POMALYST®. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

POMALYST® can only be given to patients who are registered in and meet all conditions of the RevAid® program. RevAid® is a controlled distribution program of POMALYST®.

What the medication is used for:
POMALYST® is used to treat adults with multiple myeloma. This is a cancer of plasma cells (a type of white blood cell found in the bone marrow).

POMALYST® is either used with
- dexamethasone and bortezomib for patients who:
  - have already had at least one prior treatment regimen including lenalidomide, and
  - had their disease worsen on their last treatment.

Or
- dexamethasone for patients whose disease has gotten worse after at least two other treatments including lenalidomide and bortezomib.

What it does:
POMALYST® works in the bone marrow. It stimulates the immune system to attack the growth of cancerous myeloma cells. POMALYST® can also slow down the growth of cancer cells.

POMALYST® when used with dexamethasone and/or bortezomib can stop multiple myeloma from getting worse.

When it should not be used:

Do not take POMALYST® if:
- You are pregnant
- You are at risk of becoming pregnant
- You become pregnant during POMALYST® treatment
- You are breastfeeding
- You are a male patient and are unable to follow or comply with the contraceptive measures of the RevAid® Program.
- You are allergic to pomalidomide, lenalidomide or thalidomide or any of the other ingredients in POMALYST®

Female patients who can get pregnant should not take POMALYST® unless all conditions of the RevAid® program are met.

What the medicinal ingredient is:
Pomalidomide

What the nonmedicinal ingredients are:
Each capsule contains mannitol, pregelatinized starch, and sodium stearyl fumarate. The additional composition of the different capsule strengths is provided in the table below.

Strength	Imprint	Composition	Colour	Package size
1 mg	POML 1 mg	Gelatin, titanium dioxide, FD&C blue #2, yellow iron oxide	Dark blue opaque and yellow opaque	21 count blisters
2 mg	POML 2 mg	Gelatin, titanium dioxide, FD&C blue #2, yellow iron oxide, FD&C red #3	Dark blue opaque and orange opaque	21 count blisters
3 mg	POML 3 mg	Gelatin, titanium dioxide, FD&C blue #2, yellow iron oxide	Dark blue opaque and green opaque	21 count blisters
4 mg	POML 4 mg	Gelatin, titanium dioxide, FD&C blue #1, FD&C blue #2	Dark blue opaque and blue opaque	21 count blisters

What dosage forms it comes in:
Capsules. Each capsule contains 1 mg, 2 mg, 3 mg, or 4 mg of pomalidomide.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

POMALYST® should only be prescribed by a doctor experienced in the use of anti-cancer drugs and registered with the RevAid® controlled distribution program.

Serious side effects may occur with the use of POMALYST® and could include:

- **birth defects (deformed babies) or death of an unborn baby and spontaneous abortion**
- **decrease in the production of blood cells resulting in very low levels of white blood cells (neutropenia) and of platelets (thrombocytopenia)**
- **infections, which can be life-threatening**
- **blood clots in the veins (Deep Vein Thrombosis) and in the lung (Pulmonary Embolism)**
- **liver problems. Treatment with POMALYST® may lead to a higher risk of liver problems which may cause death**
- **severe allergic reaction called anaphylaxis**
- **reactivation of Hepatitis B.** This is when a previous viral infection of the liver becomes active again. This can be life threatening.
- **severe skin reactions, which can be life threatening.** These can include Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN) and drug reaction with eosinophilia and systemic symptoms (DRESS).
- **tumor lysis syndrome.** This is caused by the fast breakdown of cancer cells. When this happens they release their contents, leading to higher or lower levels of certain other chemicals in your blood.

POMALYST® is only available under a controlled distribution program called RevAid®.

BEFORE you use POMALYST® talk to your doctor or pharmacist if you:

- are pregnant or are planning to get pregnant
- are breastfeeding
- have blood problems
- have or have had heart problems (heart attack or an irregular heartbeat)
- smoke, have high blood pressure or high cholesterol levels
- have ever had an allergic reaction such as rash, itching, swelling, feeling dizzy or trouble breathing while taking related medicines called 'thalidomide' or 'lenalidomide'
- have had previous hepatitis B infection.

During treatment with pomalidomide (the active ingredient in POMALYST®), some other cancers have been reported. Your healthcare professional will monitor you for the signs of some cancers.

POMALYST® may cause birth defects. In order to take this drug you must meet the following conditions:

1. Females who can get pregnant:

- Discuss birth control with your health care provider.
- Use at least two effective methods of birth control at the same time.
- Use these two effective methods of birth control:
  - For at least 4 weeks before starting POMALYST® treatment
  - During interruptions of POMALYST® treatment
  - During POMALYST® treatment
  - For at least 4 weeks after stopping POMALYST® treatment
- You must have two negative pregnancy tests before starting treatment:
  - The first 7-14 days prior to starting treatment
  - The second within 24 hours of starting treatment.
- You must have negative pregnancy tests during treatment:
  - Once weekly for the first 4 weeks
  - Once every 4 weeks (or once every 2 weeks if your period is irregular) for

the duration of treatment and during treatment interruption

- You must have a final pregnancy test 4 weeks after stopping POMALYST®.

Any method of birth control can fail. Contact your doctor immediately if you think you may be pregnant. Be sure to also contact your doctor if you miss your period or experience unusual menstrual bleeding.

2. Males:

- POMALYST® is present in the sperm of males who take this drug. Use a condom every time you have sexual intercourse with a woman who is pregnant or can get pregnant. This must be done even if you have undergone a successful vasectomy. The condom must be used while:
  - You are taking POMALYST®
  - During interruptions of treatment
  - For 4 weeks after stopping POMALYST®
- Do not donate sperm while taking POMALYST® and for 4 weeks after stopping POMALYST®.
- Inform your sexual partner who can get pregnant that:
  - You are taking POMALYST®
  - There is a risk of birth defects, stillbirths, and spontaneous abortions if a fetus is exposed to your sperm.
  - You must use a condom.

Contact your doctor immediately if you think your female partner becomes pregnant while you are taking POMALYST®.

3. All Patients:

- Do not give blood while you take POMALYST® and for at least 4 weeks after stopping POMALYST®
- Do not share POMALYST® with other people
- Do not take POMALYST® if you are not enrolled in or do not meet the requirements of the RevAid® controlled distribution program.

POMALYST® is not recommended for use in children under 18 years of age.

Driving and using machines: Before you perform tasks that may require special attention, wait until you know how you respond to POMALYST®. If you feel dizzy or tired, do not drive or use tools or machines.

INTERACTIONS WITH THIS MEDICATION

Tell your healthcare provider about all the medicines you take including prescription and nonprescription medicines, vitamins and herbal supplements. It is possible that POMALYST® and other medicines may affect each other causing serious side effects.

Drugs that may interact with POMALYST® include: fluvoxamine, Hormonal Replacement Therapy, and Hormonal Contraception (estrogens and progestins).

POMALYST® may cause confusion, fatigue, depressed level of consciousness, and dizziness. Do not drive or operate machinery until you know how POMALYST® affects you.

Smoking can make treatment with POMALYST® less effective.

Know the medicines you take. Keep a list of them to show your healthcare provider and pharmacist.

PROPER USE OF THIS MEDICATION

Take POMALYST® exactly as prescribed.

Swallow capsules whole with water once a day. Take your dose at about the same time each day.

Do not break, chew, or open your capsules.

If you have kidney problems and are receiving hemodialysis, take your POMALYST® after hemodialysis, on hemodialysis days.

Usual dose:

Starting dose for POMALYST® in combination with dexamethasone and bortezomib: 4 mg by mouth, once per day on days 1-14 of each 21 day cycle.

Starting dose for POMALYST® in combination with dexamethasone alone: 4 mg by mouth, once per day on days 1-21 of each 28 day cycle.

Your starting dose of POMALYST® may be different. This will happen if you:

- have liver problems; or
- have kidney problems and are receiving hemodialysis; or
- are taking certain medicines.

Your doctor may change your dose during treatment. Your doctor will also decide the total duration of therapy that you need. It will depend on your response to the treatment.

Females who could become pregnant, or who plan to become pregnant must handle POMALYST® capsules if they are using latex gloves. This is important to remember for anyone helping you with your medication.

You will have regular blood tests during your treatment with POMALYST®. Your blood will be tested once every week during your first 8 weeks of treatment, and at least monthly after that. Your healthcare provider may adjust your dose of POMALYST® or interrupt your treatment based on the results of these tests and on how you are feeling.

Overdose:

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:
If less than 12 hours have passed since missing a dose, take the dose. If more than 12 hours have passed since missing a dose at the normal time, do not take the dose. Take the next dose at the normal time on the following day. Do not take 2 doses at the same time.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medicines, POMALYST® can have side effects. These are not all the possible side effects that may be experienced when taking POMALYST. If any side effects not listed here are experienced, or these bother you or do not go away, tell your healthcare professional.

Side effects include:

- tiredness
- rash, itching
- fever
- flu (influenza), nose, throat and sinus infections
- swelling of arms or legs
- changes in taste (dysgeusia)
- inflammation of mouth and lips (stomatitis)
- diarrhea, nausea, constipation, vomiting, loss of appetite, indigestion (dyspepsia), bloating (abdominal distension)
- weight loss
- abdominal pain, pelvic pain, back pain, chest pain, muscle spasm
- falls
- difficulty breathing / breathlessness (dyspnea)
- cough
- dizziness
- headache
- tremor
- difficulty sleeping

POMALYST can cause abnormal blood test results. Your healthcare professional will decide when to perform blood tests and will interpret the results.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Very Common	**Peripheral neuropathy:** numbness or tingling in feet or hands		✓	
	Neutropenia, neutropenic sepsis, leukopenia, lymphopenia (low levels of white blood cells): chills, fever, sweating, any signs of infection		✓	
	Anemia (low levels of red blood cells): fatigue, pale skin, shortness of breath, weakness		✓	
	Thrombocytopenia (low levels of platelets in the blood): bleeding from the gums or other sites, or abnormal bleeding, bruising		✓	
	Infections including chest infections, pneumonia, bronchitis, bronchial pneumonia: fever, chills, fatigue, cough, shortness of breath, coughing up thick yellow or green mucous, fast heartbeat; **urinary tract infection:** frequent urination, burning or painful urination, cloudy urine		✓	
Common	**Bone pain**	✓		
	Venous thromboembolism including deep vein thrombosis (blood clot in a blood vessel): pain with arm or leg swelling and redness**; pulmonary embolism (blood clot in the lungs):** shortness of breath, sudden chest pain or difficulty breathing			✓
	Confusion		✓	

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Common	**Urinary retention:** difficulty urinating	✓		
	Depressed level of consciousness: altered mental state			✓
	Vertigo: dizziness, spinning sensation	✓		
	Cataract: clouding of the lens of the eye, blurry or dim vision, eye pain		✓	
	Depression: feeling sad		✓	
	Kidney failure: lack of urine, shortness of breath, confusion			✓
	Hypotension (low blood pressure): lightheadedness, dizziness or fainting		✓	
	Hypertension (high blood pressure): headache, shortness of breath		✓	
Rare	**Tumor lysis syndrome** (the sudden, rapid death of cancer cells due to treatment): nausea, shortness of breath, irregular heartbeat, lack of urine, cloudy urine, severe muscle weakness, seizures			✓
	Allergic reactions (anaphylactic reactions, angioedema, urticaria): rapid swelling of the face, lips, tongue and throat; breathing or swallowing problems, red itchy welts on skin			✓
	Severe dermatologic reactions including Stevens-Johnson Syndrome or toxic epidermal necrolysis (rare skin reactions): peeling or blistered skin, changes in the appearance of your skin			✓
	Hepatitis / reactivation of hepatitis (inflammation of the liver): itchy skin, yellowing of skin and whites of eyes, pale coloured stools, dark coloured urine, abdominal pain			✓
	Lung disease or lung inflammation (pneumonitis): shortness of breath, dry cough, fatigue			✓
Very Rare	**Basal and squamous cell carcinoma** (certain types of skin cancer): changes in the appearance of your skin or growths on your skin			✓
Unknown	**Drug reaction with eosinophilia and systemic symptoms** (DRESS; rare reaction to some medicines): flu-like symptoms, rash on the face which may extend all over the body, fever			

This is not a complete list of side effects. If you have any unexpected effects after receiving POMALYST®, ask your doctor or pharmacist.

HOW TO STORE IT

Store POMALYST® at 15-30°C. Keep out of the reach and sight of children.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- **Report online at https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html**
- **Call toll-free at 1-866-234-2345**
- **Complete a Canada Vigilance Reporting Form and:**
  - **Fax toll-free to 1-866-678-6789, or**
  - **Mail to: Canada Vigilance Program**
    Health Canada
    Postal Locator 1908C
    Ottawa, Ontario
    K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

The information in this document is current as of the last revision date shown below. The most current information can be found at: www.RevAid.ca
or by contacting the sponsor, Celgene, at:
1-888-RevAid1 (1-888-738-2431) or visiting
www.celgenecanada.net.

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Last revised: August 21, 2019