PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

PrDARZALEX® SC

daratumumab injection

1800 mg/15 mL (120 mg/mL) Solution for Subcutaneous Injection

Professed Standard

Antineoplastic, monoclonal antibody

ATC code L01FC01

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RECENT MAJOR LABEL CHANGES

1 Indications	11/2024
4 Dosage and Administration, 4.2 Recommended Dose and Dosage Adjustment	11/2024
7 Warnings and Precautions	11/2024
7 Warnings and Precautions, 7.1.1 Pregnant Women	11/2024
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Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

This Product Monograph for DARZALEX® SC (daratumumab injection) includes information based on DARZALEX® (daratumumab for injection) which is the intravenous formulation.

1 INDICATIONS

Darzalex SC (daratumumab injection) is indicated:

- in combination with bortezomib, lenalidomide, and dexamethasone, followed by maintenance treatment in combination with lenalidomide, for the treatment of adult patients with newly diagnosed multiple myeloma who are eligible for autologous stem cell transplant.
- in combination with lenalidomide and dexamethasone, or with bortezomib, melphalan and prednisone, for the treatment of patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant.
- in combination with lenalidomide and dexamethasone, or bortezomib and dexamethasone, for the treatment of patients with multiple myeloma who have received at least one prior therapy.
- in combination with pomalidomide and dexamethasone for the treatment of patients with multiple myeloma who have received at least one prior line of therapy, including lenalidomide and a proteasome inhibitor.
- in combination with carfilzomib and dexamethasone for the treatment of patients with relapsed multiple myeloma who have received 1 to 3 prior lines of therapy.
- for the treatment of patients with multiple myeloma who have received at least three prior lines of therapy including a proteasome inhibitor (PI) and an immunomodulatory agent (IMiD), or who are refractory to both a PI and an IMiD.

  Marketing authorization was based on the primary efficacy endpoint of overall response rate demonstrated in a single-arm study. Progression-free survival and overall survival benefits cannot be characterized in a single-arm study (see 14 CLINICAL TRIALS).
- in combination with bortezomib, cyclophosphamide, and dexamethasone, for the treatment of adult patients with newly diagnosed light chain (AL) amyloidosis.

1.1 Pediatrics

Pediatrics (< 18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

1.2 Geriatrics

Geriatrics (≥65 years of age): No overall differences in effectiveness were observed between elderly and younger patients. Some differences in clinical safety have been identified between elderly and younger subjects (see 7.1.4 Geriatrics). No dose adjustments are considered necessary in elderly patients.

1.3 Cardiac disease

The safety and efficacy of Darzalex SC have not been established in AL amyloidosis patients with advanced cardiac disease (Mayo Stage IIIB or NYHA Class IIIB or IV).

2 CONTRAINDICATIONS

Darzalex SC is contraindicated for patients with a history of severe hypersensitivity to daratumumab or who are hypersensitive to any ingredient in the formulation or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

It is important to check the product labels to ensure that the appropriate formulation (SC or IV) is being given to the patient, as described.

- Darzalex SC should be administered under the supervision of a healthcare professional experienced in the treatment of cancer.
- Do not administer intravenously. Darzalex SC is for subcutaneous use only. Darzalex SC has different dosage and administration instructions than Darzalex intravenous daratumumab. Do not dilute (see 4.4 Administration).
- Pre- and post-injection medications should be administered to reduce the risk of administration-related reactions (see 4.4 Administration).

4.2 Recommended Dose and Dosage Adjustment

Recommended Dose for Multiple Myeloma

The recommended dose of Darzalex SC is 1800 mg administered subcutaneously, over approximately 3-5 minutes. See Table 1, Table 2, Table 3, Table 4, and Table 5 for the recommended dosing schedules when Darzalex SC is administered as monotherapy or as part of a combination.

Dosing Schedule:

Combination therapy with bortezomib/lenalidomide/dexamethasone (4-week cycle regimen)

The dosing schedule in Table 1 is for combination therapy with bortezomib, lenalidomide and dexamethasone (4-week cycle regimens) for the treatment of patients with newly diagnosed multiple myeloma who are eligible for autologous stem cell transplant (ASCT).

Table 1: Dosing schedule for Darzalex SC in combination with bortezomib, lenalidomide and dexamethasone ([VRd]; 4-week cycle dosing regimen)

Treatment phase	Weeks	Schedule
Induction	Weeks 1 to 8	weekly (total of 8 doses)
	Weeks 9 to 16[a]	every two weeks (total of 4 doses)
Stop for high dose chemotherapy and ASCT		
Consolidation	Weeks 17 to 24[b]	every two weeks (total of 4 doses)
Maintenance	Week 25 onwards until disease progression[c]	every four weeks

[a] First dose of the every-2-week dosing schedule is given at Week 9

[b] Week 17 corresponds to re-initiation of treatment following recovery from ASCT

[c] Discontinue Darzalex SC for patients who have achieved MRD negativity that is sustained for 12 months and have been treated on maintenance for at least 24 months.

For dosing instructions for medicinal products administered in combination with Darzalex SC, see 14 CLINICAL TRIALS, and consult the corresponding Product Monographs.

Combination therapy with lenalidomide/dexamethasone or pomalidomide/dexamethasone, and Monotherapy (4-week cycle regimens)

The dosing schedule in Table 2 is for combination therapy with 4-week cycle regimens (e.g. lenalidomide or pomalidomide) and for monotherapy as follows:

- combination therapy with lenalidomide and low-dose dexamethasone for patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant (ASCT).
- combination therapy with lenalidomide and low-dose dexamethasone for patients with multiple myeloma who have received at least one prior therapy.
- combination therapy with pomalidomide and dexamethasone for patients with multiple myeloma who have received at least one prior line of therapy, including lenalidomide and a proteasome inhibitor.
- monotherapy for patients with multiple myeloma who have received at least three prior lines of therapy including a PI and an IMiD, or who are refractory to both a PI and an IMiD.

Table 2: Dosing schedule for Darzalex SC monotherapy and in combination with lenalidomide/dexamethasone or pomalidomide/dexamethasone (4-week cycle dosing regimens)

Weeks	Schedule
Weeks 1 to 8	weekly (total of 8 doses)
Weeks 9 to 24[a]	every two weeks (total of 8 doses)
Week 25 onwards until disease progression[b]	every four weeks

[a] First dose of the every 2-week-dosing schedule is given at Week 9
[b] First dose of the every 4-week-dosing schedule is given at Week 25

For dosing instructions for medicinal products administered in combination with Darzalex SC, see 14 CLINICAL TRIALS, and consult the corresponding Product Monographs.

Combination therapy with carfilzomib and dexamethasone (4-week cycle regimen)

The Darzalex SC dosing schedule in Table 3 is for combination therapy with carfilzomib and dexamethasone (4-week regimen) for patients with relapsed multiple myeloma who have received one to three prior lines of therapy:

Table 3: Dosing schedule for Darzalex SC in combination with carfilzomib and dexamethasone, (4-week cycle dosing regimens)

Weeks	Schedule
Weeks 1 to 8	weekly (total of 8 doses)
Weeks 9 to 24[a]	every two weeks (total of 8 doses)
Week 25 onwards until disease progression[b]	every four weeks

[a] First dose of the every 2-week-dosing schedule is given at Week 9
[b] First dose of the every 4-week-dosing schedule is given at Week 25

In the CANDOR Study of Darzalex in combination with carfilzomib and dexamethasone, carfilzomib was administered twice-weekly (20/56 mg/m^2). For further details and dosing instructions for medicinal products administered with Darzalex SC, see 14 CLINICAL TRIALS, and consult the corresponding Product Monographs.

Combination therapy with bortezomib, melphalan and prednisone (6-week cycle regimens)

The dosing schedule in Table 4 is for combination therapy with bortezomib, melphalan and prednisone (6-week cycle regimen) for patients with newly diagnosed multiple myeloma ineligible for ASCT.

Table 4: Darzalex SC dosing schedule in combination with bortezomib, melphalan and prednisone ([VMP]; 6-week cycle dosing regimen)

Weeks	Schedule
Weeks 1 to 6	weekly (total of 6 doses)
Weeks 7 to 54[a]	every three weeks (total of 16 doses)
Week 55 onwards until disease progression[b]	every four weeks

[a] First dose of the every-3-week dosing schedule is given at Week 7
[b] First dose of the every-4-week dosing schedule is given at Week 55

Bortezomib is given twice weekly at Weeks 1, 2, 4 and 5 for the first 6-week cycle, followed by once weekly at Weeks 1, 2, 4 and 5 for eight more 6-week cycles. Melphalan (9 mg/m^2) and prednisone (60 mg/m^2) are given on days 1-4 of each cycle. For more information on the VMP dose and dosing schedule when administered with Darzalex SC, see 14 CLINICAL TRIALS.

Combination therapy with bortezomib/dexamethasone (3-week cycle regimens)

The dosing schedule in Table 5 is for combination therapy with bortezomib and dexamethasone (3-week cycle regimen) for patients with multiple myeloma who have received at least one prior therapy.

Table 5: Dosing schedule for Darzalex SC with bortezomib/dexamethasone (3-week cycle dosing regimens)

Weeks	Schedule
Weeks 1 to 9	weekly (total of 9 doses)
Weeks 10 to 24[a]	every three weeks (total of 5 doses)
Week 25 onwards until disease progression[b]	every four weeks

[a] First dose of the every 3-week dosing schedule is given at Week 10
[b] First dose of the every 4-week dosing schedule is given at Week 25

For dosing instructions for medicinal products administered in combination with Darzalex SC, see 14 CLINICAL TRIALS, and consult the corresponding Product Monographs.

Recommended Dose for AL Amyloidosis

The Darzalex SC dosing schedule in Table 6 is for combination therapy with bortezomib, cyclophosphamide and dexamethasone (4-week cycle regimen) for patients with AL amyloidosis.

The recommended dose is Darzalex SC 1800 mg administered subcutaneously, over approximately 3-5 minutes, according to the following dosing schedule:

Table 6: Darzalex SC dosing schedule for AL amyloidosis in combination with bortezomib, cyclophosphamide and dexamethasone ([VCd]; 4-week cycle dosing regimen)

Weeks	Schedule
Weeks 1 to 8	weekly (total of 8 doses)
Weeks 9 to 24[a]	every two weeks (total of 8 doses)
Week 25 onwards until disease progression or a maximum of 2 years[b]	every four weeks

[a] First dose of the every-2-week dosing schedule is given at Week 9

[b] First dose of the every-4-week dosing schedule is given at Week 25

For dosing instructions of medicinal products administered in combination with Darzalex SC, see 14 CLINICAL TRIALS, and consult the corresponding Product Monographs.

Dose modifications:

No dose reductions of Darzalex SC are recommended. Dose delay may be required to allow recovery of blood cell counts in the event of hematological toxicity (see 7 WARNINGS AND PRECAUTIONS). For information concerning medicinal products given in combination with Darzalex SC, consult the corresponding Product Monographs.

Table 7: Dose modification recommendations for hematological toxicities associated with Darzalex SC

Adverse Reaction	Severity[a]	Administration adjustment
Neutropenia	Grade 4	• Daratumumab administration should be withheld until neutrophil count improves to at least $1.0x10^9$/L. • The use of colony-stimulating factors (e.g. G-CSF) should be considered, according to local guidelines (see 7 WARNINGS AND PRECAUTIONS).

Thrombocytopenia	Grade 3/4	• Daratumumab administration should be withheld until platelet count improves to at least 50.0x10^9/L (see 7 WARNINGS AND PRECAUTIONS).

[a] Common Terminology Criteria for Adverse Events, Version 4.03. ALT

4.3 Reconstitution

Not applicable.

4.4 Administration

Recommended Concomitant Medications:

Pre-injection medication:

For all patients, to reduce the risk of administration-related reactions administer the following pre-medications approximately 1-3 hours prior to every dose of Darzalex SC:

Combination therapy:

- Administer 20 mg dexamethasone (or equivalent) prior to every Darzalex SC dose. When dexamethasone is the background-regimen specific corticosteroid, the dexamethasone treatment dose will instead serve as pre-medication on Darzalex SC injection days (see 14 CLINICAL TRIALS).
- Dexamethasone is given orally or intravenously prior to Darzalex SC injections.
- Additional background regimen specific corticosteroids (e.g. prednisone) should not be taken on Darzalex SC injection days when patients have received dexamethasone as a pre-medication.
- Antipyretics (oral paracetamol/acetaminophen 650 to 1000 mg).
- Antihistamine (oral or intravenous diphenhydramine 25 to 50 mg or equivalent).

Monotherapy:

- corticosteroid (methylprednisolone 100 mg, or equivalent dose of an intermediate-acting or long-acting corticosteroid) given intravenously or orally
- oral antipyretics (acetaminophen 650 to 1000 mg), plus
- oral or intravenous antihistamine (diphenhydramine 25 to 50 mg or equivalent).

Following the second Darzalex SC injection, the dose of corticosteroid may be reduced (e.g., methylprednisolone 60 mg IV).

Post-injection medication:

Administer post-injection medication to reduce the risk of delayed administration-related reactions as follows:

Combination therapy:

- Consider administering low-dose oral methylprednisolone (≤ 20 mg) or equivalent the day after Darzalex SC injection.
    - However, if a background regimen-specific corticosteroid (e.g. dexamethasone or prednisone) is administered the day after Darzalex SC injection, additional post-injection medications may not be needed (see 14 CLINICAL TRIALS).

Monotherapy:

- Administer oral corticosteroid (20 mg methylprednisolone or equivalent dose of a corticosteroid (intermediate or long-acting) in accordance with local standards) to patients the first and second day after each injection of Darzalex SC (beginning the day after the injection).

If the patient experiences no major systemic administration-related reactions (ARRs) after the first three injections, post-injection corticosteroids (excluding any background regimen corticosteroids) may be discontinued.

Additionally, for patients with a history of chronic obstructive pulmonary disease, consider the use of post-injection medications including bronchodilators (short and long acting), and inhaled corticosteroids. Following the first four injections, if the patient experiences no major systemic administration-related reactions, these inhaled post-injection medications may be discontinued.

Prophylaxis for herpes zoster virus reactivation:

Anti-viral prophylaxis should be considered for the prevention of herpes zoster virus reactivation.

Instructions for Use, Handling, and Disposal

To prevent medication errors, it is important to check the vial labels to ensure that the drug being prepared and administered is Darzalex SC and not intravenous Darzalex. Darzalex SC is not intended for intravenous administration and should be administered via subcutaneous injection only.

Darzalex SC is for single use only and is ready to use without dilution.

- Darzalex SC is compatible with polypropylene or polyethylene syringe material; polypropylene, polyethylene, or polyvinyl chloride (PVC) subcutaneous infusion sets; and stainless steel transfer and injection needles.

- Darzalex SC should be inspected visually for particulate matter and discolouration prior to administration, whenever solution and container permit. Do not use if opaque particles, discolouration or other foreign particles are present.
- Remove the Darzalex SC vial from refrigerated storage [2°C-8°C] and equilibrate to ambient temperature [15°C-30°C]. The unpunctured vial may be stored at ambient temperature and ambient light for a maximum of 24 hours. Keep out of direct sunlight. Do not shake.
- Prepare the dosing syringe in aseptic conditions.
- To avoid needle clogging, attach the hypodermic injection needle or subcutaneous infusion set to the syringe immediately prior to injection.

Storage of prepared syringe

- If the syringe containing Darzalex SC is not used immediately, store the Darzalex SC solution for up to 24 hours refrigerated followed by up to 12 hours at 15°C-25°C and ambient light.
- Discard if stored more than 24 hours of being refrigerated or more than 12 hours of being at 15°C-25°C.
- If stored in the refrigerator, allow the solution to come to ambient temperature before administration.

Administration

- Inject 15 mL (equivalent to 1800 mg) Darzalex SC into the subcutaneous tissue of the abdomen approximately 7.5 cm to the right or left of the navel over approximately 3-5 minutes. Do not inject Darzalex SC at other sites of the body as no data are available.
- Alternate injection sites for successive injections.
- Darzalex SC should never be injected into areas where the skin is red, bruised, tender, hard or areas where there are scars.
- Pause or slow down delivery rate if the patient experiences pain. In the event pain is not alleviated by slowing down the injection, a second injection site may be chosen on the opposite side of the abdomen to deliver the remainder of the dose.
- During treatment with Darzalex SC, do not administer other medications for subcutaneous use at the same site as Darzalex SC.
- Dispose of any waste material in accordance with local requirements.

4.5 Missed Dose

If a planned dose of Darzalex SC is missed, administer the dose as soon as possible and adjust the dosing schedule accordingly, maintaining the treatment interval.

5 OVERDOSAGE

There is no information on overdosage with Darzalex SC.

There is no known specific antidote for daratumumab overdose. In the event of an overdose, the patient should be monitored for any signs or symptoms of adverse effects and appropriate symptomatic treatment be instituted immediately.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

To ensure the traceability of biologic products, health professionals should record both the brand name and the non-proprietary (active ingredient) name as well as other product-specific identifiers such as the Drug Identification Number (DIN) and the batch/lot number of the product supplied.

Table 8 – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Subcutaneous (SC) injection	Solution for Subcutaneous Injection 1800 mg/15 mL (120 mg/mL)	Recombinant human hyaluronidase PH20 (rHuPH20)*, L-histidine, L-histidine hydrochloride monohydrate, L-methionine, polysorbate 20, sorbitol, water for injection.

*Recombinant human hyaluronidase PH20 (rHuPH20): an enzyme used to increase the dispersion and absorption of co-administered daratumumab.

Darzalex SC: supplied as a colourless to yellow, clear to opalescent, preservative-free solution for subcutaneous administration. Each single-dose vial contains 1800 mg daratumumab in 15 mL (120 mg/mL).

7 WARNINGS AND PRECAUTIONS

General

Darzalex SC (daratumumab injection) should only be administered under the supervision of a healthcare professional experienced in the treatment of cancer.

Darzalex SC can be used in combination with other medications; therefore, the warnings and precautions applicable for use with those medications also apply to Darzalex SC combination

therapy including the potential risk of fetal harm, the presence and transmission in sperm and blood, and prohibitions against blood and/or sperm donation. The prescribing information for all medications used in combination with Darzalex SC must be consulted before starting therapy. See 7.1.1 Pregnant Women and 7.1.2 Breast-Feeding.

Cardiovascular

Cardiac Toxicity in Patients with Light Chain (AL) Amyloidosis

Serious or fatal cardiac adverse reactions occurred in patients with light chain (AL) amyloidosis who received Darzalex SC in combination with bortezomib, cyclophosphamide, and dexamethasone (see 8 ADVERSE REACTIONS). Serious cardiac disorders occurred in 16% and fatal cardiac disorders occurred in 10% of patients. Patients with NYHA Class IIIA or Mayo Stage IIIA disease may be at greater risk. Patients with NYHA Class IIIB or IV were not studied.

Monitor patients with cardiac involvement of AL amyloidosis more frequently for cardiac adverse reaction and administer supportive care as appropriate.

Hematologic

Neutropenia/Thrombocytopenia

Darzalex SC alone or in combination with other medications increases neutropenia. In lower body weight patients receiving Darzalex SC, further increases in the rate of neutropenia and thrombocytopenia, including higher rates of Grade 3-4 events, were observed. When used in combination with background therapy, Darzalex SC increases neutropenia and thrombocytopenia induced by the background therapy (see 8 ADVERSE REACTIONS**)**.

Monitor complete blood cell counts periodically during treatment according to manufacturer's prescribing information for background therapies. Monitor patients with neutropenia for signs of infection. Darzalex SC dose delay may be required to allow recovery of blood cell counts (neutrophils or platelets). No dose reduction is recommended. Consider supportive care with transfusions or growth factors as needed.

Immune

Administration-Related Reactions

Darzalex SC can cause severe and/or serious administration-related reactions (ARRs), including anaphylactic reactions.

In clinical trials with Darzalex SC in patients with multiple myeloma (n=1056) or light chain (AL) amyloidosis (n=193), ARRs (defined as administration-related systemic reactions) were reported in approximately 8% of patients. Most ARRs occurred following the first injection and were Grade 1-2. ARRs occurring with subsequent injections were seen in 1% of patients. Severe ARRs occurred in 1% of patients treated with Darzalex SC.

The median time to onset of ARRs following Darzalex SC was approximately 3 hours (range 0.15-83 hours). The majority of ARRs occurred on the day of treatment. Delayed ARRs have occurred in 1% of patients.

Signs and symptoms of ARRs may include respiratory symptoms, such as nasal congestion, cough, throat irritation, allergic rhinitis, wheezing as well as pyrexia, chest pain, pruritis, chills, vomiting, nausea, hypotension, and blurred vision. Severe reactions have occurred, including bronchospasm, hypoxia, dyspnea, hypertension, tachycardia and ocular adverse events (including choroidal effusion, acute myopia and acute angle closure glaucoma) (see 8 ADVERSE REACTIONS).

Pre medicate patients with antihistamines, antipyretics and corticosteroids to reduce the risk of ARRs prior to treatment with Darzalex SC. Patients should be monitored and counselled regarding ARRs, especially during and following the first and second injections. If an anaphylactic reaction or life threatening (Grade 4) reactions occur, institute appropriate emergency care and permanently discontinue Darzalex SC.

To reduce the risk of delayed ARRs, administer oral corticosteroids to all patients after each injection of Darzalex SC. Additionally, consider the use of post-injection medications (e.g. inhaled corticosteroids, short and long acting bronchodilators) for patients with a history of chronic obstructive pulmonary disease to manage respiratory complications should they occur. Pre- and post-injection medications may vary when Darzalex SC is used in combination therapy. If ocular symptoms occur, interrupt Darzalex SC and seek immediate ophthalmologic evaluation prior to restarting Darzalex SC (see 4 DOSAGE AND ADMINISTRATION).

Hypogammaglobulinemia

Hypogammaglobulinemia can occur in patients treated with Darzalex SC. Immunoglobulin levels should be monitored during treatment with Darzalex SC. In patients with low immunoglobulin levels, pre-emptive measures according to local guidelines such as infection precautions, antibiotic prophylaxis and immunoglobulin replacement should be considered.

Infections

Patients treated with daratumumab in combination with background therapies of bortezomib/lenalidomide/dexamethasone, lenalidomide/dexamethasone, pomalidomide/dexamethasone, bortezomib/dexamethasone, carfilzomib/dexamethasone or cyclophosphamide/bortezomib/dexamethasone experienced a higher incidence of infections that could be severe, life-threatening and/or fatal, compared with those treated with background therapies alone (see 8 ADVERSE REACTIONS). Patients should be monitored for signs and symptoms of infection and treated promptly.

Hepatitis B Virus Reactivation

Hepatitis B Virus (HBV) reactivation, in some cases fatal, has been reported in patients treated with daratumumab. HBV screening should be performed in all patients before initiation of treatment with Darzalex SC.

For patients with evidence of positive HBV serology, monitor for clinical and laboratory signs of HBV reactivation during, and for at least six months following the end of Darzalex SC treatment. Manage patients according to current clinical guidelines. Consider consulting a hepatitis disease expert as clinically indicated.

In patients who develop reactivation of HBV while on Darzalex SC, suspend treatment with Darzalex SC and any concomitant steroids, chemotherapy, and institute appropriate treatment. Resumption of Darzalex SC treatment in patients whose HBV reactivation is adequately controlled should be discussed with physicians with expertise in managing HBV.

Monitoring and Laboratory Tests

Interference with indirect antiglobulin test (indirect Coombs test)

Daratumumab binds to CD38 found at low levels on red blood cells (RBCs) and may result in a positive indirect Coombs test. Daratumumab-mediated positive indirect Coombs test may persist for up to 6 months after the last daratumumab dose. Daratumumab bound to RBCs masks detection of antibodies to minor antigens in the patient's serum (see 9 DRUG INTERACTIONS). The determination of a patient's ABO and Rhesus (Rh) blood type are not impacted.

Patient's blood should be typed and screened prior to starting Darzalex SC. In the event of a planned transfusion notify blood transfusion centers of this interference with serological testing.

Interference with determination of complete response

Daratumumab is a human IgG kappa monoclonal antibody that can be detected on both the serum protein electrophoresis (SPE) and immunofixation (IFE) assays used for the clinical monitoring of endogenous M-protein. This interference can impact the determination of complete response and of disease progression in some patients with IgG kappa myeloma protein. In patients with persistent very good partial response, consider other methods to evaluate the depth of response (see 9 DRUG INTERACTIONS).

7.1 Special Populations

7.1.1 Pregnant Women

Risks of Darzalex SC use in pregnant women have not been assessed. Animal studies have not been conducted. However, immunoglobulin G1 (IgG1) monoclonal antibodies are known to transfer across the placenta. Mice that were genetically modified to eliminate all CD38 expression (CD38 knockout mice) had reduced bone density at birth that recovered by 5 months of age. In cynomolgus monkeys exposed during pregnancy to other monoclonal antibodies that affect leukocyte populations, infant monkeys had a reversible reduction in leukocytes.

Based on its mechanism of action, daratumumab may cause fetal myeloid or lymphoid-cell depletion and decreased bone density (see 16 NON-CLINICAL TOXICOLOGY).

Darzalex SC should not be used during pregnancy. If the patient becomes pregnant while taking this drug, the patient should be informed of the potential risk to the fetus. Defer

administering live vaccines to neonates and infants exposed to daratumumab in utero until a hematology evaluation is completed.

Women of childbearing potential should use effective contraception during treatment and for at least 3 months after cessation of Darzalex SC treatment.

In combination treatment, daratumumab is administered with bortezomib/ lenalidomide/dexamethasone, lenalidomide/dexamethasone, pomalidomide/dexamethasone, bortezomib/dexamethasone, bortezomib/melphalan/prednisone, carfilzomib/dexamethasone, or cyclophosphamide/bortezomib/dexamethasone. Lenalidomide and pomalidomide can cause embryo-fetal harm and is contraindicated for use in pregnancy due to the potential for lenalidomide and pomalidomide to cause fetal harm, including severe life-threatening human birth defects. Bortezomib has caused post-implantation loss in animals. Placental transfer studies have not been conducted with bortezomib and adequate and well-controlled studies have not been conducted in pregnant women. Carfilzomib can cause fetal harm when administered to a pregnant woman. Safe use of melphalan has not been established with respect to adverse effects on fetal development. Cyclophosphamide has a genotoxic effect and may cause fetal damage when administered to pregnant women. If cyclophosphamide is used during pregnancy, or if the patient becomes pregnant while taking this drug or after treatment, the patient should be apprised of the potential hazard to a fetus. Refer to the Product Monograph for lenalidomide, pomalidomide, bortezomib, carfilzomib, cyclophosphamide or melphalan for requirements regarding contraception and for additional details.

7.1.2 Breast-Feeding

It is not known whether daratumumab is excreted into human or animal milk or affects milk production. There are no studies to assess the effect of daratumumab on the breast-fed infant.

Human IgG is excreted in breast milk. Because the risks of daratumumab to the nursing infant are unknown, a decision should be made whether to discontinue breast-feeding, or discontinue Darzalex SC therapy, taking into account the benefit of breast feeding for the child and the benefit of Darzalex SC therapy for the woman.

As there is potential for serious adverse reactions in breast-fed infants from daratumumab administered in combination with bortezomib/lenalidomide/dexamethasone, lenalidomide and dexamethasone, or pomalidomide and dexamethasone, breast-feeding is not recommended. For daratumumab administered in combination with bortezomib/lenalidomide/dexamethasone, bortezomib and dexamethasone, or carfilzomib and dexamethasone, it is not known whether bortezomib or carfilzomib are excreted in milk. For daratumumab administered in combination with cyclophosphamide, bortezomib and dexamethasone, it is known that cyclophosphamide is passed into the breast milk. Neutropenia, thrombocytopenia, low hemoglobin, and diarrhea have been reported in children breast fed by women treated with cyclophosphamide. Women must not breastfeed during treatment with cyclophosphamide. Refer to the lenalidomide, pomalidomide, bortezomib, carfilzomib, cyclophosphamide and dexamethasone Product Monographs for

additional information.

7.1.3 Pediatrics

Pediatrics (< 18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

7.1.4 Geriatrics

Geriatrics (≥ 65 years of age): No overall differences in effectiveness were observed between elderly and younger patients. Some differences in clinical safety have been identified between elderly and younger subjects (see 8.2 Clinical Trial Adverse Reactions - Special Population: Geriatrics). No dose adjustments are considered necessary in elderly patients.

In the CANDOR study 308 patients were treated with daratumumab in combination with carfilzomib (twice-weekly) and dexamethasone (DKd). Of these, 146 patients (47%) were ≥ 65 years of age and 28 patients (9%) were ≥ 75 years of age. The incidence of serious adverse events was 52% in patients < 65 years of age, 61% in patients 65 to 74 years of age, and 57% in patients ≥ 75 years of age. Fatal treatment-emergent adverse events (TEAEs) occurred in 6% of patients < 65 years of age and 14% of patients ≥ 65 years of age. In the Kd arm, fatal TEAEs occurred in 8% of patients < 65 years of age and 3% of patients ≥ 65 years of age (see 8.2 Clinical Trial Adverse Reactions -Special Population: Geriatrics). There are increased risks for cardiovascular events in patients ≥ 75 years of age compared with patients < 75 years of age when treated with DKd.

7.1.5 Hepatic Impairment

No formal studies of Darzalex SC in patients with hepatic impairment have been conducted. No dosage adjustments are necessary for patients with mild hepatic impairment (Total Bilirubin [TB] 1.0 to 1.5 times upper limit of normal [ULN] or aspartate aminotransferase [AST] >ULN). Daratumumab has been studied in a limited number of patients with moderate (TB >1.5 to 3.0 times ULN) to severe (TB >3.0 times ULN) and therefore no dose recommendations can be made in these patient populations (see 10 CLINICAL PHARMACOLOGY).

7.1.6 Renal Impairment

No formal studies of Darzalex SC in patients with renal impairment have been conducted. No dosage adjustment is necessary for patients with renal impairment (see 10 CLINICAL PHARMACOLOGY).

7.1.7 Cardiac Disease

AL amyloidosis patients with advanced cardiac disease (Mayo Stage IIIB or NYHA Class IIIB or IV) have not been studied in clinical trials with Darzalex SC. Due to the potentially increased risk of cardiac toxicity, Darzalex SC is not recommended for use in patients with AL amyloidosis with advanced cardiac disease.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

SUBCUTANEOUS FORMULATION (Darzalex SC):

Monotherapy – Relapsed/Refractory Multiple Myeloma

The safety of Darzalex SC (1800 mg subcutaneously) and Darzalex (16mg/kg intravenously) monotherapy was evaluated in the Phase 3, randomized, open-label, active-controlled study MMY3012, which included 260 and 258 patients, respectively, with multiple myeloma who had received at least three prior lines of therapy including a PI and an IMiD, or who were refractory to both a PI and an IMiD. The only TEAEs occurring at a frequency ≥20% in either the Darzalex SC or Darzalex arm were anemia and upper respiratory tract infections. After a median study follow up of 7.46 months, the overall incidence of serious TEAEs was 26.2% in the SC arm and 29.5% in the IV arm. The only serious TEAE with a frequency ≥2% was pneumonia (SC: 5.0%; IV: 6.0%). Study treatment discontinuation due to a TEAE occurred in 6.9% of subjects in the SC group, and 8.1% in the IV group. Infusion-related reactions were reported in 12.7% of patients receiving Darzalex SC and 34.5% of patients receiving Darzalex. Neutropenia was the only TEAE reported at ≥ 5% higher frequency for Darzalex SC compared to intravenous Darzalex (Grade 3 or 4: 13.1 % vs 7.8%, respectively).

Combination Therapies in Multiple Myeloma

The safety of Darzalex SC was evaluated in combination therapy in the open-label Phase 2 Study MMY2040 including patients receiving bortezomib, melphalan and prednisone (D-VMP in patients with transplant ineligible newly diagnosed multiple myeloma [NDMM], n=67), lenalidomide and dexamethasone (D-Rd in patients with relapsed/refractory MM, n=65), or carfilzomib and dexamethasone (DKd in patients with relapsed/refractory MM, n=66). After a median study follow up of 6.5 and 7 months on the D-VMP and D-Rd cohorts, respectively, the most frequently reported TEAEs (≥20%) for subjects in the D-VMP cohort were thrombocytopenia, neutropenia, anemia, nausea, constipation, peripheral sensory neuropathy, pyrexia, diarrhea, fatigue, vomiting, lymphopenia, and upper respiratory tract infection. The most frequently reported TEAEs (≥20%) for subjects in the DRd cohort were neutropenia, diarrhea, thrombocytopenia, muscle spasms, dyspnea, anemia, upper respiratory tract infection, fatigue, constipation, and pyrexia. Based on an exploratory analysis of the safety profile after a median of 14 months follow-up, additional common TEAEs (≥20%) of insomnia and back pain were reported in the D-VMP cohort. The incidence of serious TEAEs was 37.3% in the D-VMP cohort, and 40.0% in the DRd cohort. The most common serious TEAEs (≥5% in any cohort) were pyrexia (D-VMP: 7.5%; DRd: 3.1%), pneumonia (D-VMP: 4.5%, DRd: 6.2%) and influenza (D-VMP: 1.5%; DRd: 4.6%). Based on an exploratory analysis of the safety profile in the D-Rd cohort after a median of 14 months follow-up, an additional common serious TEAE (≥5%) of diarrhea was reported (D-Rd: 6.2%). Study treatment discontinuation due to a TEAE occurred in 3.0% of subjects in the D-VMP cohort, and 4.6% of subjects in the DRd cohort. Infusion-related reactions were reported in 9.0% of patients in the D-VMP cohort

and in 9.0% of patients in the DRd cohort. In the DKd cohort, the median treatment duration was 8.3 months (range: 0 to 17 months). The most frequently reported TEAEs (≥20%) for patients in the DKd cohort were thrombocytopenia, anemia, insomnia, hypertension, diarrhea, nasopharyngitis, headache, neutropenia, asthenia, nausea, and pyrexia. The incidence of serious TEAEs was 27.3%. No serious TEAEs occurred in ≥5% of patients. Study treatment discontinuation due to a TEAE occurred in 6.1% of patients. Infusion-related reactions were reported in 4.5% of patients.

Patients who received Darzalex SC in combination with bortezomib, lenalidomide and dexamethasone

The safety of Darzalex SC in combination with bortezomib, lenalidomide and dexamethasone (D-VRd), followed by maintenance with Darzalex SC and lenalidomide, was evaluated in a Phase 3, randomized, open-label clinical study for the treatment of patients with newly diagnosed multiple myeloma patients who are eligible for ASCT (n=709). The most frequently reported TEAEs (≥20%) in the D-VRd arm were COVID-19, upper respiratory tract infection, neutropenia, thrombocytopenia, anemia, diarrhea, constipation, nausea, pyrexia, asthenia, fatigue, peripheral edema, peripheral sensory neuropathy, back pain, rash, cough, and insomnia. The overall incidence of serious TEAEs was 57.0% in the D-VRd arm and 49.3% in the VRd arm. Serious adverse events with a 2% higher incidence in the D-VRd arm compared to the VRd arm were pneumonia (D-VRd 20.3%; VRd: 10%), COVID-19 (D-VRd 8.2%; VRd: 3.7%), and atrial fibrillation (D-VRd 3.2; VRd: 0.7%). Study treatment discontinuation due to an AE occurred in 8.8% of subjects in the D-VRd group, and 21.3% in the VRd group.

Patients who received Darzalex SC in combination with pomalidomide and dexamethasone

The safety of Darzalex SC in combination with pomalidomide and dexamethasone (DPd) was evaluated in a Phase 3, randomized, open-label clinical study in multiple myeloma patients (n=299) who had received at least one prior line of therapy, including lenalidomide and a proteasome inhibitor. The most frequently reported TEAEs (≥20%) in the DPd arm were neutropenia, anemia, thrombocytopenia, leukopenia, upper respiratory tract infection, pneumonia, lower respiratory tract infection, fatigue, asthenia, pyrexia, and diarrhea. The overall incidence of serious TEAEs was 50.3% in the DPd arm and 39.3% in the Pd arm. Serious TEAEs with a 2% higher incidence in the DPd arm compared to the Pd arm were pneumonia (D-Pd 26.2% vs Pd 17.3%), neutropenia (DPd 4.7% vs Pd 2.7%), thrombocytopenia (DPD 2.7% vs PD 0.7%) and syncope (DPd 2.0% vs Pd 0%). Study treatment discontinuation due to an AE occurred in 2.0% of subjects in the DPd group, and 2.7% in the Pd group.

Combination Treatment for AL Amyloidosis

The safety of Darzalex SC (subcutaneous formulation, 1800 mg) with bortezomib, cyclophosphamide and dexamethasone (D-VCd; n=193) compared to bortezomib,

cyclophosphamide and dexamethasone (VCd; n=188) in patients with newly diagnosed AL amyloidosis was evaluated in an open-label, randomized, Phase 3 study, AMY3001. The median follow-up was 11.4 months.

The most common TEAEs occurring at a frequency ≥20% in the D-VCd arm were peripheral edema, fatigue, diarrhea, constipation, nausea, upper respiratory tract infection, peripheral sensory neuropathy, dyspnea, cough, insomnia, and anemia. The incidence of serious TEAEs was 43.0% in the D-VCd arm, and 36.2% in the VC-d arm. The most common serious TEAEs (≥5% in any cohort) were pneumonia (D-VCd 7.3%; VCd 4.8%) and cardiac failure/cardiac failure congestive (D-VCd 6.7%; VCd 5.3%). Serious adverse reactions that occurred in at least 2% more D-VCd than VCd patients included pneumonia, sepsis, and cardiac arrest. Fatal adverse reactions occurred in 11% of D-VCd patients. Fatal adverse reactions that occurred in more than one patient included cardiac arrest (3%), sudden death (3%), cardiac failure (3%), and sepsis (1%). Study treatment discontinuation due to a TEAE occurred in 4.1% of the D-VCd arm, and 4.3% of the VCd arm.

INTRAVENOUS FORMULATION (Darzalex):

The following sections present safety information from a separate Product Monograph for Darzalex intravenous formulation studies:

- **Patients with newly diagnosed multiple myeloma who are ineligible for ASCT**
- **Patients with multiple myeloma who have received at least one prior therapy**
- **Patients with multiple myeloma who have received at least three prior lines of therapy including a PI and an IMiD, or who are refractory to both a PI and an IMiD**

Patients with newly diagnosed multiple myeloma who are ineligible for ASCT:

The data described below reflect exposure to Darzalex intravenous formulation in two Phase 3 active-controlled trials that included 710 patients with multiple myeloma treated with Darzalex at 16 mg/kg in combination with either lenalidomide and dexamethasone (DRd) [Study MMY3008; n=364] or bortezomib, melphalan, and dexamethasone (D-VMP) [Study MMY3007; n=346].

Patients who received Darzalex in combination with lenalidomide and dexamethasone

The safety of Darzalex intravenous formulation in combination with lenalidomide and dexamethasone (DRd) was evaluated in a Phase 3, randomized, open-label study in patients with newly diagnosed multiple myeloma (MMY3008; n=729). The most frequently reported TEAEs (≥20%) in the DRd arm were infusion-related reactions, diarrhea, neutropenia, constipation, fatigue, peripheral edema, anemia, back pain, asthenia, nausea, insomnia, muscle spasms, bronchitis, dyspnea, weight decreased, cough, peripheral sensory neuropathy, pyrexia, upper respiratory tract infection, pneumonia, decreased appetite, and hypokalemia.

The overall incidence of serious TEAEs was 62.9% in the DRd arm and 62.7% in the Rd arm. Serious TEAEs with a 2% higher incidence in the DRd arm compared to the Rd arm were pneumonia (DRd 15.4% vs Rd 7.7%) and bronchitis (DRd 3.6% vs Rd 1.9%). Study treatment discontinuation due to an AE occurred in 7.4% of subjects in the DRd group, and 16.2% in the Rd group.

Patients who received Darzalex in combination with bortezomib, melphalan, and prednisone

The safety of Darzalex intravenous formulation in combination with bortezomib, melphalan, and prednisone (D-VMP) was evaluated in a Phase 3, randomized, open-label study in patients with newly diagnosed multiple myeloma (MMY3007; n=700). The most frequently reported TEAEs (≥20%) in the D-VMP arm were infusion-related reactions, neutropenia, thrombocytopenia, anemia, upper respiratory tract infection, pyrexia, diarrhea, nausea, and peripheral sensory neuropathy. The overall incidence of serious TEAEs was 41.6% in the D-VMP arm and 32.5% in the VMP arm. Serious TEAEs (≥2%) with at least a 2% higher incidence in the D-VMP arm compared to the VMP arm included infections (23.1% vs 11.9%), including pneumonia (D-VMP 10.1% vs VMP 3.1%). Study treatment discontinuation due to a TEAE occurred in 4.9% of subjects in the D-VMP group, and 9.0% in the VMP group.

Patients with multiple myeloma who have received at least one prior therapy:

The data described below reflect exposure to Darzalex intravenous formulation in two Phase 3 active-controlled trials that included 423 patients with multiple myeloma treated with Darzalex at 16 mg/kg in combination with either lenalidomide and dexamethasone (DRd) [Study MMY3003] or bortezomib and dexamethasone (DVd) [Study MMY3004].

Patients who received Darzalex in combination with lenalidomide/dexamethasone

The safety of Darzalex intravenous formulation in combination with lenalidomide and dexamethasone was evaluated in a Phase 3, randomized, open-label study in patients with relapsed/refractory multiple myeloma after at least one prior therapy (n=569). In MMY3003, the most frequently reported TEAEs (≥20%) in the DRd arm were infusion-related reactions, neutropenia, thrombocytopenia, anemia, diarrhea, constipation, upper respiratory tract infection, pneumonia, cough, dyspnea, nausea, fatigue, muscle spasms, insomnia, and pyrexia. The overall incidence of serious TEAEs was 54.1% in the DRd arm and 44.8% in the Rd arm. Serious TEAEs (≥2%) with at least a 2% higher incidence in the DRd arm compared to the Rd arm included infections (33.6% vs 23.8%) such as influenza (DRd 3.9% vs Rd 1.4%) and febrile neutropenia (DRd 4.2% vs Rd 1.4%). Study treatment discontinuation due to a TEAE occurred in 16.3% of subjects in the DRd group, and 13.9% in the Rd group. The most common TEAEs leading to study treatment discontinuation were pneumonia, septic shock and fatigue (each

1.4%), and general physical health deterioration (1.1%) in the DRd group, and pulmonary embolism (1.1%) in the Rd group.

Patients who received Darzalex in combination with bortezomib/dexamethasone

The safety of Darzalex intravenous formulation in combination with bortezomib and dexamethasone was evaluated in a Phase 3, randomized, open-label clinical study in multiple myeloma patients (n=498) who had received at least one prior therapy. In Study MMY3004, the most frequently reported TEAEs (≥20%) for the DVd group were infusion-related reactions, thrombocytopenia, anemia, peripheral sensory neuropathy, diarrhea, constipation, upper respiratory tract infection, cough, and fatigue. The overall incidence of serious TEAEs was 49% of patients in the DVd group and 34% in the Vd group. Serious TEAEs with at least a 2% higher incidence in the DVd arm compared to the Vd arm included anemia (DVd 3.3% vs Vd 0.4%), bronchitis (DVd 2.9% vs Vd 0.8%), thrombocytopenia (DVd 2.5% vs Vd 0.4%), atrial fibrillation (DVd 2.5% vs Vd 0%) and second primary malignancy (3.7% vs 0.4%). TEAEs resulting in treatment discontinuation occurred in 9.3% (n=22) of subjects in the DVd group, and 9.1% (n=22) in the Vd group.

Patients who received Darzalex in combination with carfilzomib/dexamethasone

The safety of Darzalex in combination with twice-weekly carfilzomib and dexamethasone (DKd) was evaluated in a Phase 3, randomized, open-label clinical study in multiple myeloma patients (n=461) who had received 1 to 3 prior lines of therapy (CANDOR study). The median duration of treatment for the DKd arm was 68.14 weeks (range: 0.1 to 100.3 weeks). In the CANDOR study, which included 153 patients in the Kd twice weekly dosing arm and 308 patients in the DKd dosing arm, the most common adverse reactions (> 20%) in either treatment arm included: thrombocytopenia, anemia, diarrhea, fatigue, respiratory tract infection, cough, and hypertension. Serious adverse events were reported in 56% of the patients in the DKd arm and 46% of the patients in the Kd arm. The most common serious adverse reactions that occurred with ≥ 2% incidences in either treatment arm were pneumonia, urinary tract infection, influenza, sepsis, pyrexia, pulmonary embolism, dyspnea, cardiac failure, acute kidney injury, anemia, and plasma cell myeloma. Grade ≥ 3 adverse events occurred in 82% of patients in the DKd arm as compared with 74% in the Kd arm. Discontinuation of any study treatment due to any adverse event occurred in 22% of patients in the DKd arm versus 25% in the Kd arm. The most common adverse reactions leading to discontinuation of any study drug were cardiac failure (n = 6, 2%) and fatigue (n = 6, 2%) in the DKd arm and cardiac failure (n = 3, 2%), hypertension (n = 3, 2%) and acute kidney injury (n = 3, 2%) in the Kd arm. The most common reaction leading to discontinuation of daratumumab was pneumonia (n = 4, 1%). The most common reactions leading to discontinuation of carfilzomib were cardiac failure (n = 6, 2%) and fatigue (n = 6, 2%) in the DKd arm and cardiac failure (n = 3, 2%), hypertension (n = 3, 2%) and acute kidney injury (n = 3, 2%) in the Kd arm. Additionally, deaths due to adverse events

within 30 days of the last dose of any study treatment occurred in 30/308 (10%) patients in the DKd arm compared with 8/153 (5%) patients in the Kd arm. The most common causes of death occurring in patients (%) in the two arms (DKd vs. Kd) was infections 14 (5%) vs. 4 (3%). The risk of fatal treatment-emergent adverse events was higher among patients ≥ 65 years of age.

Patients with multiple myeloma who have received at least three prior lines of therapy including a PI and an IMiD, or who are refractory to both a PI and an IMiD:

The data described below reflect exposure to Darzalex intravenous formulation in three pooled open label clinical studies that included 156 patients with relapsed and refractory multiple myeloma treated with Darzalex at 16 mg/kg. The median duration of Darzalex treatment was 3.3 months (range: 0.03 to 41.5 months).

Infusion-related reactions were the most frequently observed treatment-emergent adverse events [TEAEs] and occurred in 48% of patients treated at 16 mg/kg.

Other frequently reported (≥20%) adverse events included fatigue, pyrexia, upper respiratory tract infection, nausea, back pain, cough, anemia, neutropenia and thrombocytopenia.

Grade 3 or 4 TEAEs were reported for 57.1% of patients. The most commonly reported Grade 3 or 4 TEAEs (≥10%) were anemia (17%, all Grade 3), thrombocytopenia (8.3% Grade 3, 5.8% Grade 4), and neutropenia (9.6% Grade 3, 2.6% Grade 4).

The most common (≥ 2%) serious TEAEs were pneumonia (6%), general physical health deterioration, hypercalcemia and pyrexia (each at 3%), cross-match incompatible and herpes zoster (each at 2%). Four percent of patients discontinued Darzalex treatment due to an adverse event. The adverse events leading to discontinuation were general physical health deterioration, H1N1 influenza, hypercalcemia, pneumonia, and spinal cord compression. The median time to discontinuation was 21.5 days (1.0, 106.0). Adverse events leading to treatment delay were observed in 25 (16.0%) of patients, and the most frequent adverse event was infections, reported in 14 (9.0%) patients.

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

SUBCUTANEOUS FORMULATION (Darzalex SC)

Monotherapy

Study MMY3012

TEAEs in Table 9 reflect exposure to Darzalex SC (1800 mg SC injection) for a median treatment duration of 4.7 months (range: 0.03 to 12.91 months) or Darzalex (16 mg/kg IV infusion) for a median treatment duration of 5.4 months (range: 0.03; 12.16).

Table 9: Number of Subjects With 1 or More Treatment-emergent Adverse Events (≥5% in Any Treatment Arm) by MedDRA System-Organ Class, Preferred Term and Toxicity Grade; All Treated Analysis Set (Study 54767414MMY3012)

	Darzalex (N = 258)		Darzalex SC (N = 260)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
Blood and lymphatic system disorders				
Anaemia	60 (23.3%)	36 (14.0%)	68 (26.2%)	34 (13.1%)
Neutropenia	35 (13.6%)	20 (7.8%)	50 (19.2%)	34 (13.1%)
Thrombocytopenia	48 (18.6%)	35 (13.6%)	48 (18.5%)	36 (13.8%)
Lymphopenia	17 (6.6%)	16 (6.2%)	19 (7.3%)	13 (5.0%)
Leukopenia	10 (3.9%)	2 (0.8%)	18 (6.9%)	10 (3.8%)
Gastrointestinal disorders				
Diarrhoea	28 (10.9%)	1 (0.4%)	39 (15.0%)	2 (0.8%)
Nausea	28 (10.9%)	1 (0.4%)	21 (8.1%)	1 (0.4%)
Constipation	20 (7.8%)	0	14 (5.4%)	0
Vomiting	20 (7.8%)	2 (0.8%)	14 (5.4%)	1 (0.4%)
Abdominal pain*	15 (5.8%)	0	8 (3.1%)	0
General disorders and administration site conditions				
Fatigue*	40 (15.5%)	4 (1.6%)	38 (14.6%)	3 (1.2%)
Pyrexia	33 (12.8%)	2 (0.8%)	34 (13.1%)	0
Infusion related reaction**	89 (34.5%)	14 (5.4%)	33 (12.7%)	4 (1.5%)
Injection site reaction**	0	0	18 (6.9%)	0
Chills	32 (12.4%)	2 (0.8%)	15 (5.8%)	1 (0.4%)
Oedema peripheral*	16 (6.2%)	0	11 (4.2%)	0
Infections and infestations				
Upper respiratory tract infection*	56 (21.7%)	3 (1.2%)	63 (24.2%)	2 (0.8%)
Pneumonia*	27 (10.5%)	16 (6.2%)	21 (8.1%)	14 (5.4%)
Metabolism and nutrition disorders				
Hypercalcaemia	11 (4.3%)	6 (2.3%)	13 (5.0%)	4 (1.5%)
Hypokalaemia	15 (5.8%)	4 (1.6%)	11 (4.2%)	1 (0.4%)
Musculoskeletal and connective tissue disorders				
Back pain	32 (12.4%)	7 (2.7%)	27 (10.4%)	4 (1.5%)
Arthralgia	15 (5.8%)	0	19 (7.3%)	1 (0.4%)
Bone pain	9 (3.5%)	2 (0.8%)	18 (6.9%)	5 (1.9%)
Musculoskeletal chest pain	14 (5.4%)	1 (0.4%)	16 (6.2%)	3 (1.2%)
Pain in extremity	11 (4.3%)	0	16 (6.2%)	3 (1.2%)
Nervous system disorders				
Headache	22 (8.5%)	1 (0.4%)	13 (5.0%)	0
Psychiatric disorders				
Insomnia	13 (5.0%)	0	14 (5.4%)	0
Respiratory, thoracic and mediastinal disorders				
Cough*	37 (14.3%)	0	23 (8.8%)	2 (0.8%)
Dyspnoea*	28 (10.9%)	2 (0.8%)	15 (5.8%)	2 (0.8%)
Nasal congestion	13 (5.0%)	1 (0.4%)	10 (3.8%)	0
Vascular disorders				
Hypertension*	23 (8.9%)	16 (6.2%)	13 (5.0%)	8 (3.1%)

Table 9: Number of Subjects With 1 or More Treatment-emergent Adverse Events (≥5% in Any Treatment Arm) by MedDRA System-Organ Class, Preferred Term and Toxicity Grade; All Treated Analysis Set (Study 54767414MMY3012)

	Darzalex (N = 258)		Darzalex SC (N = 260)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4

*Includes a grouping of preferred terms.
**IRR includes terms indicated by investigator as a systemic infusion related reaction; ISR includes terms indicated by investigator as a local injection site reaction.
Note: Percentages in the total column were calculated with the number of subjects in each group as denominator.

Abdominal pain includes Abdominal pain upper, and Abdominal pain.; Cough includes Productive cough, and Cough.; Dyspnoea includes Dyspnoea exertional, and Dyspnoea; Fatigue includes Asthenia, and Fatigue; Hypertension includes Blood pressure increased, and Hypertension; Oedema peripheral includes Oedema, Peripheral swelling, and Oedema peripheral; Pneumonia includes Lower respiratory tract infection, Lung infection, Pneumocystis jirovecii pneumonia, and Pneumonia; Upper respiratory tract infection includes Acute sinusitis, Nasopharyngitis, Pharyngitis, Respiratory syncytial virus infection, Respiratory tract infection, Rhinitis, Rhinovirus infection, Sinusitis, and Upper respiratory tract infection.

Combination Therapies in Multiple Myeloma

Study MMY2040

TEAEs in Table 10 reflect exposure to Darzalex SC (1800 mg SC injection) in combination with bortezomib, melphalan and prednisone (D-VMP) in patients with newly diagnosed MM who are ineligible for transplant, and in combination with lenalidomide and dexamethasone (D-Rd) in subjects with relapsed or refractory MM (Table 11). The median treatment duration was 6.5 months (0.36 to 9.26 months) for D-VMP; and 7 months (0.49 to 8.97 months) for D-Rd. TEAEs in Table 12 reflect exposure to Darzalex SC (1800 mg SC injection) in combination with carfilzomib and dexamethasone (DKd) in patients with MM who have received one to three prior lines of therapy. The median treatment duration was 8.3 months (0 to 17.0 months).

Table 10: Number of Subjects With 1 or More Treatment-emergent Adverse Events (≥ 5% in Any Treatment Arm) by MedDRA System-Organ Class, Preferred Term and Toxicity Grade; D-VMP Treated Analysis Set (Study 54767414MMY2040)

	D-VMP (N=67)	
	Any Grade	Grade 3 or 4
Blood and lymphatic system disorders		
Thrombocytopenia	36 (53.7%)	23 (34.3%)
Neutropenia	25 (37.3%)	21 (31.3%)
Anaemia	24 (35.8%)	8 (11.9%)
Lymphopenia	14 (20.9%)	14 (20.9%)
Leukopenia	8 (11.9%)	4 (6.0%)
Gastrointestinal disorders		
Nausea	24 (35.8%)	0
Constipation	23 (34.3%)	0
Diarrhoea	20 (29.9%)	2 (3.0%)
Vomiting	14 (20.9%)	0
Abdominal pain*	6 (9.0%)	0
General disorders and administration site conditions		
Fatigue*	23 (34.3%)	1 (1.5%)
Pyrexia	22 (32.8%)	0
Oedema peripheral*	9 (13.4%)	1 (1.5%)
Infusion related reaction**	6 (9.0%)	0

Table 10: Number of Subjects With 1 or More Treatment-emergent Adverse Events (≥ 5% in Any Treatment Arm) by MedDRA System-Organ Class, Preferred Term and Toxicity Grade; D-VMP Treated Analysis Set (Study 54767414MMY2040)

	D-VMP (N=67)	
	Any Grade	Grade 3 or 4
Injection site erythema	5 (7.5%)	0
Injection site reaction**	4 (6.0%)	0
Malaise	4 (6.0%)	0
Infections and infestations		
Upper respiratory tract infection*	21 (31.3%)	0
Bronchitis	8 (11.9%)	0
Pneumonia*	6 (9.0%)	3 (4.5%)
Herpes zoster	5 (7.5%)	0
Urinary tract infection	5 (7.5%)	1 (1.5%)
Investigations		
Weight decreased	5 (7.5%)	0
Blood alkaline phosphatase increased	4 (6.0%)	0
Gamma-glutamyltransferase increased	4 (6.0%)	2 (3.0%)
Metabolism and nutrition disorders		
Decreased appetite	10 (14.9%)	1 (1.5%)
Hypokalaemia	5 (7.5%)	2 (3.0%)
Hypocalcaemia	4 (6.0%)	0
Hyponatraemia	4 (6.0%)	3 (4.5%)
Musculoskeletal and connective tissue disorders		
Back pain	13 (19.4%)	2 (3.0%)
Arthralgia	6 (9.0%)	0
Musculoskeletal chest pain	6 (9.0%)	0
Bone pain	4 (6.0%)	0
Nervous system disorders		
Peripheral sensory neuropathy	23 (34.3%)	1 (1.5%)
Dizziness	6 (9.0%)	0
Paraesthesia	6 (9.0%)	0
Headache	4 (6.0%)	0
Psychiatric disorders		
Insomnia	13 (19.4%)	0
Renal and urinary disorders		
Acute kidney injury	4 (6.0%)	2 (3.0%)
Respiratory, thoracic and mediastinal disorders		
Cough*	13 (19.4%)	0
Skin and subcutaneous tissue disorders		
Rash	8 (11.9%)	0
Pruritus	7 (10.4%)	0
Erythema	5 (7.5%)	0
Vascular disorders		
Hypertension	9 (13.4%)	4 (6.0%)
Hypotension	6 (9.0%)	2 (3.0%)

Key: D-VMP = Darzalex SC, bortezomib, melphalan, and prednisone.
*Includes a grouping of preferred terms.
**IRR includes terms indicated by investigator as a systemic infusion related reaction; ISR includes terms indicated by investigator as a local injection site reaction related to daratumumab administration.
Note: Percentages in the total column were calculated with the number of subjects in each group as denominator.

Abdominal pain includes Abdominal pain upper, and Abdominal pain; Cough includes Productive cough, and Cough; Fatigue includes Asthenia, and Fatigue; Oedema peripheral includes Oedema, Peripheral swelling, and Oedema peripheral; Pneumonia includes Pneumocystis jirovecii pneumonia, Pneumonia bacterial, and Pneumonia;
Upper respiratory tract infection includes Nasopharyngitis, Respiratory syncytial virus infection, Respiratory tract infection, Rhinitis, Tonsillitis, Viral pharyngitis, and Upper respiratory tract infection.

Table 11: Number of Subjects With 1 or More Treatment-emergent Adverse Events (≥ 5% in Any Treatment Arm) by MedDRA System-Organ Class, Preferred Term and Toxicity Grade; D-Rd Treated Analysis Set (Study 54767414MMY2040)

	D-Rd (N=65)	
	Any Grade	Grade 3 or 4
Blood and lymphatic system disorders		
Neutropenia	38 (58.5%)	31 (47.7%)
Thrombocytopenia	21 (32.3%)	4 (6.2%)
Anaemia	17 (26.2%)	3 (4.6%)
Leukopenia	10 (15.4%)	6 (9.2%)
Lymphopenia	10 (15.4%)	8 (12.3%)
Gastrointestinal disorders		
Diarrhoea	23 (35.4%)	2 (3.1%)
Constipation	15 (23.1%)	1 (1.5%)
Nausea	7 (10.8%)	0
Vomiting	5 (7.7%)	0
Abdominal pain*	4 (6.2%)	0
General disorders and administration site conditions		
Fatigue*	32 (49.2%)	2 (3.1%)
Pyrexia	14 (21.5%)	1 (1.5%)
Oedema peripheral	5 (7.7%)	0
Infections and infestations		
Upper respiratory tract infection*	23 (35.4%)	2 (3.1%)
Bronchitis*	9 (13.8%)	1 (1.5%)
Pneumonia*	8 (12.3%)	6 (9.2%)
Urinary tract infection	4 (6.2%)	0
Investigations		
Blood creatinine increased	7 (10.8%)	0
Weight decreased	6 (9.2%)	0
Metabolism and nutrition disorders		
Hyperglycaemia	7 (10.8%)	4 (6.2%)
Hypocalcaemia	6 (9.2%)	0
Hypokalaemia	5 (7.7%)	2 (3.1%)
Decreased appetite	4 (6.2%)	0
Musculoskeletal and connective tissue disorders		
Muscle spasms	18 (27.7%)	1 (1.5%)
Back pain	8 (12.3%)	0
Arthralgia	4 (6.2%)	1 (1.5%)
Myalgia	4 (6.2%)	0
Nervous system disorders		
Peripheral sensory neuropathy	9 (13.8%)	1 (1.5%)
Dizziness	5 (7.7%)	0
Dysgeusia	4 (6.2%)	0
Headache	4 (6.2%)	0
Tremor	4 (6.2%)	0
Psychiatric disorders		
Insomnia	10 (15.4%)	3 (4.6%)
Renal and urinary disorders		
Acute kidney injury	5 (7.7%)	2 (3.1%)
Respiratory, thoracic and mediastinal disorders		
Dyspnoea*	13 (20.0%)	2 (3.1%)
Cough*	7 (10.8%)	0
Skin and subcutaneous tissue disorders		
Rash	5 (7.7%)	0
Rash maculo-papular	4 (6.2%)	2 (3.1%)
Vascular disorders		
Hypotension	4 (6.2%)	0

Table 11: Number of Subjects With 1 or More Treatment-emergent Adverse Events (≥ 5% in Any Treatment Arm) by MedDRA System-Organ Class, Preferred Term and Toxicity Grade; D-Rd Treated Analysis Set (Study 54767414MMY2040)

	D-Rd (N=65)	
	Any Grade	Grade 3 or 4

Key: D-Rd = Darzalex SC, lenalidomide, and dexamethasone.
*Includes a grouping of preferred terms.
**IRR includes terms indicated by investigator as a systemic infusion related reaction; ISR includes terms indicated by investigator as a local injection site reaction related to daratumumab administration.
Note: Percentages in the total column were calculated with the number of subjects in each group as denominator.

Abdominal pain includes Abdominal pain upper, and Abdominal pain; Bronchitis includes Bronchitis viral, and Bronchitis; Cough includes Productive cough, and Cough; Dyspnoea includes Dyspnoea exertional, and Dyspnoea;
Fatigue includes Asthenia, and Fatigue; Pneumonia includes Lower respiratory tract infection, Lung infection, and Pneumonia; Upper respiratory tract infection includes Nasopharyngitis, Pharyngitis, Respiratory tract infection viral, Rhinitis, Sinusitis, Upper respiratory tract infection bacterial, and Upper respiratory tract infection.

Table 12: Number of Subjects With 1 or More Treatment-emergent Adverse Events (≥5%) by MedDRA System-Organ Class, Preferred Term and Toxicity Grade; DKd Treated Analysis Set (Study 54767414MMY2040)

	DKd	
	Any Grade	Grade 3 or 4
Analysis set: all treated	66	
MedDRA system organ class / Preferred term		
Blood and lymphatic system disorders		
Thrombocytopenia	34 (51.5%)	13 (19.7%)
Anaemia	24 (36.4%)	7 (10.6%)
Neutropenia	15 (22.7%)	7 (10.6%)
Lymphopenia	12 (18.2%)	8 (12.1%)
Leukopenia	6 (9.1%)	2 (3.0%)
Ear and labyrinth disorders		
Vertigo	6 (9.1%)	0
Gastrointestinal disorders		
Diarrhoea	19 (28.8%)	0
Nausea	14 (21.2%)	0
Vomiting	10 (15.2%)	0
Abdominal pain*	6 (9.1%)	0
Constipation	6 (9.1%)	0
Odynophagia	4 (6.1%)	0
General disorders and administration site conditions		
Fatigue*	26 (39.4%)	1 (1.5%)
Pyrexia	14 (21.2%)	1 (1.5%)
Oedema peripheral*	13 (19.7%)	0
Injection site reaction*	5 (7.6%)	0
Injection site erythema	4 (6.1%)	0
Infections and infestations		
Upper respiratory tract infection*	34 (51.5%)	0
Bronchitis*	8 (12.1%)	1 (1.5%)
Pneumonia*	6 (9.1%)	2 (3.0%)
Influenza	4 (6.1%)	1 (1.5%)
Investigations		
Gamma-glutamyltransferase increased	8 (12.1%)	2 (3.0%)
Alanine aminotransferase increased	7 (10.6%)	1 (1.5%)
Blood alkaline phosphatase increased	5 (7.6%)	1 (1.5%)

Table 12: Number of Subjects With 1 or More Treatment-emergent Adverse Events (≥5%) by MedDRA System-Organ Class, Preferred Term and Toxicity Grade; DKd Treated Analysis Set (Study 54767414MMY2040)

	DKd	
	Any Grade	Grade 3 or 4
Metabolism and nutrition disorders		
Hyperglycaemia	6 (9.1%)	1 (1.5%)
Decreased appetite	4 (6.1%)	0
Hypocalcaemia	4 (6.1%)	0
Musculoskeletal and connective tissue disorders		
Back pain	11 (16.7%)	1 (1.5%)
Bone pain	7 (10.6%)	2 (3.0%)
Musculoskeletal chest pain	7 (10.6%)	0
Musculoskeletal pain	7 (10.6%)	0
Muscle spasms	6 (9.1%)	0
Arthralgia	5 (7.6%)	0
Pain in extremity	4 (6.1%)	0
Spinal pain	4 (6.1%)	2 (3.0%)
Nervous system disorders		
Headache	15 (22.7%)	0
Peripheral sensory neuropathy	7 (10.6%)	0
Paraesthesia	6 (9.1%)	0
Psychiatric disorders		
Insomnia	22 (33.3%)	4 (6.1%)
Anxiety	5 (7.6%)	1 (1.5%)
Irritability	4 (6.1%)	1 (1.5%)
Respiratory, thoracic and mediastinal disorders		
Cough*	16 (24.2%)	0
Dyspnoea*	15 (22.7%)	1 (1.5%)
Rhinorrhoea	4 (6.1%)	0
Skin and subcutaneous tissue disorders		
Rash	5 (7.6%)	0
Erythema	4 (6.1%)	0
Pruritus	4 (6.1%)	0
Vascular disorders		
Hypertension*	21 (31.8%)	14 (21.2%)

Key: Dara-SC = daratumumab and recombinant human hyaluronidase for subcutaneous injection: co-formulated; DKd = daratumumab-carfilzomib-dexamethasone.
*Includes a grouping of preferred terms.
IRR includes terms indicated by investigator as a systemic infusion related reaction; ISR includes terms indicated by investigator as a local injection site reaction related to daratumumab administration.
Abdominal pain includes Abdominal pain upper, and Abdominal pain.
Bronchitis includes Bronchitis viral, and Bronchitis.
Cough includes Productive cough, and Cough.
Dyspnoea includes Dyspnoea exertional, and Dyspnoea.
Fatigue includes Asthenia, and Fatigue.
Hypertension includes Blood pressure increased, and Hypertension.
Oedema peripheral includes Generalised oedema, Peripheral swelling, and Oedema peripheral.
Percentages in the total column were calculated with the number of subjects in each group as denominator.

Study MMY3014: Darzalex SC in combination with bortezomib/lenalidomide/dexamethasone

TEAEs in Table 13 reflect exposure to Darzalex SC in combination with bortezomib, lenalidomide and dexamethasone (D-VRd), followed by maintenance with DARZALEX SC and lenalidomide for a median duration of treatment of 45.7 months (range 0.49 to 54.3 months)

and a median treatment duration of 42.2 months (range 0.07 to 53.9 months) for the bortezomib, lenalidomide and dexamethasone (VRd) followed by lenalidomide maintenance group.

Table 13: **Number of Subjects With 1 or More Treatment-emergent Adverse Events (≥ 5% in Patients Treated with D-VRd) by MedDRA System-Organ Class, Grouping of Preferred Terms and Toxicity Grade; Safety Analysis Set (Study 54767414MMY3014)**

	VRd		D-VRd	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
Analysis set: safety	347		351	
Total number of subjects with TEAE	344 (99.1%)	297 (85.6%)	349 (99.4%)	321 (91.5%)
MedDRA System Organ Class/ Preferred Term				
Blood and lymphatic system disorders				
Neutropenia*	217 (62.5%)	191 (55.0%)	256 (72.9%)	234 (66.7%)
Thrombocytopenia	119 (34.3%)	60 (17.3%)	170 (48.4%)	102 (29.1%)
Anaemia	72 (20.7%)	22 (6.3%)	78 (22.2%)	21 (6.0%)
Leukopenia	14 (4.0%)	6 (1.7%)	31 (8.8%)	13 (3.7%)
Lymphopenia	9 (2.6%)	4 (1.2%)	20 (5.7%)	14 (4.0%)
Cardiac disorders				
Atrial fibrillation	8 (2.3%)	2 (0.6%)	18 (5.1%)	9 (2.6%)
Eye disorders				
Vision blurred	16 (4.6%)	0	18 (5.1%)	1 (0.3%)
Gastrointestinal disorders				
Diarrhoea	188 (54.2%)	27 (7.8%)	214 (61.0%)	37 (10.5%)
Constipation	118 (34.0%)	6 (1.7%)	119 (33.9%)	8 (2.3%)
Nausea	58 (16.7%)	2 (0.6%)	71 (20.2%)	2 (0.6%)
Abdominal pain*	52 (15.0%)	1 (0.3%)	57 (16.2%)	2 (0.6%)
Vomiting	28 (8.1%)	3 (0.9%)	38 (10.8%)	4 (1.1%)
Dyspepsia	24 (6.9%)	1 (0.3%)	30 (8.5%)	0
Stomatitis	30 (8.6%)	20 (5.8%)	30 (8.5%)	21 (6.0%)
General disorders and administration site conditions				
Fatigue*	169 (48.7%)	27 (7.8%)	169 (48.1%)	22 (6.3%)
Pyrexia	109 (31.4%)	9 (2.6%)	111 (31.6%)	8 (2.3%)
Oedema peripheral*	81 (23.3%)	1 (0.3%)	83 (23.6%)	4 (1.1%)
Influenza like illness	33 (9.5%)	2 (0.6%)	39 (11.1%)	3 (0.9%)
Infusion related reaction[@]	0	0	21 (6.0%)	3 (0.9%)
Injection site reaction[@]	0	0	19 (5.4%)	0
Immune system disorders				
Hypogammaglobulinaemia	7 (2.0%)	1 (0.3%)	28 (8.0%)	4 (1.1%)
Infections and infestations				
Upper respiratory tract infection*	139 (40.1%)	13 (3.7%)	184 (52.4%)	8 (2.3%)
COVID-19*	87 (25.1%)	9 (2.6%)	133 (37.9%)	22 (6.3%)
Pneumonia*	58 (16.7%)	31 (8.9%)	95 (27.1%)	54 (15.4%)
Bronchitis*	40 (11.5%)	1 (0.3%)	70 (19.9%)	3 (0.9%)
Urinary tract infection	27 (7.8%)	1 (0.3%)	34 (9.7%)	4 (1.1%)
Sepsis*	16 (4.6%)	13 (3.7%)	24 (6.8%)	23 (6.6%)
Gastroenteritis	13 (3.7%)	1 (0.3%)	22 (6.3%)	2 (0.6%)
Influenza	23 (6.6%)	0	21 (6.0%)	2 (0.6%)
Herpes zoster	23 (6.6%)	1 (0.3%)	18 (5.1%)	2 (0.6%)
Investigations				
Alanine aminotransferase increased	51 (14.7%)	18 (5.2%)	57 (16.2%)	18 (5.1%)

Table 13: **Number of Subjects With 1 or More Treatment-emergent Adverse Events (≥ 5% in Patients Treated with D-VRd) by MedDRA System-Organ Class, Grouping of Preferred Terms and Toxicity Grade; Safety Analysis Set (Study 54767414MMY3014)**

	VRd		D-VRd	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
Aspartate aminotransferase increased	29 (8.4%)	7 (2.0%)	28 (8.0%)	3 (0.9%)
Gamma-glutamyltransferase increased	27 (7.8%)	13 (3.7%)	19 (5.4%)	7 (2.0%)
Blood alkaline phosphatase increased	26 (7.5%)	1 (0.3%)	18 (5.1%)	1 (0.3%)
Metabolism and nutrition disorders				
Hypokalaemia	44 (12.7%)	12 (3.5%)	51 (14.5%)	7 (2.0%)
Decreased appetite	22 (6.3%)	5 (1.4%)	30 (8.5%)	1 (0.3%)
Hypocalcaemia	27 (7.8%)	4 (1.2%)	24 (6.8%)	2 (0.6%)
Hyperglycaemia	16 (4.6%)	5 (1.4%)	18 (5.1%)	5 (1.4%)
Musculoskeletal and connective tissue disorders				
Back pain	66 (19.0%)	1 (0.3%)	80 (22.8%)	2 (0.6%)
Muscle spasms	56 (16.1%)	1 (0.3%)	67 (19.1%)	2 (0.6%)
Arthralgia	69 (19.9%)	0	62 (17.7%)	1 (0.3%)
Pain in extremity	38 (11.0%)	0	40 (11.4%)	0
Bone pain	29 (8.4%)	2 (0.6%)	29 (8.3%)	0
Myalgia	20 (5.8%)	1 (0.3%)	29 (8.3%)	1 (0.3%)
Musculoskeletal chest pain	16 (4.6%)	0	22 (6.3%)	0
Nervous system disorders				
Peripheral sensory neuropathy	179 (51.6%)	14 (4.0%)	188 (53.6%)	15 (4.3%)
Paraesthesia	42 (12.1%)	1 (0.3%)	46 (13.1%)	2 (0.6%)
Neuralgia	30 (8.6%)	1 (0.3%)	35 (10.0%)	2 (0.6%)
Headache	37 (10.7%)	0	31 (8.8%)	0
Dizziness	34 (9.8%)	0	27 (7.7%)	0
Tremor	18 (5.2%)	1 (0.3%)	27 (7.7%)	4 (1.1%)
Dysgeusia	16 (4.6%)	0	24 (6.8%)	0
Psychiatric disorders				
Insomnia	61 (17.6%)	6 (1.7%)	95 (27.1%)	8 (2.3%)
Anxiety	18 (5.2%)	2 (0.6%)	18 (5.1%)	2 (0.6%)
Respiratory, thoracic and mediastinal disorders				
Cough*	58 (16.7%)	0	91 (25.9%)	1 (0.3%)
Dyspnoea*	30 (8.6%)	3 (0.9%)	43 (12.3%)	1 (0.3%)
Skin and subcutaneous tissue disorders				
Rash	94 (27.1%)	17 (4.9%)	82 (23.4%)	9 (2.6%)
Erythema	18 (5.2%)	1 (0.3%)	27 (7.7%)	1 (0.3%)
Pruritus	16 (4.6%)	0	26 (7.4%)	1 (0.3%)
Rash maculo-papular	27 (7.8%)	3 (0.9%)	26 (7.4%)	5 (1.4%)
Dry skin	13 (3.7%)	0	21 (6.0%)	0
Vascular disorders				
Hypertension	21 (6.1%)	6 (1.7%)	30 (8.5%)	10 (2.8%)
Hypotension	16 (4.6%)	2 (0.6%)	23 (6.6%)	3 (0.9%)

Table 13: **Number of Subjects With 1 or More Treatment-emergent Adverse Events (≥ 5% in Patients Treated with D-VRd) by MedDRA System-Organ Class, Grouping of Preferred Terms and Toxicity Grade; Safety Analysis Set (Study 54767414MMY3014)**

	VRd		D-VRd	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4

Key: VRd = bortezomib (VELCADE) + lenalidomide + dexamethasone; D-VRd = daratumumab + bortezomib (VELCADE) + lenalidomide + dexamethasone; TEAE = treatment-emergent adverse event.
[@]IRR includes terms indicated by investigator as a systemic infusion related reaction; ISR includes terms indicated by investigator as a local injection site reaction related to daratumumab administration.
*Includes a grouping of preferred terms:
Abdominal pain includes abdominal pain upper, and abdominal pain.
Bronchitis includes bronchiolitis, bronchitis bacterial, bronchitis viral, respiratory syncytial virus bronchitis, and bronchitis.
COVID-19 includes COVID-19 pneumonia, post-acute COVID-19 syndrome, and COVID-19.
Cough includes productive cough, and cough.
Dyspnoea includes dyspnoea exertional, and dyspnoea.
Fatigue includes asthenia, and fatigue.
Neutropenia includes febrile neutropenia, and neutropenia.
Oedema peripheral includes generalised oedema, oedema, peripheral swelling, and oedema peripheral.
Pneumonia includes bronchopulmonary aspergillosis, lower respiratory tract infection, pneumocystis jirovecii pneumonia, pneumonia bacterial, pneumonia cytomegaloviral, pneumonia haemophilus, pneumonia influenzal, pneumonia klebsiella, pneumonia legionella, pneumonia parainfluenzae viral, pneumonia pneumococcal, pneumonia respiratory syncytial viral, pneumonia streptococcal, pneumonia viral, and pneumonia.
Sepsis includes campylobacter sepsis, escherichia sepsis, klebsiella sepsis, listeria sepsis, neutropenic sepsis, post procedural sepsis, pseudomonal sepsis, septic shock, staphylococcal sepsis, streptococcal sepsis, urosepsis, and sepsis.
Upper respiratory tract infection includes acute sinusitis, bacterial rhinitis, laryngitis, laryngitis viral, metapneumovirus infection, nasopharyngitis, oropharyngeal candidiasis, pharyngitis, respiratory moniliasis, respiratory syncytial virus infection, respiratory tract infection, respiratory tract infection viral, rhinitis, rhinovirus infection, sinusitis, tonsillitis, tracheitis, upper respiratory tract infection bacterial, viral pharyngitis, viral rhinitis, viral upper respiratory tract infection, and upper respiratory tract infection.
Note: Subjects are counted only once for any given event, regardless of the number of times they actually experienced the event. Percentages are calculated with the number of subjects in each group as denominator.
Note: Adverse events are coded using MedDRA version 26.0.

Study MMY3013: Darzalex SC in combination with pomalidomide/dexamethasone

TEAEs in Table 14 reflect exposure to Darzalex SC in combination with pomalidomide and dexamethasone (DPd) for a median treatment duration of 11.5 months (range: 0 to 36.0 months) and a median treatment duration of 6.6 months (range: 0 to 27.0 months) for the pomalidomide/dexamethasone (Pd) group. Among patients receiving DPd, 71% were exposed for 6 months or longer and 50% were exposed for greater than one year.

Table 14: Number of Subjects With 1 or More Treatment-emergent Adverse Events (≥ 5% in Patients Treated with DPd) by MedDRA System-Organ Class, Grouping of Preferred Terms and Toxicity Grade; Safety Analysis Set (Study 54767414MMY3013)

	Pd		DPd	
	All Grades n (%)	Grade 3 or 4 n (%)	All Grades n (%)	Grade 3 or 4 n (%)
Analysis set: safety	150		149	
MedDRA system organ class / preferred term				
Blood and lymphatic system disorders				
Neutropenia[a]	80 (53.3%)	76 (50.7%)	109 (73.2%)	105 (70.5%)
Anaemia[b]	67 (44.7%)	32 (21.3%)	55 (36.9%)	25 (16.8%)
Thrombocytopenia	50 (33.3%)	27 (18.0%)	48 (32.2%)	26 (17.4%)
Leukopenia	18 (12.0%)	7 (4.7%)	39 (26.2%)	25 (16.8%)
Lymphopenia	12 (8.0%)	5 (3.3%)	22 (14.8%)	18 (12.1%)
Gastrointestinal disorders				
Diarrhoea	21 (14.0%)	1 (0.7%)	33 (22.1%)	8 (5.4%)
Constipation	22 (14.7%)	1 (0.7%)	21 (14.1%)	1 (0.7%)
Nausea	10 (6.7%)	0	11 (7.4%)	0
Vomiting	3 (2.0%)	0	8 (5.4%)	0
General disorders and administration site conditions				
Fatigue	38 (25.3%)	7 (4.7%)	38 (25.5%)	12 (8.1%)
Asthenia	24 (16.0%)	1 (0.7%)	33 (22.1%)	8 (5.4%)
Pyrexia	21 (14.0%)	0	29 (19.5%)	0
Oedema peripheral[c]	14 (9.3%)	0	22 (14.8%)	0
Infections and infestations				
Pneumonia[d]	41 (27.3%)	23 (15.3%)	56 (37.6%)	34 (22.8%)
Upper respiratory tract infection[e]	33 (22.0%)	3 (2.0%)	54 (36.2%)	1 (0.7%)
Bronchitis	18 (12.0%)	3 (2.0%)	20 (13.4%)	0
Fungal infection[f]	1 (0.7%)	0	8 (5.4%)	0
Urinary tract infection	6 (4.0%)	1 (0.7%)	8 (5.4%)	2 (1.3%)
Metabolism and nutrition disorders				
Hyperglycaemia	19 (12.7%)	7 (4.7%)	15 (10.1%)	8 (5.4%)
Hypocalcaemia	9 (6.0%)	3 (2.0%)	13 (8.7%)	2 (1.3%)
Hypokalaemia	7 (4.7%)	1 (0.7%)	12 (8.1%)	7 (4.7%)
Musculoskeletal and connective tissue disorders				
Back pain	14 (9.3%)	1 (0.7%)	15 (10.1%)	0
Bone pain	19 (12.7%)	2 (1.3%)	14 (9.4%)	1 (0.7%)
Muscle spasms	7 (4.7%)	0	12 (8.1%)	0
Muscular weakness	5 (3.3%)	0	10 (6.7%)	1 (0.7%)
Pain in extremity	10 (6.7%)	0	9 (6.0%)	0
Musculoskeletal chest pain	4 (2.7%)	0	8 (5.4%)	0
Nervous system disorders				
Tremor	13 (8.7%)	2 (1.3%)	15 (10.1%)	2 (1.3%)
Peripheral sensory neuropathy	11 (7.3%)	0	14 (9.4%)	2 (1.3%)
Syncope	1 (0.7%)	1 (0.7%)	10 (6.7%)	6 (4.0%)
Psychiatric disorders				
Insomnia	18 (12.0%)	5 (3.3%)	12 (8.1%)	7 (4.7%)
Respiratory, thoracic and mediastinal disorders				
Cough[g]	12 (8.0%)	0	19 (12.8%)	0
Dyspnoea[h]	12 (8.0%)	1 (0.7%)	17 (11.4%)	4 (2.7%)
Skin and subcutaneous tissue disorders				
Rash	8 (5.3%)	1 (0.7%)	10 (6.7%)	0
Vascular disorders				
Hypotension	5 (3.3%)	1 (0.7%)	8 (5.4%)	2 (1.3%)

Table 14: Number of Subjects With 1 or More Treatment-emergent Adverse Events (≥ 5% in Patients Treated with DPd) by MedDRA System-Organ Class, Grouping of Preferred Terms and Toxicity Grade; Safety Analysis Set (Study 54767414MMY3013)

	Pd		DPd	
	All Grades n (%)	Grade 3 or 4 n (%)	All Grades n (%)	Grade 3 or 4 n (%)

Key: Pd = pomalidomide - dexamethasone; DPd = daratumumab - pomalidomide - dexamethasone; SC = subcutaneous.
[a]Febrile neutropenia, Neutropenia
[b]Anaemia, Anaemia macrocytic, Iron deficiency anaemia
[c]Oedema, Oedema peripheral, Peripheral swelling
[d]Atypical pneumonia, Lower respiratory tract infection, Pneumonia, Pneumonia aspiration, Pneumonia bacterial, Pneumonia respiratory syncytial viral
[e]Nasopharyngitis, Pharyngitis, Respiratory syncytial virus infection, Respiratory tract infection, Respiratory tract infection viral, Rhinitis, Sinusitis, Tonsillitis, Upper respiratory tract infection, Viral upper respiratory tract infection
[f]Candida infection, Fungal disease carrier, Fungal infection, Oral candidiasis
[g]Cough, Productive cough
[h]Dyspnoea, Dyspnoea exertional
Note: Adverse events are reported using MedDRA version 23.0.
Note: Percentages are calculated with the number of subjects in each group as denominator.

Combination Treatment for AL Amyloidosis

Study AMY3001: Darzalex SC in combination with bortezomib, cyclophosphamide and dexamethasone

TEAEs in Table 15 reflect exposure to Darzalex SC (1800 mg) in combination with bortezomib, cyclophosphamide and dexamethasone (D-VCd) or bortezomib, cyclophosphamide and dexamethasone (VCd) for cycles 1-6 of treatment.

Table 15: Number of Subjects With 1 or More Treatment-emergent Adverse Events (≥ 5% in Any Treatment Arm) during Cycles 1-6 by MedDRA System-Organ Class, Preferred Term and Toxicity Grade; Safety Analysis Set (Study 54767414AMY3001)

	VCd		D-VCd	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
Analysis set: safety	188		193	
MedDRA system organ class / Preferred term				
Blood and lymphatic system disorders				
Anaemia	44 (23.4%)	9 (4.8%)	46 (23.8%)	8 (4.1%)
Lymphopenia	28 (14.9%)	19 (10.1%)	36 (18.7%)	25 (13.0%)
Thrombocytopenia	22 (11.7%)	5 (2.7%)	32 (16.6%)	6 (3.1%)
Neutropenia	12 (6.4%)	5 (2.7%)	20 (10.4%)	9 (4.7%)
Leukopenia	7 (3.7%)	2 (1.1%)	11 (5.7%)	2 (1.0%)
Cardiac disorders				
Cardiac failure[b]	20 (10.6%)	9 (4.8%)	21 (10.9%)	15 (7.8%)
Arrhythmia[d]	10 (5.3%)	2 (1.1%)	18 (9.3%)	6 (3.1%)
Gastrointestinal disorders				
Constipation	54 (28.7%)	0	64 (33.2%)	2 (1.0%)
Diarrhoea	57 (30.3%)	7 (3.7%)	59 (30.6%)	11 (5.7%)

Table 15: Number of Subjects With 1 or More Treatment-emergent Adverse Events (≥ 5% in Any Treatment Arm) during Cycles 1-6 by MedDRA System-Organ Class, Preferred Term and Toxicity Grade; Safety Analysis Set (Study 54767414AMY3001)

	VCd		D-VCd	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
Nausea	52 (27.7%)	0	46 (23.8%)	3 (1.6%)
Abdominal pain[l]	28 (14.9%)	1 (0.5%)	28 (14.5%)	2 (1.0%)
Vomiting	21 (11.2%)	1 (0.5%)	22 (11.4%)	0
Abdominal distension	12 (6.4%)	0	10 (5.2%)	0
Dyspepsia	12 (6.4%)	1 (0.5%)	5 (2.6%)	0
General disorders and administration site conditions				
Fatigue[j]	73 (38.8%)	8 (4.3%)	72 (37.3%)	11 (5.7%)
Oedema peripheral[k]	73 (38.8%)	14 (7.4%)	72 (37.3%)	9 (4.7%)
Pyrexia	16 (8.5%)	1 (0.5%)	24 (12.4%)	0
Injection Site Reactions[h]	0	0	18 (9.3%)	0
Injection site erythema	21 (11.2%)	0	17 (8.8%)	0
Infusion Related Reactions[i]	0	0	14 (7.3%)	0
Chills	4 (2.1%)	0	10 (5.2%)	1 (0.5%)
Infections and infestations				
Upper respiratory tract infection[g]	40 (21.3%)	1 (0.5%)	55 (28.5%)	2 (1.0%)
Pneumonia[a]	16 (8.5%)	10 (5.3%)	22 (11.4%)	15 (7.8%)
Conjunctivitis	5 (2.7%)	0	11 (5.7%)	0
Sepsis[c]	1 (0.5%)	1 (0.5%)	10 (5.2%)	9 (4.7%)
Herpes zoster	12 (6.4%)	2 (1.1%)	9 (4.7%)	0
Hordeolum	11 (5.9%)	0	8 (4.1%)	0
Injury, poisoning and procedural complications				
Contusion	6 (3.2%)	0	10 (5.2%)	0
Fall	8 (4.3%)	0	10 (5.2%)	0
Investigations				
Alanine aminotransferase increased	10 (5.3%)	1 (0.5%)	15 (7.8%)	3 (1.6%)
Blood creatinine increased	16 (8.5%)	2 (1.1%)	15 (7.8%)	4 (2.1%)
Aspartate aminotransferase increased	8 (4.3%)	1 (0.5%)	12 (6.2%)	2 (1.0%)
Gamma-glutamyltransferase increased	11 (5.9%)	6 (3.2%)	11 (5.7%)	2 (1.0%)
Blood alkaline phosphatase increased	11 (5.9%)	1 (0.5%)	6 (3.1%)	1 (0.5%)
Metabolism and nutrition disorders				
Hypokalaemia	28 (14.9%)	10 (5.3%)	21 (10.9%)	3 (1.6%)
Decreased appetite	23 (12.2%)	0	18 (9.3%)	0
Hyponatraemia	7 (3.7%)	5 (2.7%)	14 (7.3%)	5 (2.6%)
Hyperglycaemia	7 (3.7%)	1 (0.5%)	11 (5.7%)	4 (2.1%)
Hypocalcaemia	9 (4.8%)	0	10 (5.2%)	1 (0.5%)
Hypoalbuminaemia	11 (5.9%)	5 (2.7%)	8 (4.1%)	1 (0.5%)
Musculoskeletal and connective tissue disorders				
Back pain	11 (5.9%)	0	17 (8.8%)	1 (0.5%)
Muscle spasms	10 (5.3%)	0	16 (8.3%)	1 (0.5%)
Muscular weakness	11 (5.9%)	1 (0.5%)	16 (8.3%)	3 (1.6%)
Myalgia	7 (3.7%)	0	15 (7.8%)	0
Pain in extremity	9 (4.8%)	0	12 (6.2%)	0
Arthralgia	9 (4.8%)	0	10 (5.2%)	0
Nervous system disorders				
Peripheral sensory neuropathy	37 (19.7%)	4 (2.1%)	54 (28.0%)	5 (2.6%)
Dizziness	26 (13.8%)	0	28 (14.5%)	0
Headache	18 (9.6%)	0	23 (11.9%)	1 (0.5%)
Dysgeusia	11 (5.9%)	0	15 (7.8%)	0
Paraesthesia	12 (6.4%)	0	14 (7.3%)	0
Syncope	12 (6.4%)	12 (6.4%)	14 (7.3%)	10 (5.2%)
Tremor	2 (1.1%)	0	10 (5.2%)	0
Psychiatric disorders				

Table 15: Number of Subjects With 1 or More Treatment-emergent Adverse Events (≥ 5% in Any Treatment Arm) during Cycles 1-6 by MedDRA System-Organ Class, Preferred Term and Toxicity Grade; Safety Analysis Set (Study 54767414AMY3001)

	VCd		D-VCd	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
Insomnia	47 (25.0%)	2 (1.1%)	41 (21.2%)	0
Anxiety	12 (6.4%)	2 (1.1%)	6 (3.1%)	0
Renal and urinary disorders				
Renal impairment	11 (5.9%)	4 (2.1%)	8 (4.1%)	0
Respiratory, thoracic and mediastinal disorders				
Dyspnoea[f]	37 (19.7%)	7 (3.7%)	41 (21.2%)	6 (3.1%)
Cough[e]	20 (10.6%)	0	28 (14.5%)	1 (0.5%)
Epistaxis	3 (1.6%)	0	10 (5.2%)	1 (0.5%)
Pleural effusion	10 (5.3%)	1 (0.5%)	9 (4.7%)	1 (0.5%)
Skin and subcutaneous tissue disorders				
Rash	13 (6.9%)	0	12 (6.2%)	0
Erythema	3 (1.6%)	0	11 (5.7%)	0
Vascular disorders				
Hypotension	21 (11.2%)	5 (2.7%)	26 (13.5%)	4 (2.1%)
Orthostatic hypotension	11 (5.9%)	0	6 (3.1%)	2 (1.0%)

Keys: VCd = cyclophosphamide-bortezomib-dexamethasone; D-VCd = daratumumab subcutaneous + VCd.
[a]Pneumonia includes pneumonia, pneumonia pneumococcal, pneumonia aspiration and lower respiratory tract infection.
[b]Cardiac failure includes cardiac failure, cardiac failure congestive, diastolic dysfunction, cardiac dysfunction, left ventricular dysfunction, acute left ventricular failure, cardiovascular insufficiency and pulmonary oedema.
[c]Sepsis includes sepsis, septic shock, candida sepsis, neutropenic sepsis and pulmonary sepsis.
[d]Arrhythmia includes arrhythmia, atrial flutter, atrial fibrillation, supraventricular tachycardia, bradycardia, bradyarrhythmia, cardiac flutter, extrasystoles, ventricular arrhythmia, ventricular extrasystoles, atrial tachycardia and ventricular tachycardia.
[e]Cough includes cough and productive cough.
[f]Dyspnoea includes dyspnoea and dyspnoea exertional.
[g]Upper respiratory tract infection includes nasopharyngitis, pharyngitis, respiratory syncytial virus infection, respiratory tract infection, respiratory tract infection viral, rhinitis, rhinovirus infection, sinusitis, tracheitis, upper respiratory tract infection, upper respiratory tract infection bacterial and viral upper respiratory tract infection.
[h]Injection site reactions includes terms determined by investigators to be related to daratumumab injection.
[i]Infusion related reactions includes terms determined by investigators to be related to daratumumab infusion.
[j]Fatigue includes fatigue and asthenia.
[k]Oedema peripheral includes oedema, generalised oedema,gravitational oedema, oedema peripheral and peripheral swelling.
[l]Abdominal pain includes abdominal pain and abdominal pain upper.

INTRAVENOUS FORMULATION (Darzalex)

The following sections present data from a separate Product Monograph for Darzalex intravenous formulation studies:

- **Patients with newly diagnosed multiple myeloma who are ineligible for ASCT**
- **Patients with multiple myeloma who have received at least one prior therapy**
- **Patients with multiple myeloma who have received at least three prior lines of therapy including a PI and an IMiD, or who are refractory to both a PI and an IMiD**

Patients with newly diagnosed multiple myeloma who are ineligible for ASCT

Study MMY3008: Darzalex in combination with lenalidomide and dexamethasone

TEAEs described in Table 16 reflect exposure to Darzalex intravenous formulation in combination with lenalidomide and dexamethasone (DRd) for a median treatment duration of

25.3 months (range: 0.1 to 40.44 months) and a median treatment duration of 21.3 months (range: 0.03 to 40.64 months) for the lenalidomide-dexamethasone group (Rd).

Infusion-related reactions (including terms determined by investigators to be related to infusion; see Infusion-Related Reactions (IRRs) from Pooled Clinical Studies) were reported in 40.9% of patients in the DRd group.

Table 16: Number of Subjects With 1 or More Treatment-emergent Adverse Events (≥ 5% in Patients Treated with DRd) by MedDRA System-Organ Class, Grouping of Preferred Terms and Toxicity Grade; Safety Analysis Set (Study 54767414MMY3008)

	Rd		DRd	
	All Grades n (%)	Grade 3 or 4 n (%)	All Grades n (%)	Grade 3 or 4 n (%)
Analysis set: safety	365		364	
MedDRA system organ class / preferred term				
Blood and lymphatic system disorders				
Neutropenia[a]	156 (42.7%)	131 (35.9%)	208 (57.1%)	183 (50.3%)
Anaemia[b]	140 (38.4%)	72 (19.7%)	130 (35.7%)	43 (11.8%)
Leukopenia	34 (9.3%)	18 (4.9%)	68 (18.7%)	40 (11.0%)
Thrombocytopenia	69 (18.9%)	32 (8.8%)	68 (18.7%)	27 (7.4%)
Lymphopenia	45 (12.3%)	39 (10.7%)	66 (18.1%)	55 (15.1%)
Cardiac disorders				
Atrial fibrillation	37 (10.1%)	11 (3.0%)	23 (6.3%)	10 (2.7%)
Eye disorders				
Cataract	59 (16.2%)	29 (7.9%)	54 (14.8%)	26 (7.1%)
Vision blurred	16 (4.4%)	0	26 (7.1%)	0
Gastrointestinal disorders				
Diarrhoea	168 (46.0%)	15 (4.1%)	207 (56.9%)	24 (6.6%)
Constipation	130 (35.6%)	1 (0.3%)	149 (40.9%)	6 (1.6%)
Nausea	84 (23.0%)	2 (0.5%)	115 (31.6%)	5 (1.4%)
Vomiting	45 (12.3%)	1 (0.3%)	61 (16.8%)	2 (0.5%)
Abdominal pain	33 (9.0%)	1 (0.3%)	43 (11.8%)	5 (1.4%)
Abdominal pain upper	28 (7.7%)	0	34 (9.3%)	1 (0.3%)
Dyspepsia	28 (7.7%)	1 (0.3%)	26 (7.1%)	1 (0.3%)
Stomatitis	13 (3.6%)	0	22 (6.0%)	2 (0.5%)
General disorders and administration site conditions				
Oedema peripheral[c]	122 (33.4%)	2 (0.5%)	151 (41.5%)	7 (1.9%)
Fatigue	104 (28.5%)	14 (3.8%)	147 (40.4%)	29 (8.0%)
Asthenia	90 (24.7%)	13 (3.6%)	117 (32.1%)	16 (4.4%)
Pyrexia	65 (17.8%)	9 (2.5%)	84 (23.1%)	8 (2.2%)
Chills	6 (1.6%)	0	46 (12.6%)	0
Non-cardiac chest pain	16 (4.4%)	5 (1.4%)	20 (5.5%)	4 (1.1%)
Infections and infestations				
Upper respiratory tract infection[d]	133 (36.4%)	8 (2.2%)	190 (52.2%)	9 (2.5%)
Bronchitis[e]	75 (20.5%)	5 (1.4%)	106 (29.1%)	10 (2.7%)
Pneumonia[f]	52 (14.2%)	31 (8.5%)	93 (25.5%)	57 (15.7%)
Urinary tract infection	38 (10.4%)	8 (2.2%)	64 (17.6%)	9 (2.5%)
Influenza	21 (5.8%)	6 (1.6%)	34 (9.3%)	8 (2.2%)
Gastroenteritis	15 (4.1%)	0	19 (5.2%)	0
Lower respiratory tract infection	23 (6.3%)	10 (2.7%)	19 (5.2%)	9 (2.5%)
Injury, poisoning and procedural complications				
Contusion	22 (6.0%)	0	27 (7.4%)	0
Investigations				
Weight decreased	63 (17.3%)	9 (2.5%)	101 (27.7%)	9 (2.5%)

Table 16: Number of Subjects With 1 or More Treatment-emergent Adverse Events (≥ 5% in Patients Treated with DRd) by MedDRA System-Organ Class, Grouping of Preferred Terms and Toxicity Grade; Safety Analysis Set (Study 54767414MMY3008)

	Rd		DRd	
	All Grades n (%)	Grade 3 or 4 n (%)	All Grades n (%)	Grade 3 or 4 n (%)
Weight increased	6 (1.6%)	1 (0.3%)	25 (6.9%)	1 (0.3%)
Blood creatinine increased	15 (4.1%)	1 (0.3%)	24 (6.6%)	0
Metabolism and nutrition disorders				
Decreased appetite	55 (15.1%)	2 (0.5%)	80 (22.0%)	3 (0.8%)
Hypokalaemia	61 (16.7%)	32 (8.8%)	75 (20.6%)	32 (8.8%)
Hyperglycaemia	28 (7.7%)	14 (3.8%)	50 (13.7%)	26 (7.1%)
Hypocalcaemia	32 (8.8%)	8 (2.2%)	50 (13.7%)	6 (1.6%)
Dehydration	17 (4.7%)	1 (0.3%)	25 (6.9%)	8 (2.2%)
Hyponatraemia	13 (3.6%)	9 (2.5%)	19 (5.2%)	9 (2.5%)
Hypophosphataemia	7 (1.9%)	3 (0.8%)	19 (5.2%)	10 (2.7%)
Musculoskeletal and connective tissue disorders				
Back pain	96 (26.3%)	11 (3.0%)	123 (33.8%)	11 (3.0%)
Muscle spasms	79 (21.6%)	4 (1.1%)	107 (29.4%)	2 (0.5%)
Arthralgia	64 (17.5%)	5 (1.4%)	70 (19.2%)	3 (0.8%)
Pain in extremity	50 (13.7%)	0	60 (16.5%)	4 (1.1%)
Musculoskeletal pain	40 (11.0%)	1 (0.3%)	51 (14.0%)	1 (0.3%)
Bone pain	36 (9.9%)	7 (1.9%)	37 (10.2%)	5 (1.4%)
Muscular weakness	23 (6.3%)	4 (1.1%)	33 (9.1%)	6 (1.6%)
Musculoskeletal chest pain	43 (11.8%)	3 (0.8%)	27 (7.4%)	3 (0.8%)
Myalgia	25 (6.8%)	0	25 (6.9%)	3 (0.8%)
Neck pain	26 (7.1%)	0	21 (5.8%)	0
Nervous system disorders				
Peripheral sensory neuropathy	54 (14.8%)	0	87 (23.9%)	5 (1.4%)
Dizziness	58 (15.9%)	1 (0.3%)	69 (19.0%)	3 (0.8%)
Headache	39 (10.7%)	0	69 (19.0%)	2 (0.5%)
Paraesthesia	30 (8.2%)	0	58 (15.9%)	0
Tremor	51 (14.0%)	1 (0.3%)	57 (15.7%)	0
Dysgeusia	35 (9.6%)	0	40 (11.0%)	0
Hypoaesthesia	16 (4.4%)	0	19 (5.2%)	0
Psychiatric disorders				
Insomnia	107 (29.3%)	11 (3.0%)	109 (29.9%)	9 (2.5%)
Anxiety	34 (9.3%)	4 (1.1%)	32 (8.8%)	2 (0.5%)
Depression	32 (8.8%)	4 (1.1%)	30 (8.2%)	2 (0.5%)
Confusional state	20 (5.5%)	2 (0.5%)	23 (6.3%)	7 (1.9%)
Renal and urinary disorders				
Acute kidney injury	28 (7.7%)	11 (3.0%)	28 (7.7%)	14 (3.8%)
Renal impairment	28 (7.7%)	8 (2.2%)	26 (7.1%)	3 (0.8%)
Chronic kidney disease	18 (4.9%)	9 (2.5%)	22 (6.0%)	9 (2.5%)
Respiratory, thoracic and mediastinal disorders				
Dyspnoea[g]	74 (20.3%)	4 (1.1%)	116 (31.9%)	13 (3.6%)
Cough[h]	65 (17.8%)	0	111 (30.5%)	1 (0.3%)
Dysphonia	18 (4.9%)	0	27 (7.4%)	0
Rhinorrhoea	11 (3.0%)	0	25 (6.9%)	0
Oropharyngeal pain	9 (2.5%)	0	24 (6.6%)	0
Pulmonary embolism	20 (5.5%)	19 (5.2%)	19 (5.2%)	19 (5.2%)
Skin and subcutaneous tissue disorders				
Rash	43 (11.8%)	1 (0.3%)	57 (15.7%)	4 (1.1%)
Pruritus	29 (7.9%)	0	32 (8.8%)	0
Dry skin	14 (3.8%)	0	25 (6.9%)	0
Erythema	18 (4.9%)	0	23 (6.3%)	0
Rash maculo-papular	9 (2.5%)	4 (1.1%)	21 (5.8%)	1 (0.3%)
Hyperhidrosis	5 (1.4%)	0	19 (5.2%)	0

Table 16: Number of Subjects With 1 or More Treatment-emergent Adverse Events (≥ 5% in Patients Treated with DRd) by MedDRA System-Organ Class, Grouping of Preferred Terms and Toxicity Grade; Safety Analysis Set (Study 54767414MMY3008)

	Rd		DRd	
	All Grades n (%)	Grade 3 or 4 n (%)	All Grades n (%)	Grade 3 or 4 n (%)
Vascular disorders				
Hypertension[i]	26 (7.1%)	13 (3.6%)	48 (13.2%)	24 (6.6%)
Hypotension	33 (9.0%)	3 (0.8%)	36 (9.9%)	3 (0.8%)
Deep vein thrombosis	35 (9.6%)	8 (2.2%)	31 (8.5%)	7 (1.9%)

Key: Rd = lenalidomide-dexamethasone; DRd = daratumumab-lenalidomide-dexamethasone; TEAE = treatment-emergent adverse event.
[a] "Neutropenia" includes Febrile neutropenia, Neutropenia, Neutropenic infection, Neutropenic sepsis
[b] "Anaemia" includes Anaemia, Anaemia macrocytic, Haematocrit decreased, Iron deficiency anaemia, Microcytic anaemia
[c] "Oedema peripheral" includes Generalised oedema, Gravitational oedema, Oedema, Oedema peripheral, Peripheral swelling
[d] "Upper respiratory tract infection" includes Acute sinusitis, Bacterial rhinitis, Laryngitis, Metapneumovirus infection, Nasopharyngitis, Oropharyngeal candidiasis, Pharyngitis, Respiratory syncytial virus infection, Respiratory tract infection, Respiratory tract infection viral, Rhinitis, Rhinovirus infection, Sinusitis, Tonsillitis, Tracheitis, Upper respiratory tract infection, Viral pharyngitis, Viral rhinitis, Viral upper respiratory tract infection
[e] "Bronchitis" includes Bronchiolitis, Bronchitis, Bronchitis viral, Respiratory syncytial virus bronchiolitis, Tracheobronchitis
[f] "Pneumonia" includes Atypical pneumonia, Bronchopulmonary aspergillosis, Lung infection, Pneumocystis jirovecii infection, Pneumocystis jirovecii pneumonia, Pneumonia, Pneumonia aspiration, Pneumonia pneumococcal, Pneumonia viral, Pulmonary mycosis
[g] "Dyspnoea" includes Dyspnoea, Dyspnoea exertional
[h] "Cough" includes Cough, Productive cough
[i] "Hypertension" includes Blood pressure increased, Hypertension
Note: Adverse events are reported using MedDRA version 20.0.
Note: Percentages are calculated with the number of subjects in each group as denominator.

Study MMY3007: Darzalex in combination with bortezomib, melphalan, and prednisone

TEAEs described in Table 17 reflect exposure to Darzalex intravenous formulation in combination with bortezomib, melphalan, and prednisone (D-VMP) for a median treatment duration of 14.7 months (range: 0 to 25.8 months) and a median treatment duration of 12 months (range: 0.1 to 14.8 months) for the bortezomib, melphalan, and prednisone (VMP) group.

Infusion-related reactions (including terms determined by investigators to be related to infusion; see Infusion-Related Reactions (IRRs) from Pooled Clinical Studies) were reported in 27.7% of patients in the D-VMP group.

Table 17: Number of Subjects With 1 or More Treatment-emergent Adverse Events (≥ 5%) in Patients Treated with D-VMP by MedDRA System-Organ Class, Preferred Term and Toxicity Grade; Safety Analysis Set (Study 54767414MMY3007)

	VMP		D-VMP	
	All Grades n (%)	Grade 3 or 4 n (%)	All Grades n (%)	Grade 3 or 4 n (%)
Analysis set: safety	354		346	
MedDRA system organ class / preferred term				

Table 17: Number of Subjects With 1 or More Treatment-emergent Adverse Events (≥ 5%) in Patients Treated with D-VMP by MedDRA System-Organ Class, Preferred Term and Toxicity Grade; Safety Analysis Set (Study 54767414MMY3007)

	VMP		D-VMP	
	All Grades n (%)	Grade 3 or 4 n (%)	All Grades n (%)	Grade 3 or 4 n (%)
Blood and lymphatic system disorders				
Neutropenia	186 (52.5%)	137 (38.7%)	172 (49.7%)	138 (39.9%)
Thrombocytopenia	190 (53.7%)	133 (37.6%)	169 (48.8%)	119 (34.4%)
Anaemia	133 (37.6%)	70 (19.8%)	97 (28.0%)	55 (15.9%)
Leukopenia	53 (15.0%)	30 (8.5%)	46 (13.3%)	28 (8.1%)
Lymphopenia	36 (10.2%)	22 (6.2%)	37 (10.7%)	26 (7.5%)
Infections and infestations				
Upper respiratory tract infection	49 (13.8%)	5 (1.4%)	91 (26.3%)	7 (2.0%)
Pneumonia	17 (4.8%)	14 (4.0%)	53 (15.3%)	39 (11.3%)
Bronchitis	27 (7.6%)	3 (0.8%)	50 (14.5%)	8 (2.3%)
Urinary tract infection	12 (3.4%)	1 (0.3%)	29 (8.4%)	6 (1.7%)
Nasopharyngitis	20 (5.6%)	0	19 (5.5%)	0
General disorders and administration site conditions				
Pyrexia	74 (20.9%)	2 (0.6%)	80 (23.1%)	2 (0.6%)
Oedema peripheral	39 (11.0%)	1 (0.3%)	62 (17.9%)	3 (0.9%)
Fatigue	51 (14.4%)	9 (2.5%)	48 (13.9%)	11 (3.2%)
Asthenia	42 (11.9%)	7 (2.0%)	40 (11.6%)	4 (1.2%)
Chills	6 (1.7%)	0	26 (7.5%)	0
Gastrointestinal disorders				
Diarrhoea	87 (24.6%)	11 (3.1%)	82 (23.7%)	9 (2.6%)
Nausea	76 (21.5%)	4 (1.1%)	72 (20.8%)	3 (0.9%)
Constipation	65 (18.4%)	1 (0.3%)	63 (18.2%)	3 (0.9%)
Vomiting	55 (15.5%)	6 (1.7%)	59 (17.1%)	5 (1.4%)
Abdominal pain	25 (7.1%)	0	18 (5.2%)	1 (0.3%)
Dyspepsia	12 (3.4%)	0	18 (5.2%)	0
Nervous system disorders				
Peripheral sensory neuropathy	121 (34.2%)	14 (4.0%)	98 (28.3%)	5 (1.4%)
Neuralgia	16 (4.5%)	0	25 (7.2%)	1 (0.3%)
Headache	14 (4.0%)	1 (0.3%)	23 (6.6%)	0
Dizziness	22 (6.2%)	1 (0.3%)	22 (6.4%)	1 (0.3%)
Musculoskeletal and connective tissue disorders				
Back pain	42 (11.9%)	4 (1.1%)	48 (13.9%)	6 (1.7%)
Pain in extremity	22 (6.2%)	1 (0.3%)	29 (8.4%)	0
Arthralgia	22 (6.2%)	0	27 (7.8%)	0
Bone pain	9 (2.5%)	0	20 (5.8%)	4 (1.2%)
Respiratory, thoracic and mediastinal disorders				
Cough	27 (7.6%)	1 (0.3%)	52 (15.0%)	1 (0.3%)
Dyspnoea	16 (4.5%)	3 (0.8%)	43 (12.4%)	9 (2.6%)
Metabolism and nutrition disorders				
Decreased appetite	46 (13.0%)	1 (0.3%)	40 (11.6%)	2 (0.6%)
Hyperglycaemia	13 (3.7%)	8 (2.3%)	21 (6.1%)	10 (2.9%)
Hypocalcaemia	17 (4.8%)	8 (2.3%)	20 (5.8%)	8 (2.3%)
Hypokalaemia	17 (4.8%)	6 (1.7%)	19 (5.5%)	5 (1.4%)
Skin and subcutaneous tissue disorders				
Rash	39 (11.0%)	2 (0.6%)	29 (8.4%)	1 (0.3%)
Pruritus	10 (2.8%)	1 (0.3%)	19 (5.5%)	0
Vascular disorders				
Hypertension	11 (3.1%)	6 (1.7%)	35 (10.1%)	14 (4.0%)
Hypotension	24 (6.8%)	2 (0.6%)	31 (9.0%)	2 (0.6%)
Psychiatric disorders				
Insomnia	32 (9.0%)	2 (0.6%)	26 (7.5%)	1 (0.3%)

Table 17: Number of Subjects With 1 or More Treatment-emergent Adverse Events (≥ 5%) in Patients Treated with D-VMP by MedDRA System-Organ Class, Preferred Term and Toxicity Grade; Safety Analysis Set (Study 54767414MMY3007)

	VMP		D-VMP	
	All Grades n (%)	Grade 3 or 4 n (%)	All Grades n (%)	Grade 3 or 4 n (%)

Key: VMP=bortezomib-melphalan-prednisone; D-VMP=daratumumab-bortezomib-melphalan-prednisone.
Key: TEAE = treatment-emergent adverse event.
Note: Adverse events are reported using MedDRA version 20.0.
Note: Percentages are calculated with the number of subjects in each group as denominator.

Patients with multiple myeloma who have received at least one prior therapy

Study MMY3003: Darzalex in combination with lenalidomide/dexamethasone

TEAEs described in Table 18 reflect exposure to Darzalex intravenous formulation in combination with lenalidomide and dexamethasone (DRd) for a median treatment duration of 16.6 months (range: 0 to 24.4 months) and to lenalidomide and dexamethasone (Rd) for a median treatment duration of 14.8 months (range: 0.2 to 24.0 months).

Infusion-related reactions (including terms determined by investigators to be related to infusion; see Infusion-Related Reactions (IRRs) from Pooled Clinical Studies) were reported in 48% of patients in the DRd group.

Table 18: Number of Subjects With 1 or More Treatment-emergent Adverse Events (≥5%) in patients treated with DRd by MedDRA System-Organ Class, Preferred Term and Toxicity Grade; Safety Analysis Set (Study 54767414MMY3003)

	MMY3003			
	Rd (N=281)		DRd (N=283)	
	Any Grade (%)	Grade 3/4 (%)	Any Grade (%)	Grade 3/4 (%)
Infections and infestations				
Upper respiratory tract infection[a]	147 (52.3%)	12 (4.3%)	194 (68.6%)	21 (7.4%)
Pneumonia[b]	43 (15.3%)	26 (9.3%)	62 (21.9%)	40 (14.1%)
Influenza	14 (5.0%)	2 (0.7%)	25 (8.8%)	9 (3.2%)
Lower respiratory tract infection[c]	9 (3.2%)	3 (1.1%)	19 (6.7%)	5 (1.8%)
Urinary tract infection	12 (4.3%)	1 (0.4%)	17 (6.0%)	5 (1.8%)
Gastrointestinal disorders				
Diarrhoea	79 (28.1%)	9 (3.2%)	133 (47.0%)	18 (6.4%)
Constipation	72 (25.6%)	2 (0.7%)	84 (29.7%)	3 (1.1%)
Nausea	44 (15.7%)	1 (0.4%)	71 (25.1%)	4 (1.4%)
Vomiting	17 (6.0%)	3 (1.1%)	48 (17.0%)	3 (1.1%)
Abdominal pain upper	10 (3.6%)	0	22 (7.8%)	0
Abdominal pain	11 (3.9%)	0	20 (7.1%)	0
Dyspepsia	7 (2.5%)	0	19 (6.7%)	0
Stomatitis	6 (2.1%)	0	18 (6.4%)	0
General disorders and administration site conditions				
Fatigue	82 (29.2%)	9 (3.2%)	100 (35.3%)	18 (6.4%)

Table 18: Number of Subjects With 1 or More Treatment-emergent Adverse Events (≥5%) in patients treated with DRd by MedDRA System-Organ Class, Preferred Term and Toxicity Grade; Safety Analysis Set (Study 54767414MMY3003)

	MMY3003			
	Rd (N=281)		DRd (N=283)	
	Any Grade (%)	Grade 3/4 (%)	Any Grade (%)	Grade 3/4 (%)
Pyrexia	32 (11.4%)	4 (1.4%)	60 (21.2%)	6 (2.1%)
Oedema peripheral[d]	44 (15.7%)	3 (1.1%)	54 (19.1%)	2 (0.7%)
Asthenia	37 (13.2%)	8 (2.8%)	48 (17.0%)	9 (3.2%)
Chills	9 (3.2%)	0	18 (6.4%)	1 (0.4%)
Influenza like illness	13 (4.6%)	1 (0.4%)	17 (6.0%)	0
Blood and lymphatic system disorders				
Neutropenia[e]	124 (44.1%)	109 (38.8%)	169 (59.7%)	149 (52.7%)
Anaemia	102 (36.3%)	58 (20.6%)	97 (34.3%)	39 (13.8%)
Thrombocytopenia	85 (30.2%)	43 (15.3%)	79 (27.9%)	38 (13.4%)
Leukopenia	18 (6.4%)	7 (2.5%)	21 (7.4%)	8 (2.8%)
Lymphopenia	15 (5.3%)	10 (3.6%)	17 (6.0%)	15 (5.3%)
Respiratory, thoracic and mediastinal disorders				
Cough[f]	42 (14.9%)	0	90 (31.8%)	0
Dyspnoea[g]	38 (13.5%)	2 (0.7%)	64 (22.6%)	10 (3.5%)
Nasal congestion	5 (1.8%)	0	15 (5.3%)	0
Rhinitis allergic	3 (1.1%)	0	15 (5.3%)	0
Musculoskeletal and connective tissue disorders				
Muscle spasms	57 (20.3%)	5 (1.8%)	77 (27.2%)	2 (0.7%)
Back pain	49 (17.4%)	4 (1.4%)	52 (18.4%)	4 (1.4%)
Arthralgia	25 (8.9%)	1 (0.4%)	29 (10.2%)	3 (1.1%)
Muscular weakness	26 (9.3%)	2 (0.7%)	24 (8.5%)	0
Pain in extremity	34 (12.1%)	1 (0.4%)	24 (8.5%)	0
Bone pain	14 (5.0%)	1 (0.4%)	21 (7.4%)	2 (0.7%)
Musculoskeletal pain	18 (6.4%)	3 (1.1%)	20 (7.1%)	1 (0.4%)
Musculoskeletal chest pain	17 (6.0%)	0	16 (5.7%)	1 (0.4%)
Myalgia	10 (3.6%)	0	16 (5.7%)	0
Nervous system disorders				
Headache	21 (7.5%)	0	41 (14.5%)	0
Tremor	24 (8.5%)	0	26 (9.2%)	1 (0.4%)
Peripheral sensory neuropathy	21 (7.5%)	1 (0.4%)	25 (8.8%)	1 (0.4%)
Dizziness	24 (8.5%)	0	23 (8.1%)	0
Dysgeusia	16 (5.7%)	0	23 (8.1%)	0
Neuropathy peripheral	15 (5.3%)	1 (0.4%)	16 (5.7%)	2 (0.7%)
Metabolism and nutrition disorders				
Decreased appetite	32 (11.4%)	1 (0.4%)	36 (12.7%)	4 (1.4%)
Hypokalaemia	23 (8.2%)	7 (2.5%)	34 (12.0%)	10 (3.5%)
Hyperglycaemia	22 (7.8%)	10 (3.6%)	27 (9.5%)	11 (3.9%)
Hypocalcaemia	11 (3.9%)	2 (0.7%)	19 (6.7%)	4 (1.4%)
Hypophosphataemia	11 (3.9%)	7 (2.5%)	17 (6.0%)	12 (4.2%)
Skin and subcutaneous tissue disorders				
Rash[h]	33 (11.7%)	0	49 (17.3%)	2 (0.7%)
Pruritus	29 (10.3%)	0	29 (10.2%)	2 (0.7%)
Hyperhidrosis	8 (2.8%)	0	22 (7.8%)	0
Psychiatric disorders				
Insomnia	59 (21.0%)	3 (1.1%)	61 (21.6%)	2 (0.7%)
Anxiety	13 (4.6%)	2 (0.7%)	21 (7.4%)	1 (0.4%)
Depression	8 (2.8%)	0	20 (7.1%)	2 (0.7%)
Vascular disorders				
Hypertension[i]	10 (3.6%)	2 (0.7%)	27 (9.5%)	11 (3.9%)

Table 18: Number of Subjects With 1 or More Treatment-emergent Adverse Events (≥5%) in patients treated with DRd by MedDRA System-Organ Class, Preferred Term and Toxicity Grade; Safety Analysis Set (Study 54767414MMY3003)

	MMY3003			
	Rd (N=281)		DRd (N=283)	
	Any Grade (%)	Grade 3/4 (%)	Any Grade (%)	Grade 3/4 (%)
Hypotension	6 (2.1%)	1 (0.4%)	20 (7.1%)	2 (0.7%)
Eye disorders				
Cataract	14 (5.0%)	6 (2.1%)	26 (9.2%)	7 (2.5%)
Vision blurred	16 (5.7%)	0	23 (8.1%)	0
Investigations				
Weight decreased	11 (3.9%)	1 (0.4%)	19 (6.7%)	0
Alanine aminotransferase increased	11 (3.9%)	3 (1.1%)	16 (5.7%)	7 (2.5%)
Renal and urinary disorders				
Renal impairment	13 (4.6%)	1 (0.4%)	22 (7.8%)	1 (0.4%)

Key: DRd=Daratumumab-lenalidomide-dexamethasone, Rd=lenalidomide-dexamethasone.

[a] "Upper respiratory tract infection" includes bronchitis, sinusitis, respiratory tract infection viral, rhinitis, pharyngitis, respiratory tract infection, metapneumovirus infection, tracheobronchitis, viral upper respiratory tract infection, laryngitis, respiratory syncytial virus infection, staphylococcal pharyngitis, tonsillitis, viral pharyngitis, acute sinusitis, nasopharyngitis, bronchiolitis, bronchitis viral, pharyngitis streptococcal, tracheitis, upper respiratory tract infection bacterial, bronchitis bacterial, epiglottitis, laryngitis viral, oropharyngeal candidiasis, respiratory moniliasis, viral rhinitis, acute tonsillitis, rhinovirus infection.

[b] "Pneumonia" includes lobar pneumonia, pneumonia cytomegaloviral, pneumocystis jirovecii pneumonia, pneumonia pneumococcal, bronchopneumonia, lung infection, pulmonary sepsis, pneumonia legionalle, pneumonia bacterial, pneumonia influenza, pneumonia haemophilus, pneumonia Klebsiella, pneumonia streptococcal, pneumonia aspiration, pneumonia viral

[c] "Lower respiratory tract infection" includes lower respiratory tract infection and lower respiratory tract infection viral

[d] "Oedema peripheral" includes oedema, generalised oedema, peripheral swelling

[e] "Neutropenia" includes febrile neutropenia

[f] "Cough" includes productive cough, allergic cough

[g] "Dyspnoea" include dyspnoea exertional

[h] "Rash" includes rash erythematous, rash maculo-papular, rash pruritic, rash macular

[i] "Hypertension" includes blood pressure increased

Note: Adverse events are reported using MedDRA version 18.0.
Note: Percentages are calculated with the number of subjects in each group as denominator.

Study MMY3004: Darzalex in combination with bortezomib/dexamethasone

TEAEs described in Table 19 reflect exposure to Darzalex intravenous formulation in combination with bortezomib and dexamethasone (DVd) for a median treatment duration of 11.1 months (range: 0 to 21.2 months) and to bortezomib and dexamethasone (Vd) for a median treatment duration of 5.2 months (range: 0.2 to 8.0 months).

Infusion-related reactions (including terms determined by investigators to be related to infusion; see Infusion-Related Reactions (IRRs) from Pooled Clinical Studies) were reported in 45% of patients in the DVd group.

Table 19: Number of Subjects With 1 or More Treatment-emergent Adverse Events (≥5%) in patients treated with DVd by MedDRA System-Organ Class, Preferred Term and Toxicity Grade; Safety Analysis Set (Study 54767414MMY3004)

	MMY3004			
	Vd (N=237)		DVd (N=243)	
	Any Grade (%)	Grade 3/4 (%)	Any Grade (%)	Grade 3/4 (%)
Infections and infestations				
Upper respiratory tract infection[a]	73 (30.8%)	6 (2.5%)	119 (49.0%)	19 (7.8%)
Pneumonia[b]	33 (13.9%)	25 (10.5%)	44 (18.1%)	32 (13.2%)
Conjunctivitis	8 (3.4%)	1 (0.4%)	22 (9.1%)	0
Herpes zoster	7 (3.0%)	1 (0.4%)	15 (6.2%)	6 (2.5%)
Urinary tract infection	6 (2.5%)	1 (0.4%)	15 (6.2%)	2 (0.8%)
Blood and lymphatic system disorders				
Thrombocytopenia	105 (44.3%)	78 (32.9%)	145 (59.7%)	110 (45.3%)
Anaemia	75 (31.6%)	38 (16.0%)	67 (27.6%)	36 (14.8%)
Neutropenia[c]	23 (9.7%)	11 (4.6%)	46 (18.9%)	33 (13.6%)
Lymphopenia	9 (3.8%)	6 (2.5%)	32 (13.2%)	24 (9.9%)
Leukopenia	12 (5.1%)	5 (2.1%)	21 (8.6%)	6 (2.5%)
Nervous system disorders				
Peripheral sensory neuropathy	90 (38.0%)	16 (6.8%)	120 (49.4%)	11 (4.5%)
Neuralgia	26 (11.0%)	2 (0.8%)	33 (13.6%)	2 (0.8%)
Headache	14 (5.9%)	0	27 (11.1%)	1 (0.4%)
Dizziness	25 (10.5%)	0	25 (10.3%)	1 (0.4%)
Gastrointestinal disorders				
Diarrhoea	53 (22.4%)	3 (1.3%)	83 (34.2%)	9 (3.7%)
Constipation	38 (16.0%)	2 (0.8%)	52 (21.4%)	0
Nausea	27 (11.4%)	0	34 (14.0%)	2 (0.8%)
Vomiting	9 (3.8%)	0	27 (11.1%)	0
Abdominal pain upper	7 (3.0%)	0	18 (7.4%)	1 (0.4%)
Respiratory, thoracic and mediastinal disorders				
Cough[d]	32 (13.5%)	0	73 (30.0%)	0
Dyspnoea[e]	26 (11.0%)	3 (1.3%)	51 (21.0%)	10 (4.1%)
Bronchospasm	1 (0.4%)	0	23 (9.5%)	6 (2.5%)
Throat irritation[f]	1 (0.4%)	0	15 (6.2%)	0
Epistaxis	12 (5.1%)	1 (0.4%)	13 (5.3%)	1 (0.4%)
Nasal congestion	3 (1.3%)	0	13 (5.3%)	1 (0.4%)
General disorders and administration site conditions				
Oedema peripheral[g]	32 (13.5%)	0	58 (23.9%)	2 (0.8%)
Fatigue	58 (24.5%)	8 (3.4%)	53 (21.8%)	12 (4.9%)
Pyrexia	28 (11.8%)	3 (1.3%)	42 (17.3%)	3 (1.2%)
Asthenia	37 (15.6%)	5 (2.1%)	24 (9.9%)	2 (0.8%)
Musculoskeletal and connective tissue disorders				
Back pain	24 (10.1%)	3 (1.3%)	44 (18.1%)	5 (2.1%)
Arthralgia	13 (5.5%)	0	29 (11.9%)	4 (1.6%)
Pain in extremity	16 (6.8%)	2 (0.8%)	26 (10.7%)	4 (1.6%)
Muscle spasms	5 (2.1%)	0	21 (8.6%)	0
Bone pain	14 (5.9%)	3 (1.3%)	19 (7.8%)	4 (1.6%)
Musculoskeletal chest pain	5 (2.1%)	0	19 (7.8%)	1 (0.4%)
Musculoskeletal pain	3 (1.3%)	0	14 (5.8%)	1 (0.4%)
Metabolism and nutrition disorders				
Decreased appetite	12 (5.1%)	1 (0.4%)	26 (10.7%)	2 (0.8%)
Hypokalaemia	11 (4.6%)	3 (1.3%)	25 (10.3%)	6 (2.5%)
Hyperglycaemia	18 (7.6%)	6 (2.5%)	22 (9.1%)	9 (3.7%)
Hypocalcaemia	11 (4.6%)	2 (0.8%)	14 (5.8%)	4 (1.6%)
Hypophosphataemia	7 (3.0%)	1 (0.4%)	13 (5.3%)	5 (2.1%)
Psychiatric disorders				

Table 19: Number of Subjects With 1 or More Treatment-emergent Adverse Events (≥5%) in patients treated with DVd by MedDRA System-Organ Class, Preferred Term and Toxicity Grade; Safety Analysis Set (Study 54767414MMY3004)

	MMY3004			
	Vd (N=237)		DVd (N=243)	
	Any Grade (%)	Grade 3/4 (%)	Any Grade (%)	Grade 3/4 (%)
Insomnia	36 (15.2%)	3 (1.3%)	42 (17.3%)	1 (0.4%)
Skin and subcutaneous tissue disorders				
Rash[h]	8 (3.4%)	0	20 (8.2%)	0
Vascular disorders				
Hypertension[i]	8 (3.4%)	2 (0.8%)	22 (9.1%)	16 (6.6%)
Hypotension	10 (4.2%)	4 (1.7%)	13 (5.3%)	4 (1.6%)
Investigations				
Alanine aminotransferase increased	10 (4.2%)	0	17 (7.0%)	4 (1.6%)
Weight decreased	3 (1.3%)	0	16 (6.6%)	0
Aspartate aminotransferase increased	5 (2.1%)	0	13 (5.3%)	0

Key: DVd=Daratumumab-bortezomib-dexamethasone, Vd=bortezomib-dexamethasone.

[a] "Upper respiratory tract infection" includes bronchitis, sinusitis, respiratory tract infection viral, rhinitis, pharyngitis, respiratory tract infection, metapneumovirus infection, tracheobronchitis, viral upper respiratory tract infection, laryngitis, respiratory syncytial virus infection, staphylococcal pharyngitis, tonsillitis, viral pharyngitis, acute sinusitis, nasopharyngitis, bronchiolitis, bronchitis viral, pharyngitis streptococcal, tracheitis, upper respiratory tract infection bacterial, bronchitis bacterial, epiglottitis, laryngitis viral, oropharyngeal candidiasis, respiratory moniliasis, viral rhinitis, acute tonsillitis, rhinovirus infection.

[b] "Pneumonia" includes lobar pneumonia, pneumonia cytomegaloviral, pneumocystis jirovecii pneumonia, pneumonia pneumococcal, bronchopneumonia, lung infection, pulmonary sepsis, pneumonia legionalle, pneumonia bacterial, pneumonia influenza, pneumonia haemophilus, pneumonia Klebsiella, pneumonia streptococcal, pneumonia aspiration, pneumonia viral

[c] "Neutropenia" includes febrile neutropenia

[d] "Oedema peripheral" includes oedema, generalised oedema, peripheral swelling

[e] "Cough" includes productive cough, allergic cough

[f] "Dyspnoea" include dyspnoea exertional

[g] "Rash" includes rash erythematous, rash maculo-papular, rash pruritic, rash macular

[h] "Hypertension" includes blood pressure increased

Note: Adverse events are reported using MedDRA version 18.0.

Note: Percentages are calculated with the number of subjects in each group as denominator.

CANDOR Study: Darzalex in combination with carfilzomib and dexamethasone

Patients received treatment with any study drug for a median duration of 70 weeks in the DKd arm and 40 weeks in the Kd arm. Patients received a median of 68 weeks of treatment with daratumumab and a median of 58 weeks of carfilzomib treatment in the DKd arm; patients in the Kd arm received a median of 40 weeks of carfilzomib. Adverse events that occurred in ≥ 5% of patients are presented in Table 20.

Table 20: Number of Subjects With Adverse Reactions (≥5%) in Patients Treated with Either Kd or DKd by MedDRA System-Organ Class, Grouping of Preferred Terms and Toxicity Grade; Safety Population (CANDOR Study)

	CANDOR			
	Kd (N=153)		DKd (N=308)	
	Any Grade (%)	≥ Grade 3 (%)	Any Grade (%)	≥ Grade 3 (%)
Blood and lymphatic system disorders				
Thrombocytopenia[a]	46 (30.1)	25 (16.3)	115 (37.3)	76 (24.7)
Anaemia[b]	48 (31.4)	22 (14.4)	101 (32.8)	51 (16.6)
Neutropenia[c]	15 (9.8)	9 (5.9)	45 (14.6)	28 (9.1)

	CANDOR			
	Kd (N=153)		DKd (N=308)	
	Any Grade (%)	≥ Grade 3 (%)	Any Grade (%)	≥ Grade 3 (%)
Lymphopenia[d]	12 (7.8)	11 (7.2)	27 (8.8)	21 (6.8)
Leukopenia[e]	6 (3.9)	2 (1.3)	20 (6.5)	9 (2.9)
Cardiac disorders				
Cardiac failure[f]	8 (5.2)	7 (4.6)	15 (4.9)	7 (2.3)
Eye disorders				
Cataract	5 (3.3)	3 (2.0)	17 (5.5)	7 (2.3)
Gastrointestinal disorders				
Diarrhoea	22 (14.4)	1 (0.7)	97 (31.5)	12 (3.9)
Nausea	20 (13.1)	1 (0.7)	56 (18.2)	0
Vomiting	13 (8.5)	0	37 (12.0)	0
Constipation	6 (3.9)	0	22 (7.1)	0
Abdominal pain[g]	11 (7.2)	2 (1.3)	20 (6.5)	0
General disorders and administration site conditions				
Fatigue	28 (18.3)	7 (4.6)	75 (24.4)	24 (7.8)
Pyrexia	23 (15.0)	1 (0.7)	60 (19.5)	6 (1.9)
Edema peripheral	14 (9.2)	1 (0.7)	33 (10.7)	0
Asthenia	17 (11.1)	5 (3.3)	30 (9.7)	9 (2.9)
Chills	6 (3.9)	0	17 (5.5)	0
Infections and infestations				
Respiratory tract infection[h]	45 (29.4)	5 (3.3)	124 (40.3)	22 (7.1)
Pneumonia	19 (12.4)	13 (8.5)	55 (17.9)	41 (13.3)
Bronchitis	18 (11.8)	2 (1.3)	52 (16.9)	8 (2.6)
Influenza	10 (6.5)	1 (0.7)	34 (11.0)	11 (3.6)
Nasopharyngitis	13 (8.5)	1 (0.7)	27 (8.8)	1 (0.3)
Urinary tract infection	4 (2.6)	3 (2.0)	18 (5.8)	4 (1.3)
Injury, poisoning and procedural complications				
Infusion-related reaction	3 (2.0)	0	18 (5.8)	4 (1.3)
Metabolism and nutrition disorders				
Hyperglycemia	11 (7.2)	5 (3.3)	28 (9.1)	13 (4.2)
Decreased appetite	9 (5.9)	1 (0.7)	27 (8.8)	3 (1.0)
Hypokalemia	9 (5.9	2 (1.3)	18 (5.8)	5 (1.6)
Musculoskeletal and connective tissue disorders				
Back pain	15 (9.8)	2 (1.3)	50 (16.2)	6 (1.9)
Muscle spasms	18 (11.8)	2 (1.3)	36 (11.7)	2 (0.6)
Arthralgia	8 (5.2)	1 (0.7)	26 (8.4)	2 (0.6)
Pain in extremity	10 (6.5)	1 (0.7)	19 (6.2)	1 (0.3)
Nervous system disorders				
Peripheral neuropathy[i]	7 (4.6)	0	45 (14.6)	0
Headache	18 (11.8)	1 (0.7)	41 (13.3)	2 (0.6)
Dizziness	4 (2.6)	0	23 (7.5)	2 (0.6)
Psychiatric disorders				
Insomnia	17 (11.1)	3 (2.0)	55 (17.9)	12 (3.9)
Renal and urinary disorders				
Acute kidney injury	9 (5.9)	7 (4.6)	12 (3.9)	7 (2.3)
Respiratory, thoracic and mediastinal disorders				
Cough[j]	32 (20.9)	0	63 (20.5)	0
Dyspnea	34 (22.2)	4 (2.6)	61 (19.8)	12 (3.9)
Skin and subcutaneous tissue disorders				
Rash	10 (6.5)	1 (0.7)	17 (5.5)	0
Vascular disorders				
Hypertension	42 (27.5)	20 (13.1)	94 (30.5)	54 (17.5)

	CANDOR			
	Kd (N=153)		DKd (N=308)	
	Any Grade (%)	≥ Grade 3 (%)	Any Grade (%)	≥ Grade 3 (%)

Key: DKd=Daratumumab-carfilzomib-dexamethasone, Kd=carfilzomib-dexamethasone.
[a] 'Thrombocytopenia' includes Platelet Count Decreased PT and Thrombocytopenia PT.
[b] 'Anemia' includes Anemia PT, Hematocrit Decreased PT and Hemoglobin Decreased PT.
[c] 'Neutropenia' includes Neutrophil Count Decreased PT and Neutropenia PT.
[d] 'Lymphopenia' includes Lymphocyte Count Decreased PT and Lymphopenia PT.
[e] 'Leukopenia' includes Leukopenia PT and White Blood Cell Count Decreased PT.
[f] 'Cardiac Failure' includes Cardiac Failure PT, and Cardiac Failure Congestive PT.
[g] 'Abdominal Pain' includes Abdominal Pain PT, and Abdominal Pain Upper PT.
[h] 'Respiratory Tract Infection' includes Respiratory Tract Infection PT, Lower Respiratory Tract Infection, Upper Respiratory Tract Infection PT and Viral Upper Respiratory Tract Infection.
[i] 'Peripheral Neuropathy' includes Peripheral Sensory Neuropathy PT and Neuropathy Peripheral PT.
[j] 'Cough' includes Productive Cough PT, and Cough PT.

Patients with multiple myeloma who have received at least three prior lines of therapy including a PI and an IMiD, or who are refractory to both a PI and an IMiD

Studies MMY2002 and GEN501: Darzalex monotherapy

The information below reflect exposure to Darzalex intravenous formulation. TEAEs occurring at a rate of ≥2% are presented in Table 21.

Table 21: Treatment-emergent adverse events (≥ 2%) in multiple myeloma patients treated with Darzalex 16 mg/kg

	All Grades n (%) N= 156	Grades 3-4 n (%) N= 156
General disorders and administration site conditions		
Fatigue	62 (39.7%)	3 (1.9%)
Pyrexia	34 (21.8%)	2 (1.3%)
Chills	16 (10.3%)	0
Asthenia	13 (8.3%)	1 (0.6%)
Oedema peripheral	11 (7.1%)	1 (0.6%)
Chest pain	9 (5.8%)	0
Pain	8 (5.1%)	1 (0.6%)
Influenza like illness	7 (4.5%)	1 (0.6%)
Non-cardiac chest pain	7 (4.5%)	0
General physical health deterioration	5 (3.2%)	1 (0.6%)
Chest discomfort	4 (2.6%)	0
Respiratory, thoracic and mediastinal disorders		
Cough	38 (24.4%)	0
Nasal congestion	29 (18.6%)	0
Dyspnoea	25 (16.0%)	1 (0.6%)
Oropharyngeal pain	15 (9.6%)	0
Rhinitis allergic	11 (7.1%)	0
Throat irritation	10 (6.4%)	0
Dyspnoea exertional	9 (5.8%)	0
Epistaxis	9 (5.8%)	0
Productive cough	8 (5.1%)	0
Wheezing	8 (5.1%)	0
Bronchospasm	5 (3.2%)	2 (1.3%)
Pleural effusion	4 (2.6%)	0
Sinus congestion	4 (2.6%)	0

Table 21: Treatment-emergent adverse events (≥ 2%) in multiple myeloma patients treated with Darzalex 16 mg/kg

	All Grades n (%) N= 156	Grades 3-4 n (%) N= 156
Sneezing	4 (2.6%)	0
Musculoskeletal and connective tissue disorders		
Back pain	40 (25.6%)	4 (2.6%)
Arthralgia	28 (17.9%)	0
Pain in extremity	26 (16.7%)	1 (0.6%)
Musculoskeletal chest pain	19 (12.2%)	2 (1.3%)
Musculoskeletal pain	16 (10.3%)	1 (0.6%)
Bone pain	15 (9.6%)	1 (0.6%)
Muscle spasms	10 (6.4%)	0
Myalgia	7 (4.5%)	0
Neck pain	5 (3.2%)	2 (1.3%)
Groin pain	4 (2.6%)	1 (0.6%)
Infections and infestations		
Upper respiratory tract infection[a]	63 (40.4%)	12 (7.7%)
Nasopharyngitis[b]	25 (16.0%)	0
Pneumonia[c]	17 (10.9%)	9 (5.8%)
Sinusitis[b]	11 (7.1%)	0
Urinary tract infection	9 (5.8%)	0
Bronchitis[b]	8 (5.1%)	1 (0.6%)
Herpes zoster	5 (3.2%)	2 (1.3%)
Influenza	4 (2.6%)	0
Gastrointestinal disorders		
Nausea	44 (28.2%)	0
Diarrhoea	28 (17.9%)	1 (0.6%)
Constipation	24 (15.4%)	0
Vomiting	21 (13.5%)	0
Abdominal pain	9 (5.8%)	2 (1.3%)
Abdominal discomfort	4 (2.6%)	0
Dyspepsia	4 (2.6%)	0
Stomatitis	4 (2.6%)	0
Toothache	4 (2.6%)	0
Blood and lymphatic system disorders		
Anaemia	43 (27.6%)	27 (17.3%)
Neutropenia	36 (23.1%)	19 (12.2%)
Thrombocytopenia	32 (20.5%)	22 (14.1%)
Leukopenia	15 (9.6%)	7 (4.5%)
Lymphopenia	10 (6.4%)	9 (5.8%)
Metabolism and nutrition disorders		
Decreased appetite	23 (14.7%)	1 (0.6%)
Hypercalcaemia	18 (11.5%)	5 (3.2%)
Hyperglycaemia	14 (9.0%)	4 (2.6%)
Hypokalaemia	12 (7.7%)	1 (0.6%)
Hypomagnesaemia	10 (6.4%)	0
Hyponatraemia	8 (5.1%)	0
Hyperkalaemia	5 (3.2%)	1 (0.6%)
Hypoalbuminaemia	5 (3.2%)	0
Hyperuricaemia	4 (2.6%)	1 (0.6%)
Nervous system disorders		
Headache	19 (12.2%)	2 (1.3%)
Dizziness	14 (9.0%)	0
Hypoaesthesia	8 (5.1%)	0
Peripheral sensory neuropathy	7 (4.5%)	0
Somnolence	5 (3.2%)	1 (0.6%)
Tremor	4 (2.6%)	0

Table 21: Treatment-emergent adverse events (≥ 2%) in multiple myeloma patients treated with Darzalex 16 mg/kg

	All Grades n (%) N= 156	Grades 3-4 n (%) N= 156
Investigations		
Blood creatinine increased	10 (6.4%)	2 (1.3%)
Weight decreased	8 (5.1%)	1 (0.6%)
Aspartate aminotransferase increased	6 (3.8%)	0
Alanine aminotransferase increased	4 (2.6%)	1 (0.6%)
Blood alkaline phosphatase increased	4 (2.6%)	0
Weight increased	4 (2.6%)	0
Skin and subcutaneous tissue disorders		
Pruritus	5 (3.2%)	0
Dry skin	4 (2.6%)	0
Hyperhidrosis	4 (2.6%)	0
Rash	4 (2.6%)	0
Injury, poisoning and procedural complications		
Contusion	5 (3.2%)	0
Fall	5 (3.2%)	1 (0.6%)
Rib fracture	4 (2.6%)	0
Psychiatric disorders		
Anxiety	10 (6.4%)	0
Insomnia	9 (5.8%)	0
Confusional state	8 (5.1%)	2 (1.3%)
Vascular disorders		
Hypertension	15 (9.6%)	7 (4.5%)
Hypotension	7 (4.5%)	1 (0.6%)
Flushing	4 (2.6%)	0
Haematoma	4 (2.6%)	0
Eye disorders		
Vision blurred	10 (6.4%)	0
Renal and urinary disorders		
Dysuria	4 (2.6%)	0
Cardiac disorders		
Palpitations	5 (3.2%)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		
Basal cell carcinoma	4 (2.6%)	0

[a] includes upper respiratory tract infection, nasopharyngitis, sinusitis, bronchitis, pharyngitis, rhinitis, viral upper respiratory tract infection, respiratory tract infection, lower respiratory tract infection, pneumonia, lobar pneumonia, and pneumonia streptococcal.
[b] includes upper respiratory tract infection, nasopharyngitis, sinusitis, bronchitis, pharyngitis, rhinitis, viral upper respiratory tract infection, and respiratory tract infection.
[c] includes pneumonia, lobar pneumonia, and pneumonia streptococcal.

There were 4 deaths due to TEAEs (cardio-respiratory arrest [n=1], pneumonia [n=2] and general physical health deterioration [n=1]).

Bleeding events occurred in 20 patients (18.9%) in Study MMY2002 and 2 patients (4.4%) in Study GEN501. These were mainly Grade 1/2, with two Grade 3 events. Of these patients, 9 patients also had thrombocytopenia.

Adverse Events from Clinical Trials

Cardiac Disorders

Multiple myeloma

In Darzalex SC monotherapy Study MMY3012, the incidence of all grade cardiac disorder TEAEs was comparable between the Darzalex SC (7.3%) and Darzalex IV (6.6%) groups. Grade 3 and 4 cardiac disorder TEAEs were generally balanced between the 2 treatment groups (Darzalex SC: 1.2%; Darzalex IV 1.9%)

In Darzalex SC combination therapy Study MMY2040, for patients with newly diagnosed multiple myeloma treated with D-VMP the incidence of all grade cardiac disorder TEAEs was 7.5%, and the incidence of Grade 3 and 4 cardiac disorder TEAEs was 3.0%. For patients with relapsed or refractory multiple myeloma treated with D-Rd the incidence of all grade cardiac disorder TEAEs was 16.9%, and the incidence of Grade 3 and 4 cardiac disorder TEAEs was 6.2%. For patients with relapsed or refractory multiple myeloma treated with DKd the incidence of all Grade cardiac disorder TEAEs was 7.6%, and the incidence of Grade 3 and 4 cardiac disorder TEAEs was 3.0%.

In Darzalex SC Study MMY3013, the incidence of all grade cardiac disorder TEAEs was 12.7% in the DPd arm and 9.3% in the Pd arm. The incidence of Grade 3 and 4 cardiac disorder TEAEs was 4.2% and 4.0% in the DPd and Pd arms, respectively. The most commonly reported cardiac disorder TEAEs in the DPd arm were atrial fibrillation (DPd: 4.7%, Pd: 2.0%) and sinus tachycardia (DPd: 2.0%, Pd: 0%).

In Darzalex SC Study MMY3014, the incidence of all grade cardiac disorder TEAEs was 17.1% in the D-VRd arm and 10.1% in the VRd arm. The incidence of Grade 3 and 4 cardiac disorder TEAEs was 6.6% and 2.6% in the D-VRd and VRd arms, respectively. The most commonly reported cardiac disorder TEAEs in the D-VRd arm were atrial fibrillation (D-VRd: 5.1%, VRd: 2.3%) and sinus tachycardia (D-VRd: 2.8%, VRd: 0.6%).

In Darzalex intravenous formulation combination therapy studies, a higher incidence of all grade cardiac disorder TEAEs occurred in the Darzalex arm compared with the control arm: in Study MMY3008 (DRd: 27.5 vs Rd: 26.3%); in Study MMY3007 (D-VMP: 14.7% vs VMP: 11.3%); in Study MMY3003 (DRd: 16.3% vs Rd: 10.0%); and in Study MMY3004 (DVd: 14.0% vs Vd: 6.3%). Grade 3 and 4 cardiac disorder TEAEs were generally balanced between the 2 arms in the studies (MMY3008, DRd: 8.2 % vs Rd: 8.2%; MMY3007, D-VMP: 3.8% vs VMP: 3.1%; MMY3003, DRd: 3.9% vs Rd: 3.2%; MMY3004, DVd: 4.5% vs Vd: 3.0%).

In Study MMY3008, the most commonly reported cardiac disorder TEAEs in the DRd arm were atrial fibrillation (DRd: 6.3%, Rd: 10.1%), palpitations (DRd: 3.3%, Rd: 2.2%), and cardiac failure (DRd: 3.0%, Rd: 3.6%).

In Study MMY3007, the most commonly reported cardiac disorder TEAE (≥2% incidence vs VMP arm) was atrial fibrillation (D-VMP: 4.9%; VMP: 2.0%).

In Study MMY3003, the most commonly reported cardiac disorder TEAEs in the DRd arm were atrial fibrillation (DRd 3.5%; Rd 2.8%), tachycardia (DRd 3.5%; Rd 0.7%), and angina pectoris (DRd 2.8%; Rd 0.4%).

In Study MMY3004, the most commonly reported cardiac disorder TEAEs in the DVd arm were atrial fibrillation (DVd 4.5%; Vd 1.7%), sinus tachycardia (DVd 2.5%; Vd 0.4%), and palpitations (DVd 2.1%; Vd 0.8%). Deaths due to cardiac disorders occurred in 1.2% of patients in the DVd arm and 0.4% of patients in the Vd arm.

In the CANDOR study, the most commonly reported cardiac disorder TEAEs in the DKd arm was cardiac failure (DKd 7.5%; Kd 10.5%). Deaths due to cardiac disorders occurred in 1.3% of patients in the DKd arm and none in the Kd arm.

AL Amyloidosis

Among patients who received Darzalex SC in combination with VCd, 72% of patients had baseline cardiac involvement with Mayo Cardiac Stage I (3%), Stage II (46%), and Stage III (51%). Serious cardiac disorders occurred in 16% of patients (8% of patients with Mayo Cardiac Stage I and II and 28% of patients with Stage III). Serious cardiac disorders that occurred in >2% of patients included cardiac failure (8%), cardiac arrest (4%), and arrhythmia (4%). Fatal cardiac disorders occurred in 10% of patients (5% of patients with Mayo Cardiac Stage I and II and 19% of patients with Stage III) who received Darzalex SC in combination with VCd. Fatal cardiac disorders that occurred in more than one patient in the D-VCd arm included cardiac arrest (4%), sudden death (3%), and cardiac failure (3%).

Herpes Zoster Virus Reactivation

Multiple myeloma

In the Darzalex SC monotherapy study MMY3012, systemic anti-viral medications were used in 77% of patients. Herpes zoster was reported in 1.2% of patients. In the Darzalex SC combination study, systemic anti-viral medications were used in 94%, 83%, and 94% of patients in the D-VMP, D-Rd, and DKd cohorts, respectively. Herpes zoster was reported in 7.5%, 1.5%, and 1.5% of patients in the D-VMP, D-Rd, and DKd cohorts, respectively.

In Darzalex SC Study MMY3013, prophylactic anti-viral medication for herpes infection was used in 91.3% of patients in the DPd arm and 78.0% of patients in the Pd arm. Herpes zoster infection was reported in one patient in the DPd arm.

In Darzalex SC Study MMY3014, systemic anti-viral medications were used in 97.2% of patients in the D-VRd arm and 96.3% of patients in the VRd arm. Herpes zoster infection was reported in 5.1% and 6.6% of subjects in the D-VRd and VRd arms, respectively.

In Darzalex intravenous formulation 16 mg/kg monotherapy studies, systemic anti-viral medications were used in 75% of patients. Herpes zoster was reported in 3% of patients.

In Darzalex intravenous formulation combination studies for patients with relapsed or refractory multiple myeloma, systemic anti-viral medications were used in 61.4% of patients. Herpes zoster was reported in 2.8% of patients. In Darzalex intravenous formulation combination studies for patients with newly diagnosed multiple myeloma, systemic anti-viral medications were used in 75% of patients. Herpes zoster was reported in 3.0% of patients.

AL Amyloidosis

In the Darzalex SC study AMY3001 in patients with newly diagnosed AL amyloidosis, systemic anti-viral medication was used in 76.1% of patients and prophylactic antivirals were administered in 82.4% of patients. Herpes zoster was reported in 5.2% and 6.4% of patients in the D-VCd and VCd cohorts, respectively.

Infections

Multiple myeloma

In patients receiving Darzalex SC monotherapy in Study MMY3012, the incidence of infections was similar between Darzalex SC (45.8%) and intravenous Darzalex groups (45.3%). Additionally, Grade 3 or 4 infections also occurred at similar frequencies between Darzalex SC (10.4%) and intravenous Darzalex (11.2%). Most infections were manageable and rarely led to treatment discontinuation (SC: 1.2%; IV:3.5%). Pneumonia was the most commonly reported severe (Grade 3 or 4) infection (SC: 2.7%; IV: 3.9%).

In the Darzalex SC combination therapy Study MMY2040 for patients with newly diagnosed multiple myeloma treated with D-VMP, the incidence of infections was 68.7%. Grade 3 or 4 infections were reported in 11.9% of patients. Pneumonia was the most commonly reported severe (Grade 3 or 4) infection (4.5%). Discontinuations from treatment due to infection were reported in 1.5% of patients. For patients with relapsed or refractory myeloma treated with D-Rd, infections were reported in 72.3%, and Grade 3 or 4 infections were reported in 23.1% of treated patients. Pneumonia was the most commonly reported severe (grade 3 or 4) infection (6.2%). Discontinuations from treatment due to infection were reported in 3.1% of patients. For patients with relapsed or refractory myeloma treated with DKd, infections were reported in 74.2%, and Grade 3 or 4 infections were reported in 10.6% of treated patients. Pneumonia was the most commonly reported severe (Grade 3 or 4) infection (3.0%).

In the Darzalex SC combination therapy Study MMY3013 for patients with relapsed or refractory multiple myeloma treated with DPd, the incidence of infections was 70.5% compared to 55.3% for patients treated with Pd. Grade 3 or 4 infections were reported in 28.2% of DPd treated patients compared to 22.7% of Pd treated patients. The most commonly reported severe (Grade 3 or 4) infection were pneumonia (13.4%) and lower respiratory tract infection (11.4%). Grade 5 (fatal) infections were reported for 5% of DPd patients (pneumonia, 3 patients; COVID-19, lower respiratory tract infection, sepsis, septic shock, 1 patient each; campylobacter infection and systemic candida in 1 patient) and for 3% of Pd treated patients

(pneumonia, 2 patients; septic shock, 2 patients; lower respiratory tract infection, 1 patient). Discontinuations from treatment due to infection was reported for one patient.

In the Darzalex SC combination therapy Study MMY3014 of D-VRd for the treatment of patients with newly diagnosed multiple myeloma who are eligible for ASCT, the incidence of infections was 86.9% compared to 76.7% for patients treated with VRd. Grade 3 or 4 infections were reported in 35.3% of D-VRd treated patients compared to 27.4% of VRd treated patients. The most commonly (≥5%) reported severe (Grade 3 or 4) infection was pneumonia (10.5% D-VRd and 6.1% VRd). Grade 5 (fatal) infections were reported for 2.3% of D-VRd patients (COVID-19, COVID-19 pneumonia, and sepsis: 2 patients each; post-procedural sepsis, and septic shock: 1 patient each) and for 2.6% of VRd treated patients (sepsis, and septic shock: 3 patients each; COVID-19, pneumonia, and pneumonia influenzal: 1 patient each). The rate of infections leading to discontinuation 2.3% in D-VRd patients and 2.0% in VRd patients. Opportunistic infections occurred in 5.7% and 4.6% of patients treated with D-VRd and VRd, respectively.

In the Darzalex intravenous formulation combination therapy studies for patients with newly diagnosed multiple myeloma, infections were reported with Darzalex combinations and background therapies (DRd: 86%, Rd: 73%, D-VMP: 67%, VMP: 48%). Grade 3 or 4 infections were reported (DRd: 32%, Rd: 23%, D-VMP: 23%, VMP: 15%). Discontinuations from treatment due to infection were reported (DRd: 0.5%, Rd: 1.4%, D-VMP: 0.9%, VMP: 1.4%). Fatal infections were reported in 1.4% to 2.2% of patients across studies primarily due to pneumonia, sepsis, peritonitis, or upper respiratory tract infection.

In Darzalex intravenous formulation combination therapy studies for patients with relapsed or refractory multiple myeloma, infections were reported in 87% and 73% of patients in the DRd and DVd groups, respectively. Grade 1 or 2 infections were reported with Darzalex combinations and background therapies (Grade 1 - DVd: 7.8%, Vd: 10%, DRd: 14.1%, Rd: 10.7%; Grade 2 – DVd: 39.1%, Vd: 24.9%, DRd: 41.0%, Rd: 39.5%). Grade 3 or 4 infections were reported with Darzalex combinations and background therapies (DVd: 26%, Vd: 19%, DRd: 31%, Rd: 24%). Grade 5 infections were also reported (DVd: 1.2%, Vd: 1.7%, DRd: 2.8%, Rd: 1.4%). Pneumonia was the most commonly reported severe (Grade 3 or 4) infection across studies. Discontinuations from treatment due to infection were reported (DVd: 4.1%, Vd: 2.5%, DRd: 4.6%, Rd: 2.5%). Fatal infections were reported in 1.2% to 2.8% of patients across studies primarily due to pneumonia and sepsis. Higher rates of fatal infections (5%) have been observed when daratumumab is combined with carfilzomib/dexamethasone. In Darzalex intravenous formulation 16 mg/kg monotherapy studies, infections were reported in 59% of patients, the majority were respiratory tract infections (including upper respiratory tract infections and pneumonia) (48.1%). Most infections were Grade 1/2 in severity and Grade 3/4 infections were reported in 10% of patients. Pneumonia was the most common Grade 3/4 infection (5.8%).

In the CANDOR study for patients with relapsed or refractory multiple myeloma who had received 1 to 3 prior therapies, infections were reported in 81.2% of patients in the DKd group. Grade ≥3 infections were reported for 37.3% of patients in the DKd group and 29.4% in the Kd group. Grade 5 infections were reported in 4.5% of patients in the DKd group and 2.6% in the Kd group. Pneumonia was the most commonly reported Grade ≥3 infection (DKd: 13.3%; Kd: 8.5%). Discontinuations from treatment due to infection were occurred in 4.5% of patients in the DKd group and 2.0% in the Kd group.

Opportunistic infections occurred at a higher incidence in patients receiving DVd (14%) compared to Vd alone (9%). Grade 3 and 4 TEAEs of opportunistic infection occurred in 5% of patients in the DVd arm and 0.4% of patients in the Vd arm. The incidence of opportunistic infections (any grade) was 13.1% in the DRd arm compared with 11.4% in the Rd arm. Serious opportunistic infection occurred in 2.5% of patients in the DRd arm and in 1.4% of patients in the Rd arm. In the CANDOR study, the incidence of opportunistic infections was 9.1% in the DKd arm and 3.9% in the Kd arm. Opportunistic infections were observed in 10.9% of the patients in Darzalex 16 mg/kg monotherapy studies.

Cytomegalovirus (CMV) infection was reported in 0.7% of patients treated with daratumumab in randomized clinical trials, with 0.5% of patients reporting serious events. These included cytomegalovirus infection, cytomegaloviral pneumonia, cytomegalovirus chorioretinitis, cytomegalovirus gastroenteritis and cytomegalovirus esophagitis.

AL amyloidosis

In patients with AL amyloidosis receiving Darzalex SC combination therapy with VCd, the incidence of Grade 3 or 4 infections was 16.6% in the D-VCd arm, and 10.1% in the VCd arm. The incidence of Grade 5 (fatal) infections was 1% in both the D-VCd and VCd arms. The most commonly reported Grade 3 or 4 infection was pneumonia (D-VCd: 7.8%; VCd: 4.3%). The incidence of discontinuation due to infection was 1.6% in the D-VCd arm and 0.5% in the VCd arm.

Infusion-related Reactions (IRRs) from Pooled Clinical Studies

In clinical trials with Darzalex SC (monotherapy and combination treatments; N=1249), the incidence of any grade infusion related reactions was approximately 8% with the first (Week 1) injection, 0.3% with the Week 2 injection, and 1.0% with subsequent injections. Grades 3 and 4 IRRs were seen in 0.7% and 0.1% of patients, respectively.

In clinical trials with intravenous Darzalex (monotherapy and combination treatments, n=2356), the majority of IRRs were Grades 1 and 2. Grade 3 and Grade 4 IRRs were reported in approximately 4% and 0.2% of patients, respectively. The incidence of any grade infusion-related reactions was approximately 33% with the first (16 mg/kg, Week 1) infusion of Darzalex, 2% with the Week 2 infusion, and 6% with subsequent infusions. Less than 1% of patients had a Grade ≥3 infusion reaction with Week 2 or subsequent infusions. The median

time to onset of a reaction was 1.5 hours (range: 0.0 to 72.8 hours). The incidence of infusion modifications due to reactions was approximately 32%. Median durations of 16 mg/kg infusions for the 1st, 2nd and subsequent infusions were 6.9, 4.3 and 3.5 hours respectively. Discontinuation of daratumumab treatment due to an IRR occurred in <1% of patients.

Signs and symptoms of IRRs may include respiratory symptoms, such as nasal congestion, cough, throat irritation, allergic rhinitis, wheezing as well as pyrexia, chest pain, pruritus, chills, vomiting, nausea, and hypotension. Severe reactions have occurred, including bronchospasm, hypoxia, dyspnea, hypertension and tachycardia.

Injection site reactions (ISRs)

In clinical trials with Darzalex SC, the incidence of any grade injection site reaction was approximately 7%. There were no Grade 3 or 4 ISRs. The most common (≥ 1%) ISR was erythema.

Special Population

Geriatrics: The incidence of serious adverse reactions was higher in older than in younger patients. Among patients with relapsed and refractory multiple myeloma (n=1213), the most common serious adverse reactions that occurred more frequently in elderly patients (≥65 years of age) were pneumonia and sepsis. Among patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant (n=710), the most common serious adverse reactions that occurred more frequently in elderly patients (≥75 years of age) was pneumonia. Among patients with newly diagnosed multiple myeloma who are eligible for autologous stem cell transplant (n=351) the most common serious adverse reaction that occurred more frequently in elderly (≥65 years of age) was pneumonia.

Of the 149 patients who received Darzalex SC as combination therapy with pomalidomide and dexamethasone for relapsed and refractory multiple myeloma, 42% were 65 to <75 years of age, and 16% were 75 years of age or older. No overall differences in effectiveness were observed based on age. Adverse reactions occurring at a higher frequency (≥5% difference) in patients ≥65 years of age included fatigue, pyrexia, peripheral edema, diarrhea, and cough. Serious adverse reactions occurring at a higher frequency (≥2% difference) in patients ≥65 years of age included pneumonia and thrombocytopenia.

Among patients with newly diagnosed AL amyloidosis (n=193, including 87 aged ≥65 years), the most common serious adverse reaction that occurred more frequently in elderly patients (≥65 years of age) was pneumonia.

Other Adverse Reactions

Other adverse reactions (any grade) reported in patients treated with daratumumab in pooled clinical studies are listed in Table 22.

Table 22: Other adverse reactions reported in patients treated with daratumumab in clinical trials

System Organ Class Adverse Reaction (%, any grade)
Gastrointestinal disorders Pancreatitis[a] (1%)
Immune system disorders Hypogammaglobulinemia[b] (2%)

[a] Pancreatitis, Pancreatitis acute, Pancreatitis chronic, Hyperamylasemia, Obstructive pancreatitis, Lipase increased.

[b] Hypogammaglobulinemia, Blood immunoglobulin G decreased. Immunoglobulins decreased.

8.3 Less Common Clinical Trial Adverse Reactions

SUBCUTANEOUS FORMULATION (Darzalex SC)

Monotherapy

Study MMY3012

Other TEAEs (<5% in the Darzalex SC arm) of clinical relevance include:

Infections and infestations: bronchitis, urinary tract infection, influenza, oral herpes, viral infection, herpes zoster, rhinitis, sepsis, septic shock, abscess limb, cellulitis, fungal infection, hepatitis B virus reactivation, salmonellosis.

Blood and lymphatic system disorders: febrile neutropenia.

General disorders and administration site conditions: chest pain, pain.

Gastrointestinal disorders: abdominal pain, gastrooesophageal reflux disease, stomatitis.

Metabolism and nutrition disorders: hypokalaemia, hyponatraemia, hyperkalaemia, diabetes mellitus.

Respiratory, thoracic and mediastinal disorders: hypoxia, respiratory failure.

Nervous system disorders: dizziness, peripheral sensory neuropathy, paraesthesia, tremor, aphasia, cognitive disorder, dysgeusia, hypoaesthesia.

Skin and subcutaneous tissue disorders: erythema, rash, urticaria.

Renal and urinary disorders: acute kidney injury.

Investigations: alanine aminotransferase increased, blood creatine increased, aspartate aminotransferase increased.

Vascular disorders: hypotension, hypertensive crisis.

Psychiatric disorders: anxiety.

Cardiac disorders: tachycardia, cardiac failure, atrial fibrillation, angina pectoris.

Eye disorders: cataract.

Hepatobiliary disorders: hepatitis toxic.

Combination Therapies in Multiple Myeloma

Study MMY2040 (D-VMP and D-Rd cohorts)

Other TEAEs (<5% across all cohorts) of clinical relevance include:

General disorders and administration site conditions: chest pain, influenza like illness.

Gastrointestinal disorders: odynophagia, stomatitis.

Blood and lymphatic system disorders: febrile neutropenia.

Nervous system disorders: peripheral motor neuropathy, syncope.

Infection and infestations: cellulitis, gastroenteritis, influenza, cytomegalovirus infection, neutropenic sepsis, oral candidiasis, sepsis.

Psychiatric disorders: anxiety, depression.

Investigations: alanine aminotransferase increased, aspartate aminotransferase increased.

Metabolism and nutrition disorders: hyperkalaemia, diabetic metabolic decompensation.

Vascular disorders: deep vein thrombosis, orthostatic hypotension.

Cardiac disorders: atrial fibrillation, cardiac failure, tachycardia.

Renal and urinary disorders: renal failure.

Study MMY2040 (DKd cohort)

Other TEAEs (<5% in the DKd cohort) of clinical relevance include:

Gastrointestinal disorders: pancreatitis.

Infection and infestations: urinary tract infection, herpes zoster, sepsis.

Metabolism and nutrition disorders: decreased appetite, hypocalcemia.

Nervous system disorders: dizziness, syncope.

General disorders and administration site conditions: infusion reactions, chills.

Vascular disorders: hypotension.

Study MMY3014: Darzalex SC in combination with bortezomib/lenalidomide/dexamethasone

Other TEAEs (<5% in the D-VRd arm) of clinical relevance include:

Cardiac disorders: sinus tachycardia, palpitations.

Ear and labyrinth disorder: tinnitus, vertigo.

Eye disorders: cataract, dry eye.

Gastrointestinal disorders: hemorrhoids, dry mouth, gastroesophageal reflux disease, toothache, inguinal hernia rectal hemorrhage, abdominal distension, mouth ulceration.

General disorders and administration site conditions: injection site erythema, malaise, chills, chest pain, pain, peripheral swelling, edema.

Hepatobiliary disorders: hepatic cytolysis, hyperbilirubinemia, cholestasis.

Infection and infestations: rhinitis, sinusitis, COVID-19 pneumonia, conjunctivitis, respiratory syncytial infection, tooth infection, cystitis, ear infection, oral candidiasis, pharyngitis, parainfluenza virus infection, sepsis, Escherichia urinary tract infection, respiratory tract infection, viral upper respiratory tract infection.

Injury, poisoning and procedural complications: fall, tooth fracture.

Investigations: weight decreased, blood creatinine increased.

Metabolism and nutrition disorders: hyperglycemia, hypomagnesemia, iron deficiency, hyponatremia.

Musculoskeletal and connective tissue disorders: neck pain, muscular weakness, musculoskeletal pain, spinal pain, flank pain.

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

Nervous system disorders: peripheral motor neuropathy, peripheral sensorimotor neuropathy, syncope, presyncope, dysesthesia, somnolence, ageusia.

Psychiatric disorders: agitation, depression.

Renal and urinary disorders: renal impairment, dysuria, renal failure.

Respiratory, thoracic and mediastinal disorders: oropharyngeal pain, rhinorrhea, pulmonary embolism, dysphonia, hiccups, productive cough, dyspnea exertional, epistaxis.

Skin and subcutaneous tissue disorders: hyperhidrosis, urticaria, eczema.

Vascular disorders: deep vein thrombosis, superficial vein thrombosis, orthostatic hypotension.

Study MMY3013: Darzalex SC in combination with pomalidomide/dexamethasone

Other TEAEs (<5% in the DPd arm) of clinical relevance include:

General disorders and administration site conditions: non-cardiac chest pain, influenza like illness, chills, malaise, general physical health deterioration, pain.

Gastrointestinal disorders: dyspepsia, abdominal distension, abdominal pain, odynophagia, colitis ischemic, stomatitis.

Musculoskeletal and connective tissue disorders: arthralgia, musculoskeletal pain, spinal pain, myalgia, myopathy.

Nervous system disorders: headache, paraesthesia, dizziness, neuropathy peripheral, amnesia, balance disorder, dysgeusia, hypoesthesia.

Infection and infestations: influenza, cellulitis, fungal infection, gastroenteritis, COVID-19, conjunctivitis, otitis media, viral infection.

Psychiatric disorders: anxiety, depression, agitation, confusional state, mood altered, nervousness, affective disorder.

Investigations: ECOG performance status worsened, blood creatinine increased, alanine aminotransferase increased, aspartate aminotransferase increased, c-reactive protein increased, weight decreased, blood bicarbonate decreased, fibrin D dimer increased.

Metabolism and nutrition disorders: decreased appetite, hypophosphatemia, hypomagnesemia, hyperuricemia, type-2 diabetes mellitus, hyperlipidemia, hyponatremia.

Respiratory, thoracic and mediastinal disorders: rhinorrhea, productive cough, catarrh, hiccups, oropharyngeal pain, pulmonary embolism, respiratory failure, rhinitis allergic.

Skin and subcutaneous tissue disorders: hyperhidrosis, pruritis, erythema, alopecia, dry skin, ecchymosis.

Vascular disorders: hypertension, flushing, orthostatic hypotension, thrombosis.

Cardiac disorders: atrial fibrillation, sinus tachycardia, angina pectoris, tachycardia.

Renal and urinary disorders: renal impairment, acute kidney injury.

Injury, poisoning and procedural complications: lumbar vertebral fracture, rib fracture

Eye disorder: cataract

Endocrine disorders: cushingoid

Hepatobiliary disorders: hyperbilirubinaemia

Immune system disorders: hypogammaglobulinemia

Combination Treatment for AL Amyloidosis

Study AMY3001: Darzalex SC in combination with bortezomib, cyclophosphamide and dexamethasone

Other TEAEs (<5% in the D-VCd arm) of clinical relevance include:

General disorders and administration site conditions: chest pain, influenza-like illness, malaise, localized edema, sudden death, face edema, injection site discolouration, injection site hematoma.

Blood and lymphatic system disorders: febrile neutropenia.

Gastrointestinal disorders: dysphagia, flatulence, gastroesophageal reflux disease, hemorrhoids, stomatitis, mouth hemorrhage, hematochezia, ascites, aphthous ulcer, gastric ulcer, odynophagia.

Infection and infestations: candidiasis, urinary tract infection, gastroenteritis, otitis media, tooth infection, tooth abscess.

Nervous system disorders: neuralgia, presyncope, hypoesthesia, neuropathy peripheral, somnolence, cerebral infarction, dizziness postural, lethargy, post-herpetic neuralgia.

Respiratory, thoracic and mediastinal disorders: oropharyngeal pain, nasal congestion, dysphonia, rales, hiccups, rhinorrhea.

Metabolism and nutrition disorders: hyperkalemia, hyperuricemia, fluid retention, hypertriglyceridemia, hypoglycemia, hypercholesterolemia, hypomagnesemia.

Musculoskeletal and connective tissue disorder: musculoskeletal chest pain.

Skin and subcutaneous tissue disorders: maculo-papular rash, alopecia, dry skin, pruritis, decubitis ulcer, hyperhidrosis, dermatitis allergic, petechia, rash pruritic, urticaria.

Investigations: weight decreased, weight increased, alpha hydroxybutyrate dehydrogenase increased, blood lactate dehydrogenase increased, blood creatinine phosphokinase increased, troponin I increased.

Cardiac disorders: cardiac arrest, angina pectoris, palpitations, pericardial effusion, tachycardia.

Vascular disorders: hypertension.

Renal and urinary disorders: acute kidney injury, hematuria.

Ear and labyrinth disorder: vertigo, deafness, hypoacusis, tinnitus.

Eye disorder: blepharitis, vision blurred, conjunctival hemorrhage, eye irritation, visual impairment, vitreous floaters.

Psychiatric disorders: Confusional state, depressive symptom.

INTRAVENOUS FORMULATION (Darzalex)

The following sections present data from a separate Product Monograph for Darzalex intravenous formulation studies:

- **Patients with newly diagnosed multiple myeloma who are ineligible for ASCT**
- **Patients with multiple myeloma who have received at least one prior therapy**
- **Patients with multiple myeloma who have received at least three prior lines of therapy including a PI and an IMiD, or who are refractory to both a PI and an IMiD**

Patients with newly diagnosed multiple myeloma who are ineligible for ASCT

Study MMY3008: Darzalex in combination with lenalidomide and dexamethasone

Other TEAEs (<5% and ≥2% in the DRd arm) of clinical relevance include:

Cardiac disorders: palpitations, cardiac failure, bradycardia, sinus tachycardia.

Ear and labyrinth disorders: vertigo, tinnitus, hypoacusis.

Gastrointestinal disorders: abdominal distension, hemorrhoids, gastritis, flatulence, inguinal hernia.

General disorders and administration site conditions: influenza-like illness, pain, malaise, chest discomfort, peripheral swelling, chest pain, edema.

Hepatobiliary disorders: hyperbilirubinemia.

Infections and infestations: cystitis, pharyngitis, cellulitis, lung infection, sepsis, tooth abscess, conjunctivitis, diverticulitis, tooth infection.

Injury, poisoning and procedural complications: rib fracture, spinal compression fracture.

Investigations: alanine aminotransferase increased, blood alkaline phosphatase increased.

Metabolism and nutritional disorders: gout, hyperkalemia, vitamin D deficiency, hypoalbuminemia, hypoglycemia, vitamin B12 deficiency.

Musculoskeletal and connective tissue disorders: pain in jaw, joint swelling, arthritis.

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

Nervous system disorders: syncope, memory impairment, ageusia, cognitive disorder, neuropathy peripheral.

Psychiatric disorders: agitation, mood altered.

Renal and urinary disorders: dysuria, urinary retention, hematuria, nocturia.

Reproductive system and breast disorders: pelvic pain.

Respiratory, thoracic and mediastinal disorders: productive cough, nasal congestion, throat irritation, rhinitis allergic, wheezing, bronchospasm, hypoxia.

Skin and subcutaneous tissue disorders: skin ulcer.

Vascular disorders: hematoma, flushing, orthostatic hypotension.

Study MMY3007: Darzalex in combination with bortezomib, melphalan, and prednisone

Other TEAEs (<5% and ≥2% in the D-VMP arm) of clinical relevance include:

Infections and infestations: herpes zoster, lower respiratory tract infection, viral upper respiratory tract infection, pharyngitis, sinusitis, influenza, oral herpes, respiratory tract infection.

Gastrointestinal disorders: abdominal distension, abdominal pain or discomfort, stomatitis.

General disorders and administration site conditions: influenza-like illness, injection site erythema, malaise, non-cardiac chest pain, peripheral swelling.

Respiratory, thoracic and mediastinal disorders: oropharyngeal pain, bronchospasm, catarrh, epistaxis, nasal congestion, pleural effusion, pulmonary edema.

Musculoskeletal and connective tissue disorders: myalgia, musculoskeletal pain, musculoskeletal chest pain.

Nervous system disorders: paraesthesia, dysgeusia, peripheral sensorimotor neuropathy, syncope, tremor.

Metabolism and nutritional disorders: hyperuricemia, hyperkalemia, hyponatremia, dehydration, hypoalbuminemia.

Psychiatric disorders: depression, confusional state.

Investigations: alanine aminotransferase increased, aspartate aminotransferase increased, weight decreased, gamma-glutamyltransferase increased, blood alkaline phosphatase increased, blood creatinine increased, oxygen saturation decreased.

Renal and urinary disorders: dysuria, acute kidney injury.

Injury, poisoning and procedural complications: fall, spinal compression fracture, contusion.

Cardiac disorders: atrial fibrillation.

Patients with multiple myeloma who have received at least one prior therapy
Study MMY3003: Darzalex in combination with lenalidomide/dexamethasone

Other TEAEs (<5% in the DRd arm) of clinical relevance include:

Infections and infestations: conjunctivitis, gastroenteritis, herpes zoster, oral candidiasis, oral herpes.

Gastrointestinal disorders: toothache, abdominal distension, dry mouth, mouth ulceration, abdominal discomfort, dysphagia, hemorrhoids.

General disorders and administration site conditions: non-cardiac chest pain, malaise, chest discomfort.

Respiratory, thoracic and mediastinal disorders: dysphonia, nasal congestion, bronchospasm, rhinitis allergic, oropharyngeal pain, rhinorrhea, throat irritation, epistaxis, wheezing, hiccups, pulmonary embolism, hypoxia, laryngeal edema.

Musculoskeletal and connective tissue disorders: neck pain, pain in jaw, spinal pain.

Nervous system disorders: paraesthesia, hypoesthesia neuropathy peripheral, syncope, lethargy.

Metabolism and nutritional disorders: dehydration, hypomagnesemia, hyponatremia, hyperuricemia.

Skin and subcutaneous tissue disorders: dry skin, urticaria, erythema.

Psychiatric disorders: restlessness, agitation, irritability, mood altered.

Vascular disorders: flushing.

Investigations: aspartate aminotransferase increased, blood creatinine increased, gamma-glutamyltransferase increased, blood alkaline phosphatase increased.

Eye disorders: eye irritation, lacrimation increased.

Renal and urinary disorders: pollakiuria.

Injury, poisoning and procedural complications: fall, contusion.

Cardiac disorders: atrial fibrillation, tachycardia, angina pectoris.

Ear and labyrinth disorders: tinnitus.

Study MMY3004: Darzalex in combination with bortezomib/dexamethasone

Other TEAEs (<5% in the DVd arm) of clinical relevance include:

Infections and infestations: urinary tract infection, influenza, oral herpes, gastroenteritis.

Nervous system disorders: paraesthesia, dysgeusia, peripheral motor neuropathy, lethargy.

Gastrointestinal disorders: abdominal distension, abdominal pain, abdominal discomfort, gastroesophageal reflux disease, dyspepsia.

General disorders and administration site conditions: chills, pain, chest pain, influenza-like illness, injection site erythema, malaise.

Respiratory, thoracic and mediastinal disorders: epistaxis, nasal congestion, oropharyngeal pain, rhinorrhea, wheezing.

Musculoskeletal and connective tissue disorders: musculoskeletal pain, myalgia, myopathy, spinal pain, neck pain.

Metabolism and nutritional disorders: hypocalcemia, hyponatremia, hypoalbuminemia diabetes mellitus, hypercalcemia.

Psychiatric disorders: depression, restlessness.

Vascular disorders: hypotension, flushing, hematoma.

Investigations: aspartate aminotransferase increased, glutamyltransferase increased, weight increased, blood creatinine increased.

Skin and subcutaneous tissue disorders: hyperhidrosis, erythema, pruritis.

Eye disorders: eye irritation, lacrimation increased, dry eye, vision blurred.

Cardiac disorders: atrial fibrillation, sinus tachycardia, palpitations.

Injury, poisoning and procedural complications: fall.

Ear and labyrinth disorders: vertigo, tinnitus.

Renal and urinary disorders: renal impairment.

Endocrine disorders: cushingoid.

*CANDOR Study: Darzalex in combination with carfilzomib and dexamethasone**

* All adverse reactions < 5% based on the DKd arm:

Blood and lymphatic system disorders: febrile neutropenia, thrombotic thrombocytopenic purpura)

Cardiac disorders: cardiac failure, tachycardia, atrial fibrillation, palpitations, cardiac arrest, myocardial infarction, myocardial ischemia, pericardial effusion

Ear and labyrinth disorders: tinnitus

Eye disorders: vision blurred

Gastrointestinal disorders: dyspepsia, toothache, gastrointestinal hemorrhage

General disorders and administration site conditions: chest pain, pain, influenza like illness, malaise, infusion site reactions

Hepatobiliary disorders: hyperbilirubinemia, cholestasis

Infections and infestations: sepsis, viral infection, gastroenteritis, lung infection, rhinitis, clostridium difficile colitis

Investigations: alanine aminotransferase increased, blood creatinine increased, aspartate aminotransferase increased, gamma-glutamyltransferase increased, C-reactive protein increased, ejection fraction decreased, creatinine renal clearance decreased

Metabolism and nutrition disorders: hypocalcemia, hypomagnesaemia, hyperkalemia, hyperuricemia, hypoalbuminemia, hyponatremia, hypophosphatemia, dehydration, tumour lysis syndrome, hypercalcemia

Musculoskeletal and connective tissue disorders: myalgia, musculoskeletal chest pain, muscular weakness, bone pain, musculoskeletal pain

Nervous system disorders: hypoesthesia, cerebrovascular accident, posterior reversible encephalopathy syndrome, intracranial hemorrhage, paresthesia

Psychiatric disorders: anxiety

Renal and urinary disorders: acute kidney injury, renal impairment, renal failure

Respiratory, thoracic and mediastinal disorders: dysphonia, oropharyngeal pain, epistaxis, pulmonary embolism, pulmonary hypertension, pulmonary edema, interstitial lung disease, wheezing, pneumonitis, pulmonary hemorrhage, acute respiratory failure

Skin and subcutaneous tissue disorders: pruritus, erythema, hyperhidrosis

Vascular disorder: hypotension, deep vein thrombosis, flushing, hypertensive crisis

Of the 307 patients in the DKd arm with baseline CrCL data, 174 had CrCL ≥ 80 mL/min (normal renal function), 96 had CrCL ≥ 50 to < 80 mL/min (mild renal impairment), 32 had CrCL ≥ 30 to < 50 mL/min (moderate renal impairment), and 5 had CrCL ≥ 15 to < 30 mL/min (severe renal impairment). Serious adverse events were reported in 58.0%, 56.3%, 87.5% and 80.0% of patients with normal renal function, mild renal impairment, moderate renal impairment and severe renal impairment, respectively; fatal adverse events were reported in 9.2%, 7.3%, 18.8% and 20.0% of patients, respectively. Of the 293 patients in the DKd arm with baseline hepatic status (based on bilirubin and transaminase levels), 269 had normal hepatic function and 24 had mild hepatic impairment. Patients with moderate or severe hepatic impairment were excluded from the study. Serious adverse events were reported in 58.7% and 70.8% of patients with normal hepatic function and mild hepatic impairment, respectively; fatal adverse events were reported in 8.9% and 12.5% of patients, respectively.

Patients with multiple myeloma who have received at least three prior lines of therapy including a PI and an IMiD, or who are refractory to both a PI and an IMiD

Studies MMY2002 and GEN501: Darzalex monotherapy

Other TEAEs (<2%) of clinical relevance include:

Blood and lymphatic system disorders: red blood cell agglutination, crossmatch incompatible.

Respiratory, thoracic and mediastinal disorders: hypoxia, throat tightness, upper-airway cough syndrome, respiratory failure, dysphonia, laryngeal edema, laryngitis allergic, pulmonary edema, rhinorrhea.

Gastrointestinal disorders: abdominal distension, gastroesophageal reflux disease, colitis, dysphagia, gastritis, pancreatitis.

Infections and infestations: conjunctivitis, candida infection, varicella, cellulitis, cystitis, ear infection, gastroenteritis, oral fungal infection, pyelonephritis, parainfluenza virus infection, pharyngitis, sepsis.

Metabolism and nutrition disorders: hypocalcemia; diabetes mellitus, hypernatremia, hyperphosphatemia, hypoglycemia.

Nervous system disorders: syncope, depressed level of consciousness, encephalopathy.

Skin and subcutaneous tissue disorders: eczema, erythema, petechia, rash maculo-papular, urticaria.

Vascular disorders: flushing.

Renal and urinary disorders: hematuria, pollakiuria, proteinuria, renal failure, urinary retention.

Investigations: electrocardiogram QT prolonged.

Cardiac disorders: tachycardia, angina pectoris, atrial flutter, bradycardia, cardiac failure congestive, transient ischemic attack.

Immune system disorders: allergic edema, cytokine release syndrome, seasonal allergy.

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

SUBCUTANEOUS FORMULATION (Darzalex SC)

Monotherapy

Study MMY3012

Laboratory abnormalities worsening during treatment from baseline are listed in Table 23.

Table 23: Treatment-emergent hematology laboratory abnormalities in Study MMY3012

	Study MMY3012					
	Darzalex (N=258) n (%)			Darzalex SC (N=260) n (%)		
	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4
Anemia	100 (39)	41 (16)	0	110 (42)	37 (14)	0
Thrombocytopenia	116 (45)	19 (7)	17 (7)	112 (43)	32 (12)	10 (4)
Leukopenia	147 (57)	29 (11)	6 (2)	170 (65)	47 (18)	2 (1)
Neutropenia	112 (43)	20 (8)	9 (3)	144 (55)	43 (17)	7 (3)
Lymphopenia	144 (56)	70 (27)	23 (9)	153 (59)	72 (28)	21 (8)

Combination Therapies in Multiple Myeloma

Study MMY2040

Laboratory abnormalities worsening during treatment from baseline are listed in Table 24.

Table 24: Treatment-emergent hematology laboratory abnormalities in MMY2040

	D-VMP (N=67)			D-Rd (N=65)			D-Kd (N=66)		
	All Grade (%)	Grade 3 (%)	Grade 4 (%)	All Grade (%)	Grade 3 (%)	Grade 4 (%)	All Grade (%)	Grade 3 (%)	Grade 4 (%)
Anemia	30 (45)	11 (16)	0	27 (42)	4 (6)	0	31 (47)	4 (6)	0
Thrombocytopenia	62 (93)	16 (24)	9 (13)	56 (86)	4 (6)	2 (3)	58 (88)	7 (11)	5 (8)
Leukopenia	63 (94)	21 (31)	10 (15)	61 (94)	15 (23)	7 (11)	45 (68)	12 (18)	0
Neutropenia	57 (85)	18 (27)	10 (15)	59 (91)	24 (37)	11 (17)	36 (55)	8 (12)	2 (3)
Lymphopenia	61 (91)	42 (63)	13 (19)	52 (80)	29 (45)	9 (14)	55 (83)	19 (29)	14 (21)

Key: D=daratumumab, Rd=lenalidomide-dexamethasone, VMP=bortezomib-melphalan-prednisone, Kd=carfilzomib-dexamethasone.

Study MMY3014: Darzalex SC in combination with bortezomib/lenalidomide/dexamethasone

Laboratory abnormalities worsening during treatment from baseline are listed in Table 25.

Table 25: Treatment-emergent hematology laboratory abnormalities in MMY3014

	D-VRd (N=351)			VRd (N=347)		
	All Grade (%)	Grade 3 (%)	Grade 4 (%)	All Grade (%)	Grade 3 (%)	Grade 4 (%)
Leukopenia	97	42	16	94	27	11
Neutropenia	97	47	28	94	44	21
Lymphopenia	94	54	22	83	41	9
Thrombocytopenia	93	22	16	90	19	11
Anemia	47	9	0	48	8	0

Key: D-VRd=SC Daratumumab-bortezomib-lenalidomide-dexamethasone; VRd= bortezomib-lenalidomide-dexamethasone

The incidence of Grade 3 or 4 febrile neutropenia was 9.4% (D-VRd) and 10.1% (VRd). The incidence of all grade bleeding events (hemorrhages) were 13.7% % in the D-VRd arm and 11.5% in the VRd arm.

Study MMY3013: Darzalex SC in combination with pomalidomide/dexamethasone

Laboratory abnormalities worsening during treatment from baseline are listed in Table 26.

Table 26: Treatment-emergent hematology laboratory abnormalities in study MMY3013

	DPd (N=149)			Pd (N=150)		
	Any Grade n (%)	Grade 3 n (%)	Grade 4 n (%)	Any Grade n (%)	Grade 3 n (%)	Grade 4 n (%)
Anemia	76 (51)	23 (15)	0	85 (57)	22 (15)	0
Lymphopenia	137 (92)	66 (44)	22 (15)	117 (78)	44 (29)	5 (3)
Neutropenia	143 (96)	54 (36)	71 (48)	125 (83)	64 (43)	30 (20)
Thrombocytopenia	111 (75)	13 (9)	15 (10)	89 (59)	21 (14)	8 (5)
Leukopenia	141 (95)	63 (42)	32 (22)	122 (81)	53 (35)	6 (4)

Key: D-Pd=SC Daratumumab-pomalidomide-dexamethasone; Pd=SC pomalidomide-dexamethasone

The incidence of Grade 3 or 4 febrile neutropenia was 8.7% (DPd) and 2.7% (Pd). The incidence of all grade bleeding events (hemorrhages) were 4.0% in the DPd arm and 6.0% in the Pd arm.

Combination Treatment for AL Amyloidosis

Study AMY3001: Darzalex SC in combination with bortezomib, cyclophosphamide and dexamethasone

Laboratory abnormalities worsening during treatment from baseline are listed in Table 27.

Table 27: Treatment-emergent hematology laboratory abnormalities in study AMY3001*

	D-VCd (N=193)			VCd (N=188)		
	All Grade n (%)	Grade 3 n (%)	Grade 4 n (%)	All Grade n (%)	Grade 3 n (%)	Grade 4 n (%)
Anemia	125 (65)	11 (6)	0	131 (70)	12 (6)	0
Thrombocytopenia	87 (45)	4 (2)	2 (1)	75 (40)	6 (3)	1 (1)
Leukopenia	112 (58)	9 (5)	5 (3)	85 (45)	8 (4)	0
Neutropenia	56 (29)	6 (3)	6 (3)	34 (18)	7 (4)	0
Lymphopenia	153 (79)	67 (35)	35 (18)	132 (70)	74 (39)	12 (6)

* based on safety population; median duration of treatment 9.6 months (D-VCd) and 5.3 months (VCd).

The incidence of Grade 3 or 4 febrile neutropenia was 1.0% (D-VCd) and 0% (VCd). The incidence of all grade bleeding events (hemorrhages) were 29.5% in the D-VCd arm and 13.8% in the VCd arm.

INTRAVENOUS FORMULATION (Darzalex)

The following sections present data from a separate Product Monograph for Darzalex intravenous formulation studies:

- **Patients with newly diagnosed multiple myeloma who are ineligible for ASCT**
- **Patients with multiple myeloma who have received at least one prior therapy**
- **Patients with multiple myeloma who have received at least three prior lines of therapy including a PI and an IMiD, or who are refractory to both a PI and an IMiD**

Patients with newly diagnosed multiple myeloma who are ineligible for ASCT

Study MMY3008: Darzalex in combination with lenalidomide and dexamethasone

Laboratory abnormalities worsening during treatment from baseline are listed in Table 28.

Table 28: Treatment-emergent hematology laboratory abnormalities in Study MMY3008

	Study MMY3008					
	DRd (N=364)			Rd (N=365)		
	Any Grade n (%)	Grade 3 n (%)	Grade 4 n (%)	Any Grade n (%)	Grade 3 n (%)	Grade 4 n (%)
Anemia	172 (47)	48 (13)	0	209 (57)	87 (24)	0
Thrombocytopenia	243 (67)	21 (6)	10 (3)	213 (58)	27 (7)	13 (4)
Leukopenia	328 (90)	108 (30)	19 (5)	298 (82)	73 (20)	16 (4)
Neutropenia	331 (91)	142 (39)	63 (17)	281 (77)	103 (28)	39 (11)
Lymphopenia	305 (84)	150 (41)	39 (11)	274 (75)	131 (36)	21 (6)

Key: D=daratumumab, Rd=lenalidomide-dexamethasone.

The incidence of Grade 3 or 4 febrile neutropenia was 3.0% (DRd) and 3.0% (Rd). The incidence of all grade bleeding events (hemorrhages) were 29.4% in the DRd arm and 26.3% in the Rd arm.

Study MMY3007: Darzalex in combination with bortezomib, melphalan, and prednisone

Laboratory abnormalities worsening during treatment from baseline are listed in Table 29.

Table 29: Treatment-emergent hematology laboratory abnormalities in Study MMY3007

	Study MMY3007					
	D-VMP (n=346)			VMP (n=354)		
	Any Grade n (%)	Grade 3 n (%)	Grade 4 n (%)	Any Grade n (%)	Grade 3 n (%)	Grade 4 n (%)
Anemia	161 (47)	61 (18)	0	177 (50)	75 (21)	0
Thrombocytopenia	305 (88)	92 (27)	39 (11)	311 (88)	91 (26)	56 (16)
Neutropenia	297 (86)	116 (34)	34 (10)	307 (87)	112 (32)	38 (11)
Lymphopenia	293 (85)	158 (46)	43 (12)	294 (83)	155 (44)	33 (9)

Key: D=Daratumumab, VMP=bortezomib-melphalan-prednisone.

The incidence of Grade 3 or 4 febrile neutropenia was 1.2% (D-VMP) and 2.2% (VMP).

Patients with multiple myeloma who have received at least one prior therapy

Study MMY3003: Darzalex in combination with lenalidomide/dexamethasone

Laboratory abnormalities worsening during treatment from baseline are listed in Table 30.

Table 30: Treatment-emergent hematology laboratory abnormalities in Study MMY3003

	Study MMY3003					
	DRd (N=283)			Rd (N=281)		
	Any Grade n (%)	Grade 3 n (%)	Grade 4 n (%)	Any Grade n (%)	Grade 3 n (%)	Grade 4 n (%)
Anemia	150 (53)	42 (15)	0	167 (59)	55 (20)	0
Thrombocytopenia	209 (74)	20 (7)	20 (7)	191 (68)	31 (11)	18 (6)
Neutropenia	261 (92)	103 (36)	50 (18)	246 (88)	94 (33)	24 (9)
Lymphopenia	269 (95)	118 (42)	30 (11)	246 (88)	93 (33)	20 (7)

Key: D=Daratumumab, Rd=lenalidomide-dexamethasone.

The incidence of Grade 3 or 4 febrile neutropenia was 6% (DRd) and 3% (Rd). The incidence of all grade bleeding events was 20% (DRd) and 15% (Rd), and serious bleeding events were 1.4% (DRd) and 1.8% (Rd).

Study MMY3004: Darzalex in combination with bortezomib/dexamethasone

Laboratory abnormalities worsening during treatment from baseline are listed in Table 31.

Table 31: Treatment-emergent hematology laboratory abnormalities in Study MMY3004

	Study MMY3004					
	DVd (N=243) n (%)			Vd (N=237) n (%)		
	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4
Anemia	122 (50)	35 (14)	0	133 (56)	33 (14)	0
Thrombocytopenia	218 (90)	68 (28)	48 (20)	202 (85)	52 (22)	31 (13)
Neutropenia	147 (60)	28 (12)	11 (5)	95 (40)	14 (6)	1 (<1)
Lymphopenia	216 (89)	99 (41)	18 (7)	192 (81)	57 (24)	8 (3)

Key: D=Daratumumab, Vd=bortezomib-dexamethasone.

The incidence of Grade 3 or 4 febrile neutropenia was 2% (DVd) and 0.4% (Vd). The incidence of all grade bleeding events was 14% (DVd) and 11% (Vd), and serious bleeding events were 2.1% (DVd) and 1.3% (Vd).

CANDOR Study: Darzalex in combination with carfilzomib and dexamethasone

Table 32 and Table 33 describe Grade 3-4 hematologic and laboratory abnormalities reported in the CANDOR study.

Table 32: Abnormal Hematologic Findings in the CANDOR Study

	Grade 3 or 4 Laboratory Values	
	DKd (n=308) n (%)	Kd (n=308) n (%)
Absolute neutrophil count (ANC) decreased	31 (10.1)	13 (8.5)
Hemoglobin decreased	28 (9.1)	20 (13.1)
Lymphocyte count decreased	177 (57.5)	56 (36.6)
Platelet count decreased	59 (19.2)	16 (10.5)
Total white blood cell (WBC) count decreased	58 (18.8)	14 (9.2)

Table 33: Abnormal Clinical Chemistry Findings in the CANDOR Study

	Grade 3 or 4 Laboratory Values	
	DKd (n=308) n (%)	Kd (n=308) n (%)
ALT increased	7 (2.3)	1 (0.7)
AST increased	1 (0.3)	1 (0.7)
Hypocalcemia	6 (1.9)	1 (0.7)
Hypercalcemia	6 (1.9)	4 (2.6)
Hypokalemia	13 (4.2)	1 (0.7)
Hyperkalemia	5 (1.6)	0

Serum creatinine increased	7 (2.3)	2 (1.3)
Hyponatremia	8 (2.6)	8 (5.2)
Serum albumin decreased	1 (0.3)	3 (2.0)
Total bilirubin increased	1 (0.3)	0

Patients with multiple myeloma who have received at least three prior lines of therapy including a PI and an IMiD, or who are refractory to both a PI and an IMiD

Studies MMY2002 and GEN501: Darzalex monotherapy

Laboratory parameters with treatment-emergent worsening toxicity grade (≥20%) during treatment are presented in Table 34.

Table 34: Laboratory hematology and chemistry treatment-emergent worsening toxicity grade during treatment (incidence ≥20%) in multiple myeloma patients treated with Darzalex 16 mg/kg (n=156)

	Toxicity Grade		
	Any Grade	3	4
Hematology			
WBC low	89 (57.1%)	26 (16.7%)	3 (1.9%)
Hemoglobin low	70 (44.9%)	30 (19.2%)	0
Platelets low	75 (48.4%)	15 (9.7%)	13 (8.4%)
Neutrophils low	93 (59.6%)	26 (16.7%)	5 (3.2%)
Lymphocytes low	113 (72.4%)	46 (29.5%)	15 (9.6%)
Chemistry			
AST high	35 (23.3%)	2 (1.3%)	0
Creatinine high	33 (21.7%)	3 (2.0%)	0
Sodium low	45 (29.6%)	6 (4.0%)	0
Potassium low	32 (21.1%)	4 (2.6%)	1 (0.7%)
Corrected calcium high	49 (32.2%)	6 (3.9%)	5 (3.3%)
Corrected calcium low	48 (31.6%)	0	0
Albumin low	62 (40.8%)	5 (3.3%)	0

Keys: WBC = White Blood Cell.
Note: The laboratory toxicity grades are derived based on the NCI CTCAE (National Cancer Institute Common Terminology Criteria for Adverse Events) Version 4.03.
Note: For each lab parameter, percentages are calculated with denominator as the number of subjects with both a baseline and postbaseline laboratory value available. Only subjects with worsening toxicity grade during treatment compared to baseline are reported.

Ten subjects (6%) received granulocyte-colony stimulating factor. No treatment-emergent adverse events of febrile neutropenia were reported. Forty-six subjects (29.5%) received a red blood cell transfusion (37.7% in Study MMY2002 and 11.1% in Study GEN501). No treatment-emergent adverse events related to red blood cell transfusions were reported.

8.5 Post-Market Adverse Reactions

The following adverse reactions have been reported during daratumumab post-marketing experience. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to estimate their frequency reliably or establish a causal relationship to drug exposure.

Immune system disorders: anaphylactic reaction (see 7 WARNINGS AND PRECAUTIONS - Immune: Administration-Related Reactions)

Infections and infestations: hepatitis B virus reactivation (see 7 WARNINGS AND PRECAUTIONS -Infections), COVID-19

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

No formal drug interaction studies have been conducted with daratumumab.

9.3 Drug-Behavioural Interactions

No formal drug-behavioural interaction studies have been conducted with daratumumab.

9.4 Drug-Drug Interactions

No formal drug-drug interaction studies have been conducted with daratumumab. IgG1 molecules are biotransformed by degradation into small peptides and amino acids via catabolic pathways.

9.5 Drug-Food Interactions

No formal drug-food interaction studies have been conducted with daratumumab.

9.6 Drug-Herb Interactions

No formal drug-herb interaction studies have been conducted with daratumumab.

9.7 Drug-Laboratory Test Interactions

No formal drug-laboratory studies have been conducted with daratumumab.

Interference with Indirect Antiglobulin Tests (Coombs Test)

Daratumumab binds to CD38 on RBCs and interferes with compatibility testing, including antibody screening and cross matching. Daratumumab interference mitigation methods include treating reagent RBCs with dithiothreitol (DTT) to disrupt daratumumab binding or genotyping. Since the Kell blood group system is also sensitive to DTT treatment, K-negative units should be supplied after ruling out or identifying alloantibodies using DTT-treated RBCs.

If an emergency transfusion is required, non-cross-matched ABO/RhD-compatible RBCs can be given per local practices.

Interference with Serum Protein Electrophoresis and Immunofixation Tests

Daratumumab may be detected on serum protein electrophoresis (SPE) and immunofixation (IFE) assays used for monitoring disease monoclonal immunoglobulins (M protein). This can lead to false positive SPE and IFE assay results for patients with IgG kappa myeloma protein impacting initial assessment of complete responses by International Myeloma Working Group

(IMWG) criteria. In patients with persistent very good partial response, consider other methods to evaluate the depth of response.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Daratumumab is an IgG1κ human monoclonal antibody (mAb) that targets the CD38 protein expressed on the surface of cells in a variety of hematological malignancies, including clonal plasma cells in multiple myeloma and AL amyloidosis, as well as other cell types and tissues. CD38 protein has multiple functions such as receptor mediated adhesion, signaling and enzymatic activity.

Daratumumab has been shown to potently inhibit the *in vivo* growth of CD38-expressing tumor cells. Based on *in vitro* studies, daratumumab may utilize multiple effector functions, resulting in immune mediated tumor cell death. These studies suggest that daratumumab can induce tumor cell lysis through multifactorial effects such as activation of complement cascade, i.e. complement-dependent cytotoxicity (CDC), antibody-dependent cell-mediated cytotoxicity (ADCC), and antibody-dependent cellular phagocytosis (ADCP) in malignancies expressing CD38.

Daratumumab induced apoptosis in vitro after Fc mediated cross linking. In addition, daratumumab modulated CD38 enzymatic activity, inhibiting the cyclase enzyme activity and stimulating the hydrolase activity. The significance of these in vitro effects in a clinical setting, and the implications on tumor growth, are not well understood.

A subset of myeloid derived suppressor cells (CD38+MDSCs), regulatory T cells (CD38+T_{regs}) and B cells (CD38+B_{regs}) are decreased by daratumumab. T cells (CD3+, CD4+, and CD8+) are also known to express CD38 depending on the stage of development and the level of activation. Significant increases in CD4+ and CD8+ T cell absolute counts, and percentages of lymphocytes, were observed with daratumumab treatment in peripheral whole blood and bone marrow. In addition, T-cell receptor DNA sequencing verified that T-cell clonality was increased with daratumumab treatment, indicating immunomodulatory effects that may contribute to clinical response.

Darzalex SC contains recombinant human hyaluronidase (rHuPH20). rHuPH20 works locally and transiently to degrade hyaluronan (HA), a naturally occurring glycoaminoglycan found throughout the body in the extracellular matrix of the subcutaneous space by cleaving the linkage between the two sugars (N-acetylglucosamine and glucuronic acid) which comprise HA. rHuPH20 has a half-life in skin of less than 30 minutes. Hyaluronan levels in subcutaneous tissue return to normal within 24 to 48 hours because of the rapid biosynthesis of hyaluronan.

10.2 Pharmacodynamics

Natural killer (NK) cell count

NK cells are known to express high levels of CD38 and are susceptible to daratumumab mediated cell lysis. Decreases in absolute counts and percentages of total NK cells (CD16+CD56+) and activated (CD16+CD56^{dim}) NK cells in peripheral whole blood and bone marrow were observed with daratumumab treatment.

10.3 Pharmacokinetics

SUBCUTANEOUS FORMULATION (Darzalex SC)

Daratumumab exhibits both concentration and time-dependent pharmacokinetics with first order absorption and parallel linear and nonlinear (saturable) elimination that is characteristic of target-mediated clearance. Following the recommended dose of 1800 mg Darzalex SC, peak concentrations (C_{max}) increased 4.8-fold and total exposure ($AUC_{0\text{-}7\ days}$) increased 5.4-fold from first dose to last weekly dose (8th dose). Highest trough concentrations for Darzalex SC are typically observed at the end of the weekly dosing regimens for both monotherapy and combination therapy. In patients with multiple myeloma, daratumumab exposure in a monotherapy Study (MMY3012) following the recommended 1800 mg administration of Darzalex SC (weekly for 8 weeks, biweekly for 16 weeks, monthly thereafter) as compared to 16 mg/kg IV daratumumab for the same dosing schedule, showed non-inferiority for the co-primary endpoint of maximum C_{trough} (Cycle 3 Day 1 pre-dose), with mean ± standard deviation (SD) of 593 ± 306 µg/mL compared to 522 ± 226 µg/mL for IV daratumumab, with a geometric mean ratio of 107.93% (90% CI: 95.74-121.67). The mean ± SD maximum trough serum concentration (C_{trough}) after the 8th dose was 537 ± 277 µg/mL, 526 ± 226 µg/mL, 756 ± 276 µg/mL, and 526 ± 209 µg/mL when Darzalex SC was administered as combination with Pd, Rd, Kd, and VRd, respectively.

Table 35 lists the observed mean (±SD) maximum trough concentrations (C_{trough}) after the 8th dose, simulated median (5th-95th percentiles) maximum C_{trough} after the 8th dose, simulated median (5th-95th percentiles) C_{max} after the 8th dose, and simulated median (5th-95th percentiles) area under the curve ($AUC_{0\text{-}7day}$) after the 8th dose following DARZALEX SC 1800 mg or 16 mg/kg IV daratumumab in patients with multiple myeloma or light chain (AL) amyloidosis. The exposures following 8 weekly doses of 1800 mg Darzalex SC for combination therapy were similar to 1800 mg Darzalex SC monotherapy.

Table 35: Daratumumab Exposure for Patients with Multiple Myeloma or Light Chain (AL) Amyloidosis

Parameter	Intravenous Daratumumab 16 mg/kg Monotherapy in Patients with Multiple Myeloma	Darzalex SC 1,800 mg Monotherapy in Patients with Multiple Myeloma	Darzalex SC 1,800 mg in combination with VRd in Patients with Transplant Eligible Multiple Myeloma	Darzalex SC 1,800 mg in combination with VCd in Patients with Light Chain (AL) Amyloidosis
Observed mean±SD max C_{trough} after 8th dose (µg/mL)	522±226[a]	593±306[a]	526±209	597±232

Simulated median (5^{th}-95^{th} percentiles) max C_{trough} after 8^{th} dose (µg/mL)	472 (144-809)	563 (177-1063)	651 (413-915)	662 (315-1037)
Simulated median (5^{th}-95^{th} percentiles) C_{max} after 8^{th} dose (µg/mL)	688 (369-1061)	592 (234-1114)	678 (431-958)	729 (390-1105)
Simulated median (5^{th}-95^{th} percentiles) $AUC_{0\text{-}7days}$ after 8^{th} dose (µg/mL•day)	4019 (1740-6370)	4017 (1515-7564)	4637 (2941-6522)	4855 (2562-7522)

[a] Geometric mean ratio between 1,800 mg SC and 16 mg/kg was 108% (90% CI: 96, 122) in patients with multiple myeloma

Absorption:

The population PK model estimated, at the recommended dose of 1800 mg in multiple myeloma patients, the absolute bioavailability of Darzalex SC is 69%, with an absorption rate of 0.012 $hour^{-1}$, with peak concentrations occurring at 70 to 72 h (T_{max}). At the recommended dose of 1800 mg in AL amyloidosis patients, the absolute bioavailability could not be estimated, the absorption rate constant was 0.77 day^{-1} (8.31% CV) and peak concentrations occurred at 3 days.

Distribution:

In multiple myeloma patients, the modeled mean estimate of the volume of distribution for the central compartment (V1) is 5.25 L (36.9% CV) and peripheral compartment (V2) was 3.78 L in daratumumab monotherapy. The modeled mean estimate of the volume of distribution for V1 is 4.36 L (28.0% CV) and V2 was 2.80 L when daratumumab was administered in combination with pomalidomide and dexamethasone. The modeled mean estimate of the volume of distribution for V1 was 6.71 L (19.1% CV) and V2 was 3.84 L when daratumumab was administered in combination with bortezomib, lenalidomide and dexamethasone. In AL amyloidosis patients, the model estimated apparent volume of distribution after SC administration is 10.8 L (3.1% CV). These results suggest that daratumumab is primarily localized to the vascular system with limited extravascular tissue distribution.

Metabolism:
As an IgG1κ mAb, daratumumab is likely metabolized via degradation into small peptides and amino acids via catabolic pathways.

Daratumumab is cleared by parallel linear and nonlinear saturable target mediated clearances. In multiple myeloma patients, the population PK model estimated mean linear clearance value of daratumumab is 4.96 mL/h (58.7% CV) in daratumumab monotherapy, 4.32 mL/h

(43.5% CV) when daratumumab was administered in combination with pomalidomide and dexamethasone, and 4.29 mL/h (22.2% CV) when daratumumab was administered in combination with bortezomib, lenalidomide and dexamethasone. In AL amyloidosis patients, the apparent clearance after SC administration is 210 mL/day (4.1% CV).

Elimination:
In multiple myeloma patients, the model-based geometric mean post hoc estimate for half-life associated with linear elimination is 20.4 days (22.4% CV) in daratumumab monotherapy, 19.7 days (15.3% CV) when daratumumab was administered in combination with pomalidomide and dexamethasone, 40.1 days (20.9% CV) when daratumumab was administered in combination with bortezomib, lenalidomide and dexamethasone, and 27.5 days (74.0% CV) in AL amyloidosis patients. For the monotherapy and combination regimens, the steady state is achieved at approximately 5 months into every 4 weeks dosage at the recommended dose and schedule (1800 mg; once weekly for 8 weeks, every 2 weeks for 16 weeks, and then every 4 weeks thereafter).

INTRAVENOUS FORMULATION (Darzalex)

For pharmacokinetic information on the IV formulation, please refer to the separate Product Monograph for Darzalex.

Special Populations and Conditions

- **Light chain (AL) amyloidosis:** Daratumumab administered by IV infusion has not been studied in patients with AL amyloidosis. Daratumumab is only indicated for use in AL amyloidosis when administered using the subcutaneous formulation, Darzalex SC.
- **Pediatrics:** Daratumumab has not been studied in pediatric patients.
- **Geriatrics:** Based on a population PK analysis in patients receiving monotherapy, age (range: 33-92 years) was not a statistically significant covariate on the trough concentration of daratumumab. No clinically important influence of age on the exposure to daratumumab was observed in the population PK analyses in patients receiving daratumumab SC monotherapy and combination therapies. The difference in exposure was within 5 to 9% between younger (age <65 years, n=301) and older subjects (age ≥65 to <75 years, n=277; or age ≥75 years, n=163).
- **Sex:** Gender had a statistically significant effect but not clinically meaningful on PK parameter in patients with multiple myeloma. The higher exposures seen in females with multiple myeloma or AL amyloidosis were largely attributable to lower body weight. No individualization is necessary for patients on the basis of gender.
- **Ethnic Origin:** In an analysis of patients receiving Darzalex SC in monotherapy, there was no clinically meaningful difference in trough concentrations of daratumumab between white (n=225) and non-white subjects (n=63). There were also no clinically

meaningful differences in the exposure to daratumumab between white (n=129) and non-white (n=63) subjects in patients receiving Darzalex SC with various combination therapies.

- **Hepatic Insufficiency:** No formal studies of Darzalex SC in patients with hepatic impairment have been conducted. Population PK analyses were performed in patients with multiple myeloma receiving Darzalex SC and Darzalex monotherapy or Darzalex SC with various combination therapies in patients with multiple myeloma or AL amyloidosis, including 821 patients with normal hepatic function (total bilirubin [TB] and aspartate aminotransferase [AST] ≤upper limit of normal [ULN]), 124 with mild hepatic impairment [(total bilirubin ≤ ULN and AST > ULN) or (ULN < total bilirubin ≤ 1.5×ULN)] and 8 patients with moderate (1.5×ULN < total bilirubin ≤ 3×ULN) hepatic impairment. No clinically important differences in the exposure to Darzalex SC were observed between patients with normal hepatic function and mild hepatic impairment. There were very few patients with moderate and severe hepatic impairment to make meaningful conclusions for these populations.
- **Renal Insufficiency:** No formal studies of Darzalex SC in patients with renal impairment have been conducted. Population PK analyses were performed based on pre-existing renal function data in patients with multiple myeloma receiving Darzalex SC and Darzalex monotherapy or Darzalex SC with various combination therapies in patients with multiple myeloma or AL amyloidosis, including 295 patients with normal renal function (creatinine clearance [CRCL] ≥90 mL/min), 340 with mild renal impairment (CRCL <90 and ≥60 mL/min), 274 with moderate renal impairment (CRCL <60 and ≥30 mL/min), and 43 with severe renal impairment or end stage renal disease (CRCL <30 mL/min). No clinically important differences in exposure to daratumumab were observed between patients with renal impairment and those with normal renal function.
- **Body Weight:** After administration of the flat-dose of Darzalex SC 1800 mg as monotherapy in patients with multiple myeloma, the mean Cycle 3 Day 1 C_{trough} in the lower body-weight subgroup (≤50 kg) was 81% higher and in the higher body weight (>85 kg) subgroup, 12% lower than the intravenous Darzalex subgroup. In some patients with body weights >120 kg, lower exposures were observed, which may result in reduced efficacy. However, as a limited number of patients weighing >120 kg have been studied using Darzalex SC, no dose adjustment based on body weight can be recommended. In patients with AL amyloidosis who received Darzalex SC 1800 mg in combination with VCd, the mean maximum Ctrough was 37% higher in the lower body weight group (≤50 kg) and 22% lower in the higher body weight group (>85 kg) compared to patients with body weight 51-85 kg.

11 STORAGE, STABILITY AND DISPOSAL

Store vials at 2°C-8°C. Equilibrate Darzalex SC to ambient temperature (15°C-30°C) before use. The unpunctured vial may be stored at ambient temperature and ambient light for a maximum of 24 hours. Keep out of direct sunlight. Do not shake.

If the syringe containing Darzalex SC is not used immediately, store the solution for up to 24 hours refrigerated followed by up to 12 hours at 15°C-25°C and ambient light. Discard if stored more than 24 hours of being refrigerated or more than 12 hours of being at 15°C-25°C. If stored in the refrigerator, allow the solution to come to ambient temperature before administration.

12 SPECIAL HANDLING INSTRUCTIONS

Do not freeze or shake. Protect from light. This product contains no preservative.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

Proper name:	daratumumab
Molecular mass:	Approximately 148 kD
Structure:	Daratumumab is an IgG1κ human monoclonal antibody against CD38 antigen.
Physicochemical properties:	Darzalex SC (daratumumab injection) is supplied as a colorless solution for subcutaneous use. The pH is 6.0-7.0.

Product Characteristics:

Daratumumab is produced in a mammalian cell line (Chinese Hamster Ovary [CHO]) using recombinant DNA technology.

14 CLINICAL TRIALS

14.1 Clinical Trials by Indication

Darzalex SC (daratumumab injection) is indicated in combination with bortezomib, lenalidomide and dexamethasone, followed by maintenance treatment in combination with lenalidomide, for the treatment of adult patients with newly diagnosed multiple myeloma who are eligible for autologous stem cell transplant.

Table 36: Summary of Darzalex SC clinical trials in patients with newly diagnosed multiple myeloma who are eligible for ASCT.

Study # Trial design	Dosage, route of administration and duration	Number of subjects
Study MMY3014 (PERSEUS Study), Phase 3, open-label, randomized, active-controlled study in patients with newly diagnosed multiple myeloma eligible for ASCT that compared induction and consolidation treatment with Darzalex SC (1800 mg) in combination with bortezomib, lenalidomide and dexamethasone (D-VRd), followed by maintenance treatment in combination with lenalidomide, to treatment with bortezomib, lenalidomide and dexamethasone (VRd), followed by maintenance treatment with lenalidomide.	Darzalex SC 1800 mg subcutaneously on Days 1, 8, 15, and 22 of Cycles 1 and 2 (weekly dosing), on Days 1 and 15 of Cycles 3 to 6 (every two-week dosing). For maintenance, on Day 1 of Cycle 7 and subsequent cycles (every four-week dosing) until disease progression or unacceptable toxicity. Patients who achieved MRD negativity that was sustained for 12 months and had been treated on maintenance for at least 24 months discontinued treatment with Darzalex SC. Bortezomib 1.3 mg/m^2 body surface area subcutaneously twice-weekly on Days 1, 4, 8, and 11 of repeated 28-day (4-week) Cycles 1-6. Lenalidomide 25 mg administered orally at 25 mg daily on Days 1 to 21 during Cycles 1-6. For maintenance (Cycles 7+), patients received 10 mg lenalidomide daily on Days 1-28 (continuously) of each cycle until documented disease progression or unacceptable toxicity. Dexamethasone (oral or intravenous) was administered at 40 mg on Days 1-4 and Days 9-12 of Cycles 1-6. On the days of Darzalex SC injection, the dexamethasone dose was administered orally or intravenously as a pre-infusion medication. Dose adjustments for bortezomib, lenalidomide and dexamethasone were applied according to manufacturer's prescribing information	N=709 D-VRd arm: 355 VRd arm: 354

Study MMY3014: Darzalex in combination with bortezomib, lenalidomide and dexamethasone (D-VRd)

The clinical efficacy and safety of Darzalex SC for the treatment of patients with newly diagnosed multiple myeloma who are eligible for ASCT was demonstrated in an open-label, randomized, active-controlled study (Table 36).

See Table 36 for a summary of study design and dosing. Patients were randomized 1:1 to receive D-VRd followed by maintenance treatment with Darzalex SC and lenalidomide, or VRd followed by maintenance therapy with lenalidomide. The randomization was stratified by ISS Staging (I, II or III), and cytogenetic risk (standard risk or high risk as defined by presence of del17p, t[4;14] or t[14;16]). Key inclusion criteria included 1) newly diagnosed participants for whom ASCT is part of the intended treatment plan, b) patients 18 to 70 years of age with monoclonal plasma cells in the bone marrow ≥10% or presence of a biopsy proven plasmacytoma and documented multiple myeloma, and 3) ECOG performance score (PS) of 0, 1, or 2.

Of the 709 patients who were randomized, the median age was 60 years (range: 31 to 70 years). The majority were male (59%); 64% had an ECOG PS of 0, 31% had an ECOG PS of 1 and 5% had an ECOG PS of 2. Fifty-one percent had ISS Stage I, 34% had ISS Stage II, and 15% had ISS Stage III disease; 75% had a standard cytogenetic risk, 22% had a high cytogenetic risk, and 3% had an indeterminate cytogenetic risk. During maintenance treatment, 207 (59%) patients discontinued Darzalex SC after completing at least 24 months of maintenance treatment and achieving MRD-negativity that was sustained for at least 12 months.

Study Results:

The primary efficacy endpoint was progression free survival (PFS) based on International Myeloma Working Group (IMWG) criteria using a computer algorithm. Key secondary endpoints were complete response or better rate, minimal residual disease (MRD) negative rate, and overall survival (OS).

The median follow-up duration at the time of the primary PFS analysis was 47.5 months (range: 0.03 to 54.41 months). Efficacy results for Study MMY3014 are summarized in Table 37 and Figure 1.

Table 37: Efficacy results from Study MMY3014[a]

	D-VRd (n = 355)	**VRd** (n = 354)
Progression-Free Survival		
Number of events (%)	50 (14.1)	103 (29.1)
Median, months (95% CI)	NE (NE, NE)	NE (NE, NE)
Hazard ratio (95% CI)[b]	0.42 (0.30, 0.59)	
p-value[c]	< 0.0001	
Overall response (sCR+CR+VGPR+PR) n (%)[a]	343 (96.6)	332 (93.8)
Overall CR or better (sCR+CR)[d]	312 (87.9)	248 (70.1)
95% CI (%)	(84.0, 91.1)	(65.0, 74.8)
p-value[e]	< 0.0001	
Stringent complete response (sCR)	246 (69.3)	158 (44.6)
Complete response (CR)	66 (18.6)	90 (25.4)
Very good partial response (VGPR)	26 (7.3)	68 (19.2)
Partial response (PR)	5 (1.4)	16 (4.5)
Overall MRD Negativity Rate[f] n (%)	267 (75.2)	168 (47.5)
95% CI (%)	(70.4, 79.6)	(42.2, 52.8)
p-value[e]	< 0.0001	

D-VRd=daratumumab-bortezomib-lenalidomide-dexamethasone; VRd=bortezomib-lenalidomide-dexamethasone; NE=not estimable; MRD=minimal residual disease; CI=confidence interval

[a] Based on intent-to-treat population.

[b] Based on a stratified Cox proportional hazards model.

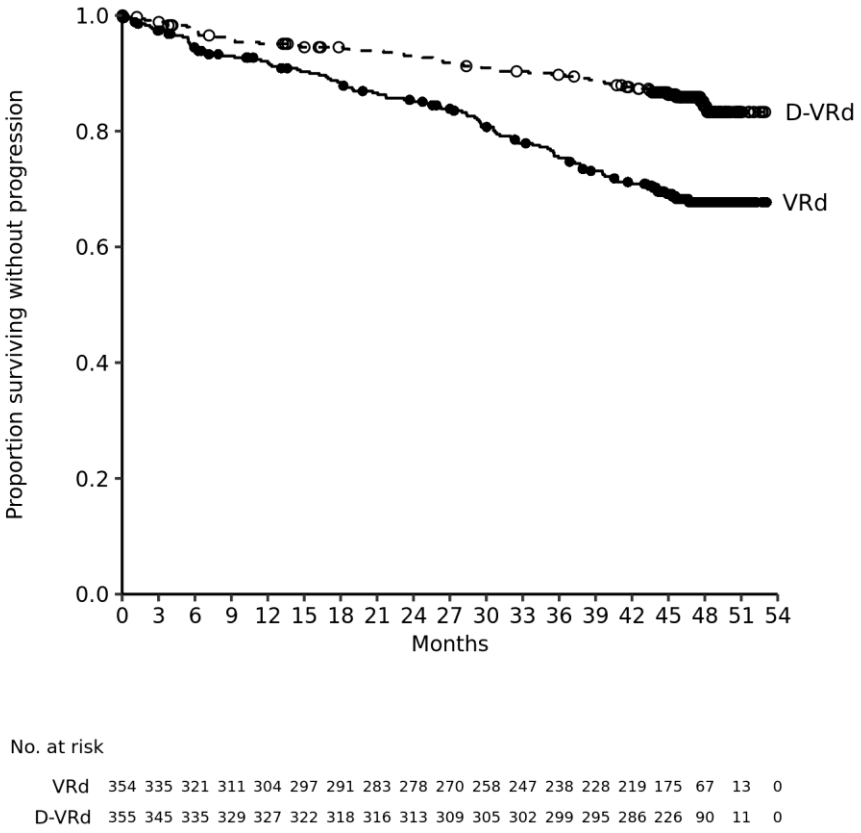
[c] Stratified log-rank test.

[d] Overall CR or better rate is defined as the percentage of ITT subjects who achieved CR or sCR status anytime during the study prior to start of subsequent therapies.

[e] p-value from Cochran Mantel-Haenszel Chi-Squared test.

[f] Overall MRD negativity rate is defined as the proportion of ITT subjects who achieve MRD negativity (at or below the threshold of 10^{-5}) and achieve CR or better response at any time during the study prior to progressive disease, subsequent therapy, or both.

Figure 1: Kaplan-Meier Curve of PFS in Study MMY3014



MRD-negativity rates by next-generation sequencing (NGS) assay post consolidation were 57.5% (95% CI: 52.1%, 62.7%) in the D-VRd arm and 32.5% (95% CI: 27.6%, 37.6%) in the VRd arm.

With a median follow-up of 47.5 months, 78 deaths were observed; 34 in the D-VRd group and 44 in the VRd group. Median overall survival (OS) was not reached for either treatment group.

Darzalex SC (daratumumab injection) is indicated in combination with lenalidomide and dexamethasone, or with bortezomib, melphalan and prednisone, for the treatment of patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant.

The clinical efficacy and safety of Darzalex for the treatment of patients with newly diagnosed multiple myeloma who are ineligible for ASCT was demonstrated in two open-label, randomized, active-controlled studies using the intravenous formulation (Table 38).

Table 38: Summary of Darzalex (intravenous formulation) clinical trials in patients with newly diagnosed multiple myeloma who are ineligible for ASCT.

Study # Trial design	Dosage, route of administration and duration	Number of subjects
Study MMY3008 (MAIA Study), Phase 3, open-label, randomized, active-controlled study comparing treatment with Darzalex in combination with lenalidomide and low-dose dexamethasone (DRd), to treatment with lenalidomide and low-dose dexamethasone (Rd) in patients with newly diagnosed multiple myeloma who are ineligible for ASCT.	Darzalex 16 mg/kg (IV) on Days 1, 8, 15, and 22 of Cycles 1 and 2 (weekly dosing), on Days 1 and 15 of Cycles 3 to 6 (every two week dosing), and on Day 1 of Cycle 7 and subsequent cycles (every four week dosing). Lenalidomide (25 mg once daily orally on Days 1-21 of repeated 28-day [4-week] cycles) with low dose oral or intravenous dexamethasone 40 mg/week (or a reduced dose of 20 mg/week for patients >75 years or body mass index [BMI] <18.5).	N=737 DRd arm: 368 Rd arm: 369
Study MMY3007 (ALCYONE Study), Phase 3, open-label, randomized, active-controlled study comparing treatment with Darzalex in combination with bortezomib - melphalan-prednisone (D-VMP), to treatment with VMP in patients with newly diagnosed multiple myeloma who are ineligible for ASCT.	Darzalex* 16 mg/kg (IV): Cycle** 1 (weeks 1-6): weekly; Cycle 2-9 (weeks 7-54): every 3 weeks; Cycle ≥10 (week 55 onwards): every 4 weeks until disease progression, unacceptable toxicity or study end (D-VMP arm only). Bortezomib 1.3 mg/m^2 body surface area (BSA), subcutaneous (SC): Cycle** 1 (week 1, 2, 4, and 5): twice-weekly; Cycle 2-9 (for week 1, 2, 4, and 5 of each cycle): once weekly Melphalan 9 mg/m^2 BSA orally (PO) and prednisone 60 mg/m^2 BSA (PO): Days 1-4 of each bortezomib cycle. * Darzalex was administered before bortezomib on treatment days when both bortezomib and Darzalex were to be administered. ** Cycle = 6 weeks.	N=706 D-VMP arm: 350 VMP arm: 356

Study MMY3008: Darzalex in combination with lenalidomide and dexamethasone (DRd)

See Table 38 for a summary of study design and dosing. Patients were randomized 1:1 to receive DRd or Rd. The randomization was stratified by ISS (I, II or III), region (North America vs Other) and age (<75 vs ≥75). Key inclusion criteria included 1) patient must be newly diagnosed and not considered a candidate for high-dose chemotherapy with stem cell transplant due to a) being ≥65 years of age, or b) in patients <65 years old, the presence of comorbid condition(s) likely to have a negative impact on tolerability of high dose chemotherapy and stem cell transplant; and 2) patient must have an ECOG score of 0-2. On Darzalex infusion days, dexamethasone served as the treatment dose of steroid for that day, as well as the required pre-infusion medication. Treatment was continued in both arms until disease progression or unacceptable toxicity.

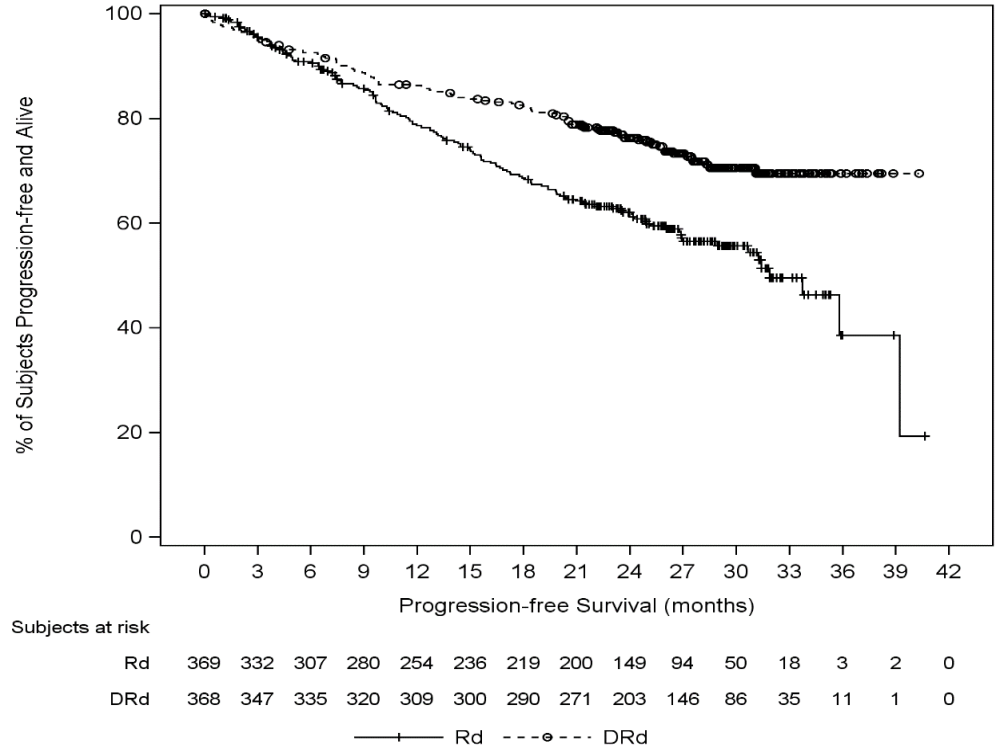
The baseline demographic and disease characteristics were similar between the two treatment groups. The median age was 73 (range 45-90) years old, with 44% of the patients ≥75 years of age. The majority were White (92%), 52% were male, and 83% had an ECOG performance score of 0 or 1. Patients had IgG/IgA/Light chain myeloma in 66%/19%/11% instances; 27% had ISS Stage I, 43% had ISS Stage II and 29% had ISS stage III disease. Of the 642 subjects who had baseline cytogenetic data reported, 14% had high-risk cytogenetic abnormalities, which included t(4;14) (5%), del17p (8%), and t(14;16) (1%), with similar proportions in the 2 arms (DRd:15%, Rd: 14%).

Study Results:

The primary efficacy endpoint was progression free survival (PFS) based on International Myeloma Working Group (IMWG) criteria using a computer algorithm. Key secondary endpoints were overall response rate (ORR), minimal residual disease (MRD) negative rate, and overall survival (OS).

With a median follow-up of 28 months, the primary analysis of PFS in Study MMY3008 demonstrated an improvement in PFS in the DRd arm as compared to the Rd arm; the median PFS had not been reached in the DRd arm and was 31.9 months in the Rd arm (hazard ratio [HR]=0.56; 95% CI: 0.43, 0.73; p<0.0001), representing a 44% reduction in the risk of disease progression or death in patients treated with DRd (Figure 2).

Figure 2: Kaplan-Meier Curve of PFS (Primary Analysis) in Study MMY3008



Pre-specified subgroup analyses based on PFS hazard ratio were generally consistent across the subgroups and showed a PFS improvement for subjects in the DRd group compared to those in the Rd group.

Efficacy results from Study MMY3008 are presented in Table 39 below.

Table 39: Efficacy results (Primary Analysis) from Study MMY3008

	DRd (n=368)	Rd (n=369)
PFS		
Number of events (%)	97 (26.1)	143 (38.8)
Hazard Ratio [95% CI][a]	0.56 (0.43, 0.73)	
Stratified log-rank test p-value[b]	<0.0001	
Median PFS in months [95% CI]	NE (NE, NE)	31.87 (28.94, NE)
Overall response (sCR+CR+VGPR+PR) n(%)	342 (92.9%)	300 (81.3%)
Risk difference [95% CI][c]	11.6% (4.5%, 18.8%)	
p-value[d]	<0.0001	
Stringent complete response (sCR)	112 (30.4%)	46 (12.5%)
Complete response (CR)	63 (17.1%)	46 (12.5%)
Very good partial response (VGPR)	117 (31.8%)	104 (28.2%)
Partial response (PR)	50 (13.6%)	104 (28.2%)
Duration of Response, median in months (95% CI)[e]	NE (NE, NE)	34.7 (30.8, NE)

DRd=daratumumab-lenalidomide-dexamethasone; Rd=lenalidomide-dexamethasone; CI=confidence interval

[a] Hazard ratio and 95% CI from a Cox proportional hazards model with treatment as the sole explanatory variable and stratified with ISS staging (I, II, III), region (North America vs. Other), and age (<75 years vs. ≥75 years) as randomized. A hazard ratio <1 indicates an advantage for DRd.

[b] p-value is based on the log-rank test stratified with ISS staging (I, II, III), region (North America vs. Other), and age (<75 years vs. ≥75 years) as randomized.

[c] exact 95% CI. A risk difference > 0 indicates a benefit for DRd.

[d] p-value from Fisher's exact test.

[e] The Kaplan-Meier estimates of duration of response were provided based on subjects with overall response of PR or better.

Note: A hierarchical testing procedure was used to control the overall Type I error rate for the primary and secondary endpoints. The corresponding alpha levels for PFS and ORR were 0.0085 and 0.0244, respectively.

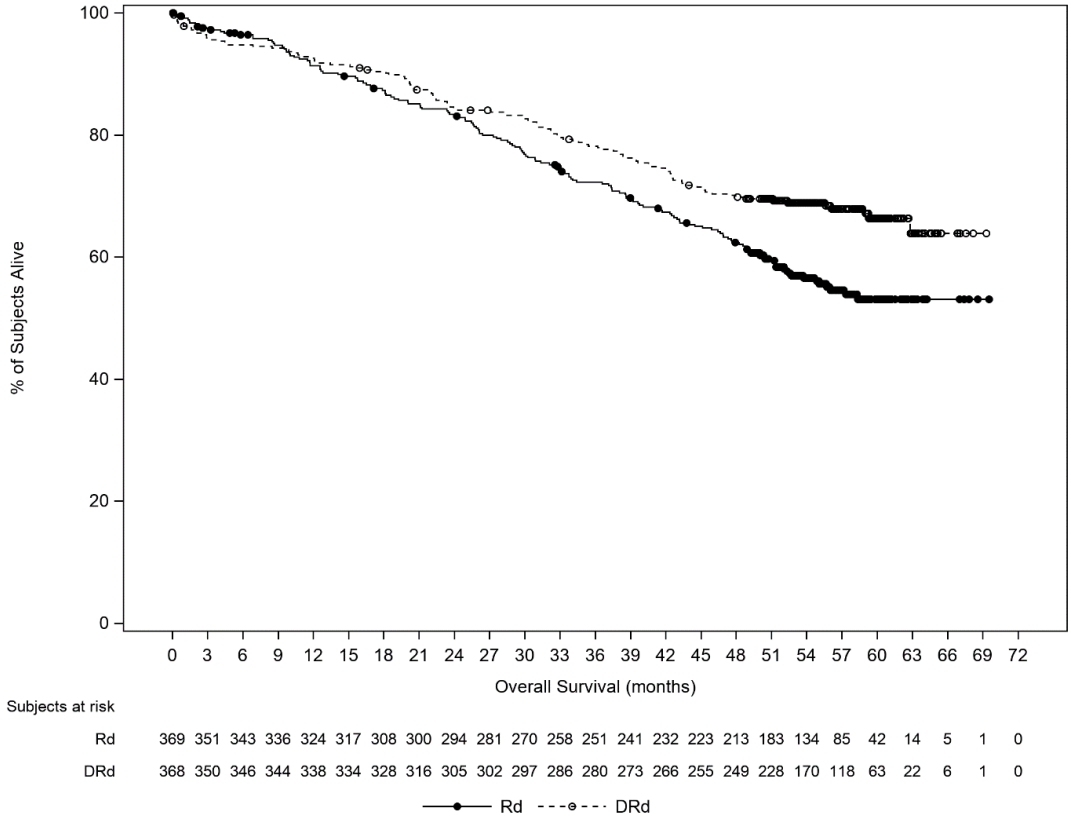
In responders, the median time to response was 1.05 months (range: 0.2 to 12.1 months) in the DRd group and 1.05 months (range: 0.3 to 15.3 months) in the Rd group.

In the ITT population, 89 (24.2%) patients in the DRd group achieved CR or better and minimal residual disease (MRD) negativity status at the threshold of 10^{-5} versus 27 (7.3%) in the Rd group (risk difference: 16.9%; 95% CI: 9.7%, 23.9%; p<0.0001). Among patients who achieved CR/sCR this corresponds to 50.9% in the DRd group versus 29.3% in the Rd group.

In an updated PFS analysis occurring after a median follow-up of 64 months (range 0.0 to 77.6 months), median PFS was 61.9 months (95% CI: 54.8, NE) in the DRd arm and 34.4 months (95% CI: 29.6, 39.2) in the Rd arm.

After a median follow-up of 56 months, the primary analysis of overall survival has demonstrated an improvement in favour of DRd over Rd with a hazard ratio of 0.68 (95% CI: 0.53, 0.86; p=0.0013), representing a 32% reduction in the risk of death in patients treated in the DRd arm. Median OS was not reached for either arm. The 60-month survival rate was 66% (95% CI: 61, 71) in the DRd arm and was 53% (95% CI: 47, 59) in the Rd arm (Figure 3).

Figure 3: Kaplan-Meier Plot for OS in Study MMY3008 (ITT population)



Study MMY3007: Darzalex in combination with bortezomib, melphalan, and prednisone (D-VMP)

See Table 38 for summary of study design and dosing. Patients were randomized 1:1 to receive D-VMP or VMP. The randomization was stratified by ISS (I, II, or III), region (Europe vs Other), and age (<75 vs ≥75).

Key inclusion criteria included 1) patient must be newly diagnosed and not considered a candidate for high-dose chemotherapy with stem cell transplant due to a) being ≥65 years of age, or b) in patients <65 years old, the presence of comorbid condition(s) likely to have a negative impact on tolerability of high dose chemotherapy and stem cell transplant; and 2) patient must have an ECOG score of 0-2. The baseline demographic and disease characteristics

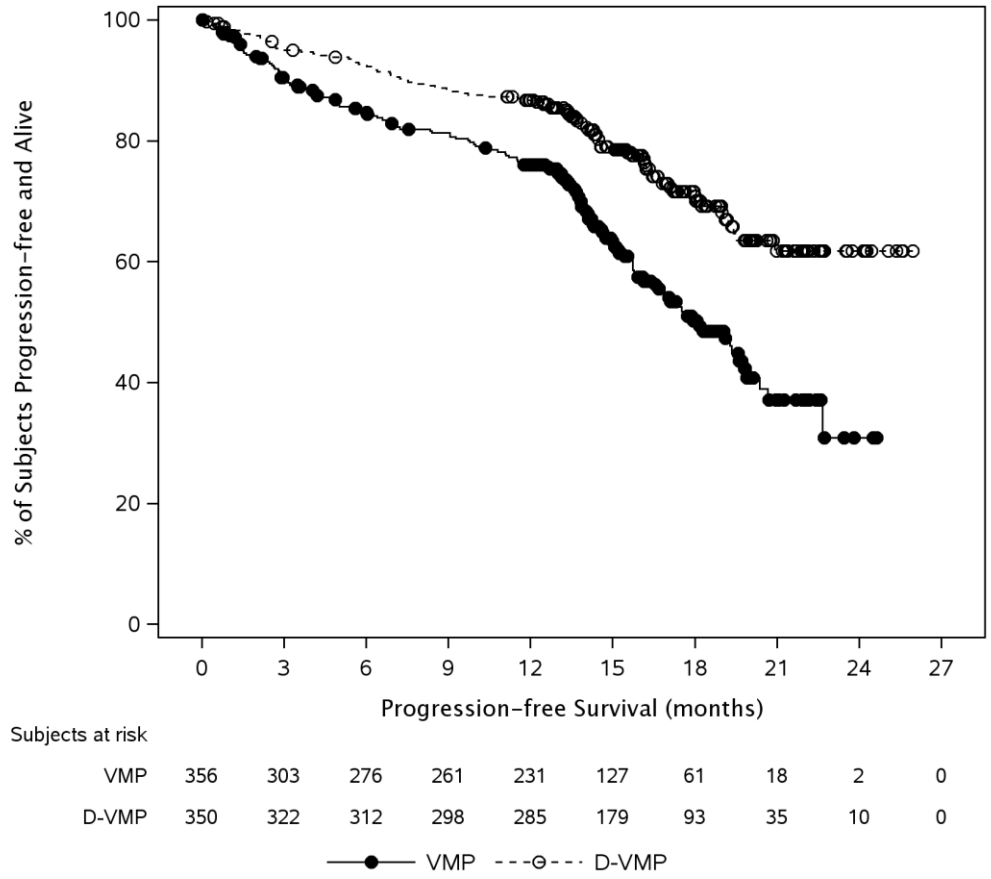
were similar between the two treatment groups. The median age was 71 (range 40-93) years old, with 29.9% of the patients ≥75 years of age. The majority were white (85%), 46% were male, and 75.4% had an ECOG performance score of 0 or 1. Patients had IgG/IgA/Light chain myeloma in 64%/22%/10% instances; 19% had ISS Stage I, 42% had ISS Stage II and 38% had ISS stage III disease. Of the 616 subjects who had baseline cytogenetic data reported, 16% had high-risk cytogenetic abnormalities, which included t(4;14) (7%), del17p (9%), and t(14;16) (2%), with similar proportions in the 2 arms (D-VMP:17%, VMP:15%).

Study Results:

The primary efficacy endpoint was progression free survival (PFS) based on International Myeloma Working Group (IMWG) criteria using a computer algorithm. Key secondary endpoints were objective response rate (ORR), minimal residual disease (MRD) negative rate, and overall survival (OS).

Based on the pre-defined interim analysis, Study MMY3007 demonstrated an improvement in PFS in the D-VMP arm as compared to the VMP arm; the median PFS had not been reached in the D-VMP arm and was 18.1 months in the VMP arm (hazard ratio [HR]=0.5; 95% CI: 0.38, 0.65; p<0.0001), representing a 50% reduction in the risk of disease progression or death in patients treated with D-VMP (Figure 4).

Figure 4: Kaplan-Meier Plot for Progression-free Survival in Study MMY3007 (median follow-up of 16.5 months)



Subgroup analyses based on PFS hazard ratio were consistent across the pre-specified subgroups and showed PFS improvement for subjects in the D-VMP group versus patients in the VMP group.

Efficacy results from Study MMY3007 are presented in Table 40 below.

Table 40: Efficacy results from Study MMY3007 (ITT population)

	D-VMP (n =350)	VMP (n =356)
PFS		
Number of events (%)	88 (25.1)	143 (40.2)
Hazard Ratio [95% CI][a]	0.50 (0.38, 0.65)	
Stratified log-rank test p-value[b]	<0.0001	
Median PFS in months [95% CI]	NE (NE, NE)	18.14 (16.53, 19.91)
Overall response (sCR+CR+VGPR+PR) n (%)	318 (90.9)	263 (73.9)
p-value[c]	<0.0001	
Stringent complete response (sCR)	63 (18.0)	25 (7.0)
Complete response (CR)	86 (24.6)	62 (17.4)
Very good partial response (VGPR)	100 (28.6)	90 (25.3)
Partial response (PR)	69 (19.7)	86 (24.2)
Time to Response, median in months (range)[d]	0.79 (0.4, 15.5)	0.82 (0.7, 12.6)
Duration of Response, median in months (range)[d]	NE (NE, NE)	21.3 (18.4, NE)

D-VMP = daratumumab-bortezomib-melphalan-prednisone; VMP = bortezomib-melphalan-prednisone; MRD = minimal residual disease; CI = confidence interval; NE = not estimable.

[a] Hazard ratio and 95% CI from a Cox proportional hazards model with treatment as the sole explanatory variable and stratified with ISS staging (I, II, III), region (Europe vs. Other), and age (<75 years vs. ≥75 years) as randomized. A hazard ratio <1 indicates an advantage for D-VMP.

[b] p-value is based on the log-rank test stratified with ISS staging (I, II, III), region (Europe vs. Other), and age (<75 years vs. ≥75 years) as randomized.

[c] p-value from Cochran Mantel-Haenszel Chi-Squared test.

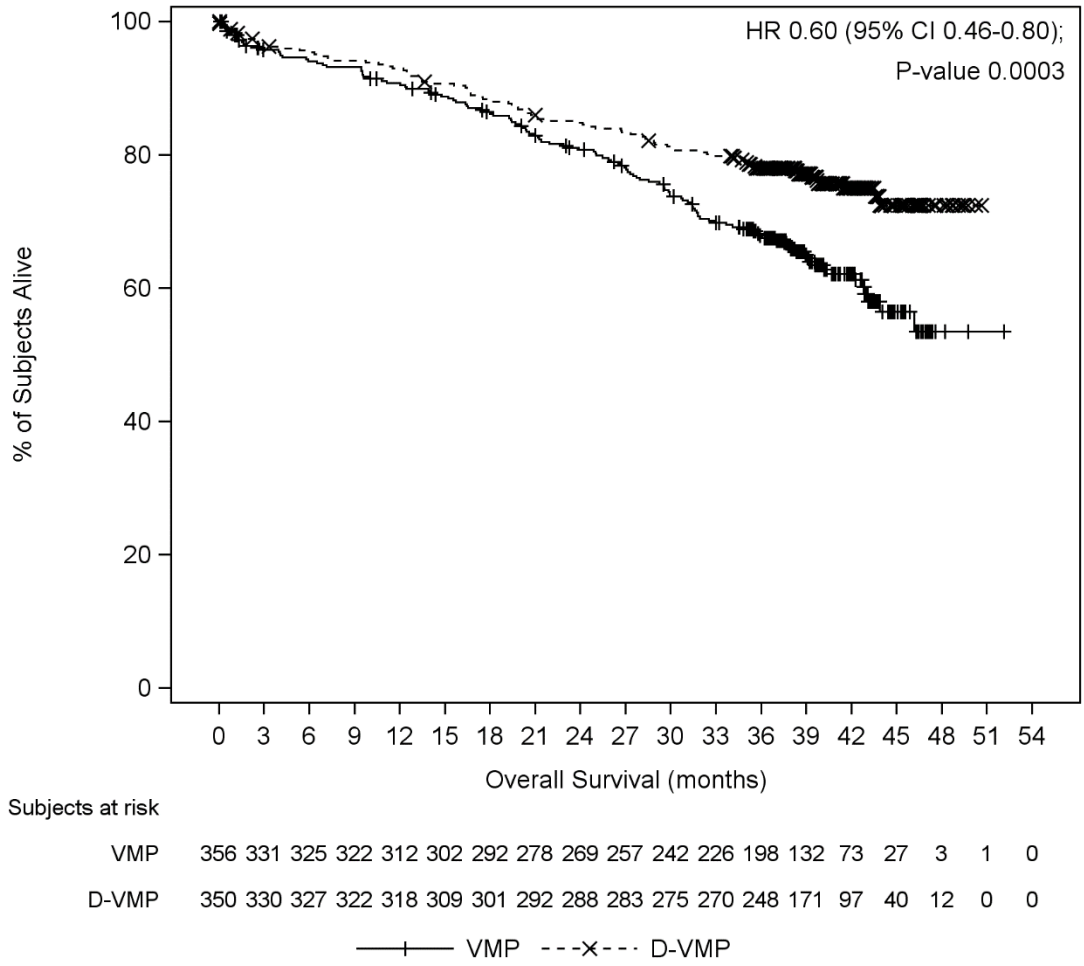
[d] The descriptive statistics of time to response and the Kaplan-Meier estimates of duration of response were provided based on subjects with overall response of PR or better.

In the ITT population, 74 (21.1%) patients in the D-VMP group achieved CR or better and MRD negativity status at the threshold of 10^{-5} versus 22 (6.2%) in the VMP group, which met the prespecified significance level of ≤0.0244. Among patients who achieved CR/sCR this corresponds to 49.7% in the D-VMP group versus 25.3% in the VMP group.

In an updated analysis of PFS occurring after a median follow-up of 40 months (range 0.0 to 52.1 months), median PFS was 36.4 months (95% CI: 32.1, 45.9) in the D-VMP arm and 19.3 months (95% CI: 18.0, 20.4) in the VMP arm.

In a pre-specified interim analysis of OS, with a median follow-up of 40 months, an OS advantage was shown for the D-VMP arm over the VMP arm (HR=0.60; 95% CI: 0.46, 0.80; p=0.0003), representing a 40% reduction in the risk of death in patients treated with D-VMP versus VMP (Figure 5). Median OS was not reached for either arm. There were 267 subjects (76.3%) still alive in the D-VMP group and 230 subjects (64.6%) still alive in the VMP group.

Figure 5: Kaplan-Meier Plot for Overall Survival; Intent-to-treat Analysis Set in Study MMY3007



Darzalex SC (daratumumab injection) is indicated in combination with lenalidomide and dexamethasone, or bortezomib and dexamethasone, for the treatment of patients with multiple myeloma who have received at least one prior therapy.

The clinical efficacy and safety of Darzalex for the treatment of patients with multiple myeloma who have received at least one prior therapy was demonstrated in two open-label, randomized, active-controlled studies using the intravenous formulation (Table 41).

Table 41: Summary of clinical trials in patients with multiple myeloma who have received at least one prior therapy who were treated with Darzalex (intravenous formulation), 16 mg/kg

Study # Trial design	Dosage, route of administration and duration	Number of subjects
Study MMY3003 (POLLUX Study), Phase 3, open-label, randomized, active-controlled study comparing treatment with Darzalex in combination with lenalidomide and low-dose dexamethasone (DRd) to treatment with lenalidomide and low-dose dexamethasone (Rd) in patients with multiple myeloma who had received at least one prior therapy.	Darzalex 16 mg/kg (IV) on Days 1, 8, 15, and 22 of Cycles 1 and 2 (weekly dosing), on Days 1 and 15 of Cycles 3 to 6 (every two week dosing), and on Day 1 of Cycle 7 and subsequent cycles (every four week dosing). Lenalidomide (25 mg once daily orally on Days 1-21 of repeated 28-day [4-week] cycles) with low dose oral or intravenous dexamethasone 40 mg/week (or a reduced dose of 20 mg/week for patients >75 years or body mass index [BMI] <18.5).	N=569 DRd arm: 286 Rd arm: 283
Study MMY3004 (CASTOR Study), Phase 3, open-label, randomized, active-controlled study comparing treatment with Darzalex in combination with bortezomib and dexamethasone (DVd), to treatment with bortezomib and dexamethasone (Vd).	Darzalex 16 mg/kg (IV) on Days 1, 8, 15 of Cycles 1 to 3, on Day 1 of Cycles 4 to 8, and on Day 1 of Cycle 9 and subsequent cycles every four weeks. Bortezomib by subcutaneous injection or IV injection at a dose of 1.3 mg/m^2 body surface area twice weekly for two weeks (Days 1, 4, 8, and 11) of repeated 21 day (3-week) treatment cycles, for a total of 8 cycles. Dexamethasone orally at a dose of 20 mg on Days 1, 2, 4, 5, 8, 9, 11, and 12 of the 8 bortezomib cycles (80 mg/week for two out of three weeks of each of the bortezomib cycle) or a reduced dose of 20 mg/week for patients >75 years, BMI <18.5, poorly controlled diabetes mellitus or prior intolerance to steroid therapy.	N=498 DVd arm: 251 Vd arm: 247

Study MMY3003: Darzalex in combination with lenalidomide and dexamethasone (DRd)

See Table 41 for a summary of study design and dosing. On Darzalex infusion days, 20 mg of the dexamethasone dose was given as a pre-infusion medication and the remainder given the day after the infusion. For patients on a reduced dexamethasone dose, the entire 20 mg dose was given as a Darzalex pre-infusion medication. Dose adjustments for lenalidomide and dexamethasone were applied according to manufacturer's prescribing information. Treatment was continued in both arms until disease progression or unacceptable toxicity. Patients were

randomized 1:1 to receive DRd or Rd. The randomization was stratified by ISS (I, II or III) at screening, number of prior lines of therapy (1 vs 2 or 3 vs >3), and prior lenalidomide (yes vs no).

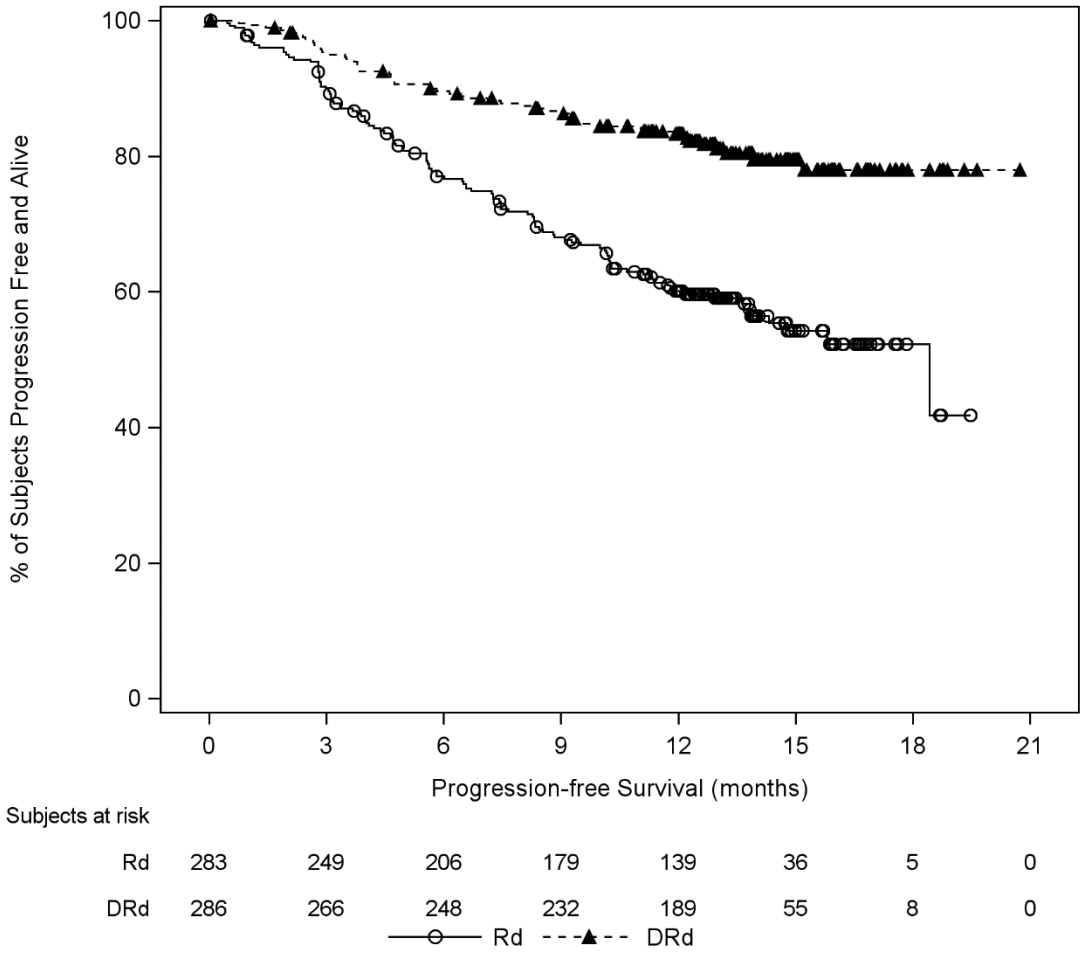
Key inclusion criteria included i) patients must have achieved a partial response or better to at least 1 prior regimen; and ii) patients must have an ECOG status 0-2. Patients refractory to lenalidomide were excluded from the study. A total of 569 patients were randomized; 286 to the DRd arm and 283 to the Rd arm. The baseline demographic and disease characteristics were generally balanced between the Darzalex and the control arm. The median patient age was 65 years (range 34 to 89 years), 11% were ≥75 years, 59% were male; 69% Caucasian, 18% Asian, and 3% African American. Patients had received a median of 1 prior line of therapy. Sixty-three percent (63%) of patients had received prior autologous stem cell transplantation (ASCT). The majority of patients (86%) received a prior proteasome inhibitor (PI) including bortezomib (84%), and carfilzomib (2%). Fifty-five percent, (55%) of patients had received a prior immunomodulatory agent (IMiD), including lenalidomide (18%) and thalidomide (43%). Forty-four percent (44%) of patients had received both a prior PI and IMiD. At baseline, 27% of patients were refractory to the last line of treatment. Eighteen percent (18%) of patients were refractory to a PI only, and 21% were refractory to bortezomib. Of the 439 subjects who had baseline cytogenetic data reported, 16% had high-risk cytogenetic abnormalities, which included t(4;14) (6%), del17p (10%), and t(14;16) (2%), with similar proportions in the 2 arms (DRd:15%, Rd:17%).

Study Results:

The primary efficacy endpoint was progression free survival (PFS) based on International Myeloma Working Group (IMWG) criteria using a computer algorithm. Key secondary endpoints were objective response rate (ORR) and overall survival (OS).

Based on the pre-defined interim analysis, Study MMY3003 demonstrated an improvement in PFS in the DRd arm as compared to the Rd arm; the median PFS had not been reached in the DRd arm and was 18.4 months in the Rd arm (hazard ratio [HR]=0.37; 99.39% CI: 0.23, 0.59; p<0.0001) representing 63% reduction in the risk of disease progression or death in patients treated with DRd (Figure 6).

Figure 6: Kaplan-Meier Plot for Progression-free Survival in Study MMY3003 (median follow-up of 13.5 months)



Subgroup analyses based on PFS hazard ratio were consistent across the pre-specified subgroups and showed PFS improvement for subjects in the DRd group versus patients in the Rd group.

Efficacy results from Study MMY3003 are presented in Table 42.

Table 42: Efficacy results from Study MMY3003

Intent-to-treat patient number	DRd (n=286)	Rd (n=283)
PFS[a]		
Number of events (%)	53 (18.5%)	116 (41.0%)
Hazard Ratio [99.39% CI]	0.37 (0.23, 0.59)	
Stratified log-rank test p-value[b]	<0.0001	
Median PFS in months [95% CI]	NE (NE, NE)	18.4 (13.9, NE)
Response[a]		
Overall response (sCR+CR+VGPR+PR) n (%)	261 (91.3)	211 (74.6)
p-value[c]	<0.0001	
Stringent complete response (sCR)	51 (17.8)	20 (7.1)
Complete response (CR)	70 (24.5)	33 (11.7)
Very good partial response (VGPR)	92 (32.2)	69 (24.4)
Partial response (PR)	48 (16.8)	89 (31.4)
Time to Response, median in months (range)[d]	1.0 (0.9, 13.0)	1.1 (0.9, 10.2)
Duration of Response, median in months (range)[d]	NR (1+, 19.8+)	17.4 (1.4, 18.5+)

DRd=daratumumab-lenalidomide-dexamethasone; Rd=lenalidomide-dexamethasone; CI=confidence interval; NE=not estimable; NR=not reached.

[a]The PFS and ORR interim analysis were based on an adjusted alpha level of 0.00612 and 0.02442 respectively.

[b] p-value was based on the log-rank test stratified with ISS (I, II, or III), number of prior lines of therapy (1 vs. 2 or 3 vs. >3), and prior lenalidomide treatment (no vs. yes).

[c] p-value from Cochran Mantel-Haenszel Chi-Squared test.

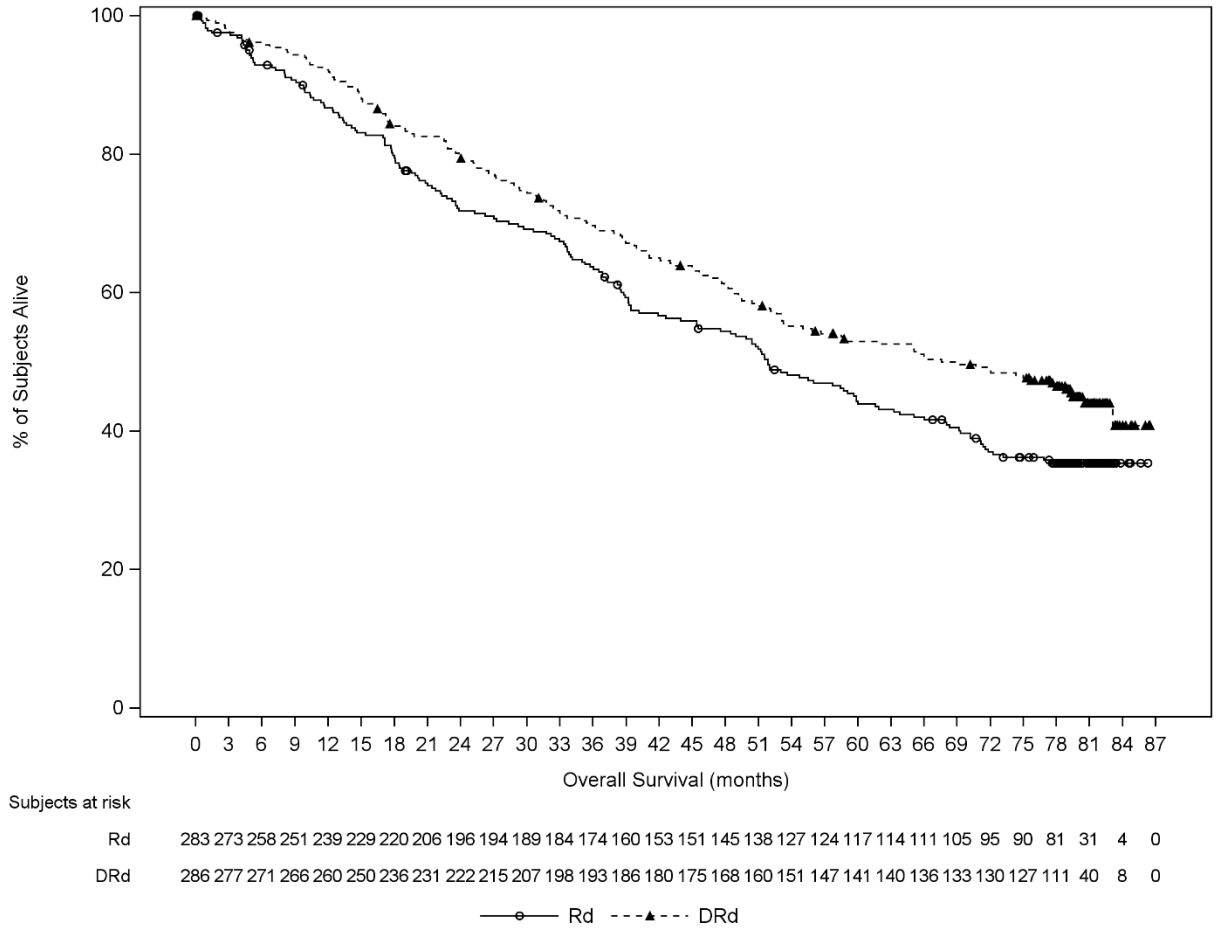
d Time to response and duration of response were based on subjects with overall response of PR or better.

Twenty-nine percent (29.0%) of the subjects in the DRd group achieved minimal residual disease (MRD) negativity status by the threshold of 10^{-4} versus 7.8% in the Rd group.

In an updated PFS analysis occurring after a median follow-up of 55 months (range 0.0 to 61.9 months), median PFS was 45.0 months (95% CI: 34.1, 53.9) in the DRd arm and 17.5 months (95% CI: 13.9, 20.8) in the Rd arm.

In the final analysis of OS, which occurred after a median follow up of 80 months, an improvement in OS was observed for the DRd arm compared to the Rd arm. The hazard ratio was 0.73 (95% CI: 0.58, 0.91; p=0.0044), in favour of DRd, representing a 27% reduction in the risk of death. The median OS was 67.6 months in the DRd arm and 51.8 months in the Rd arm (Figure 7).

Figure 7: Kaplan-Meier Plot for OS in Study MMY3003 (ITT population)



Study MMY3004: Darzalex in combination with bortezomib and dexamethasone (DVd)

See Table 41 for a summary of study design and dosing. On the days of Darzalex infusion, 20 mg of the dexamethasone dose was administered as a pre-infusion medication. For patients on a reduced dexamethasone dose, the entire 20 mg dose was given as a Darzalex pre-infusion medication. Bortezomib and dexamethasone were given for 8 three-week cycles in both treatment arms; whereas Darzalex was given until disease progression in the DVd arm. However, dexamethasone 20 mg was continued as a Darzalex pre-infusion medication in the DVd arm. Dose adjustments for bortezomib and dexamethasone were applied according to manufacturer's prescribing information. Patients were randomized 1:1 to receive DVd or Vd. The randomization was stratified by ISS (I, II or III) at screening, number of prior lines of therapy (1 vs 2 or 3 vs >3), and prior bortezomib (yes vs no).

Key inclusion criteria included i) patients must have achieved a partial response or better to at least 1 prior regimen; and ii) patients must have an ECOG status 0-2. Key exclusion criteria included i) patients refractory to bortezomib or another proteasome inhibitor; and ii) patients

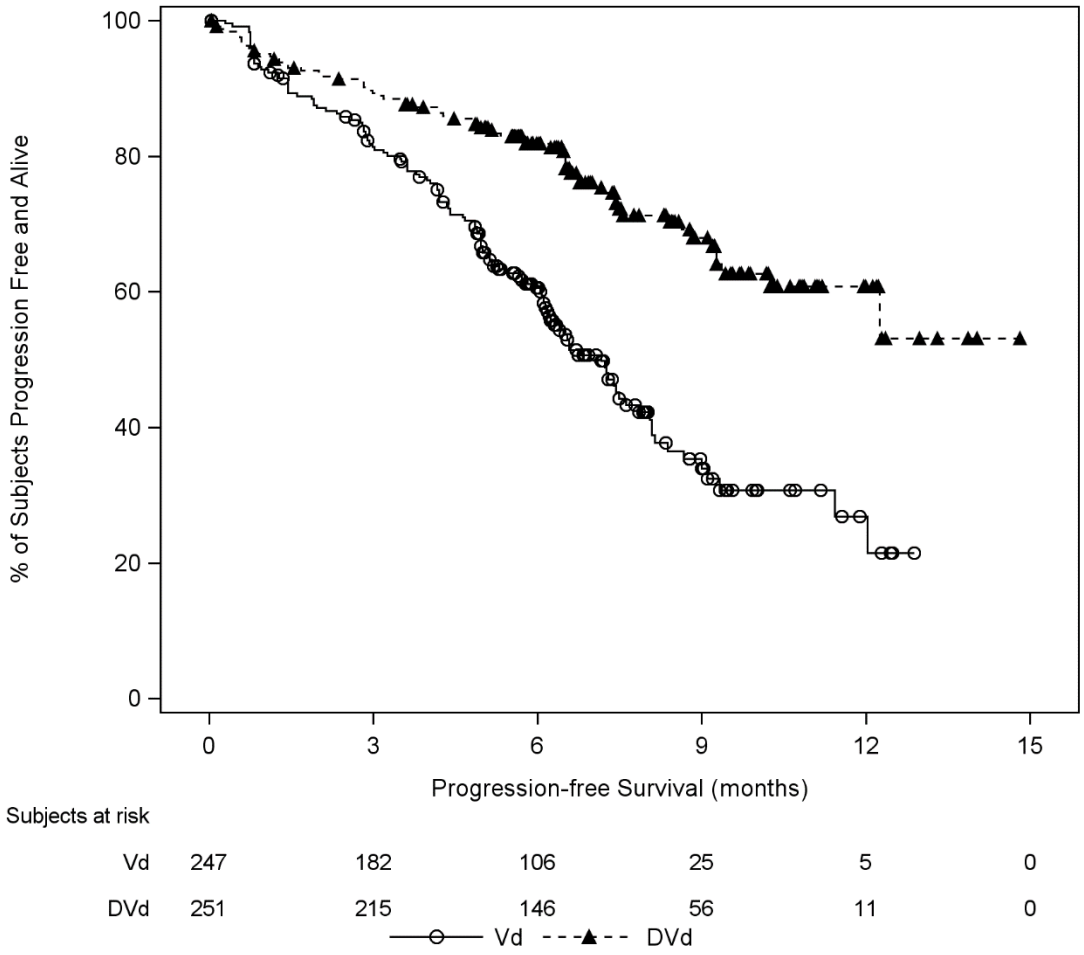
intolerant to bortezomib. A total of 498 patients were randomized; 251 to the DVd arm and 247 to the Vd arm. The baseline demographic and disease characteristics were generally balanced between the Darzalex and the control arm. The median patient age was 64 years (range 30 to 88 years); 12% were ≥75 years, 57% were male; 87% Caucasian, 5% Asian and 4% African American. Patients had received a median of 2 prior lines of therapy and 61% of patients had received prior autologous stem cell transplantation (ASCT). Sixty-nine percent (69%) of patients had received a prior PI, including bortezomib (66%) and carfilzomib (4%); 76% of patients received an IMiD, including lenalidomide (42%), pomalidomide (3%) and thalidomide (49%). At baseline, 32% of patients were refractory to the last line of treatment and the proportions of patients refractory to any specific prior therapy were well balanced between the treatment groups. Thirty-three percent (33%) of patients were refractory to an IMiD only, with 24% of patients in the DVd arm and 33% of patients in the Vd arm refractory to lenalidomide. Of the 355 patients who had baseline cytogenetic data reported, 22% had high-risk cytogenetic abnormalities by karyotype and/or FISH analysis, which included t(4;14) (8%), del17p (14%), and t(14;16) (3%), with similar proportions in the 2 arms (DVd:23%, Vd:21%).

Study Results:

The primary efficacy endpoint was progression free survival (PFS) based on International Myeloma Working Group (IMWG) criteria using a computer algorithm. Key secondary endpoints were objective response rate (ORR) and overall survival (OS).

Based on the pre-defined interim analysis, Study MMY3004 demonstrated an improvement in PFS in the DVd arm as compared to the Vd arm; the median PFS had not been reached in the DVd arm and was 7.2 months in the Vd arm (HR=0.39; 98.98% CI: 0.26, 0.58; p-value < 0.0001), representing a 61% reduction in the risk of disease progression or death for patients treated with DVd versus Vd (Figure 8).

Figure 8: Kaplan-Meier Plot for Progression-free Survival in Study MMY3004 (median follow-up of 7.4 months)



Subgroup analyses based on PFS hazard ratio were consistent across the pre-specified subgroups and showed PFS improvement for subjects in the DVd group versus patients in the Vd group.

Efficacy results from Study MMY3004 are presented Table 43 below.

Table 43: Efficacy results from Study MMY3004

Intent-to-treat patient number	DVd (n=251)	Vd (n=247)
PFS[a]		
Number of events (%)	67 (26.7%)	122 (49.4%)
Hazard Ratio [98.98% CI]	0.39 (0.26, 0.58)	
Stratified log-rank test p-value[b]	<0.0001	
Median PFS in months [95% CI]	NE (12.3, NE)	7.2 (6.2, 7.9)
Response[a]		
Overall response (sCR+CR+VGPR+PR) n (%)	199 (79.3)	148 (59.9)
P-value[c]	<0.0001	
Stringent complete response (sCR)	11 (4.4)	5 (2.0)
Complete response (CR)	35 (13.9)	16 (6.5)
Very good partial response (VGPR)	96 (38.2)	47 (19.0)
Partial response (PR)	57 (22.7)	80 (32.4)
Time to Response, median in months (range)[d]	0.8 (0.7, 4.0)	1.5 (0.7, 5.1)
Duration of Response, median in months (range)[d]	NR (1.4+, 14.1+)	7.9 (1.4+, 12.0+)

DVd=daratumumab- bortezomib-dexamethasone; Vd=bortezomib-dexamethasone; CI=confidence interval; NE=not estimable; NR=not reached

[a] The PFS and ORR interim analysis were based on an adjusted alpha level of 0.0102 and 0.02442 respectively.

[b] p-value was based on the log-rank test stratified with ISS (I, II, or III), number of prior lines of therapy (1 vs. 2 or 3 vs. >3), and prior bortezomib treatment (no vs. yes).

[c] p-value from Cochran Mantel-Haenszel Chi-Squared test.

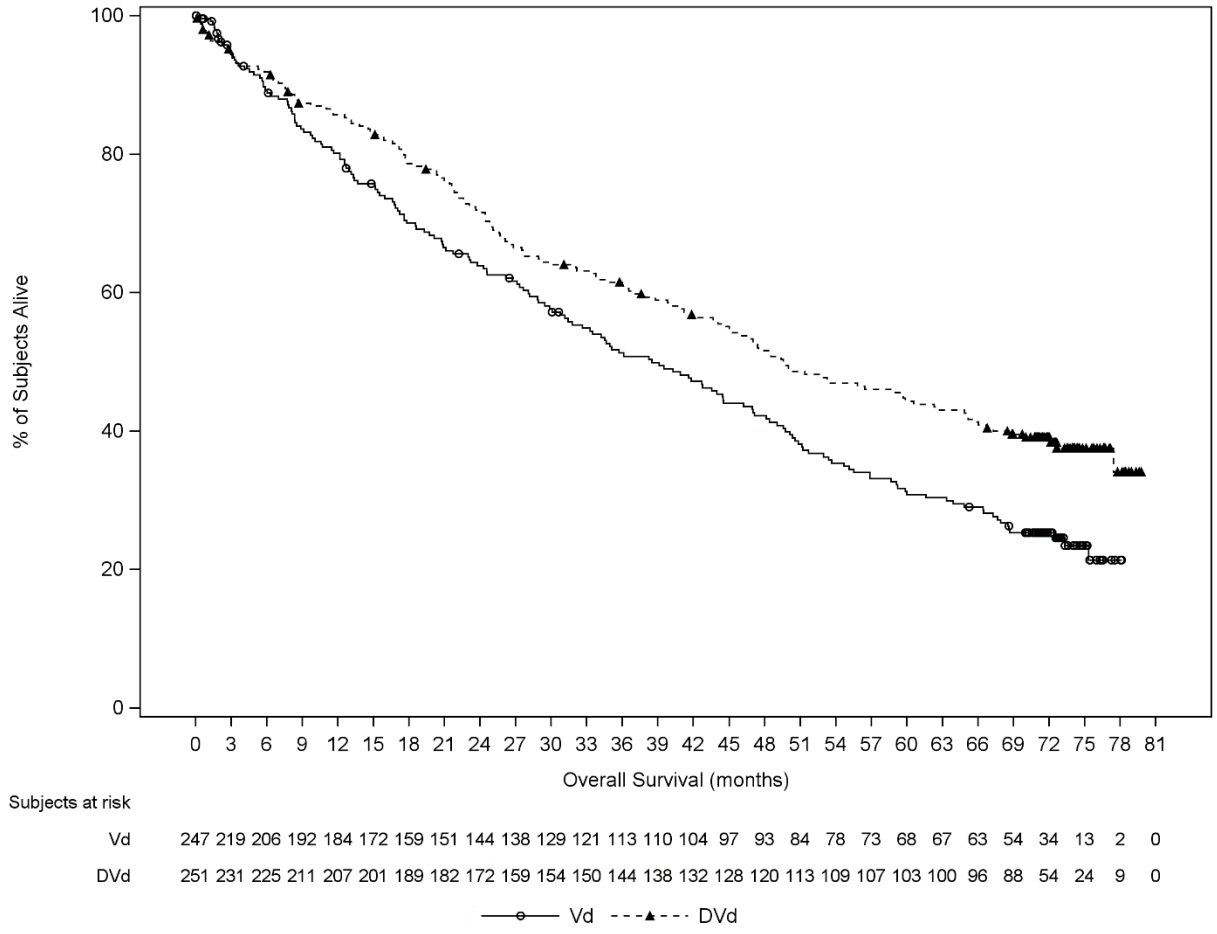
[d] Time to response and duration of response were based on subjects with overall response of PR or better.

Thirteen-point five percent (13.5%) of the subjects in the DVd group achieved MRD negativity status by the threshold of 10^{-4} versus 2.8% in the Vd group.

In an updated analysis of PFS occurring after a median follow-up of 50 months (range 0.0 to 58.6 months), median PFS was 16.7 months (95% CI: 13.1, 19.4) in the DVd arm and 7.1 months (95% CI: 6.2, 7.7) in the Vd arm.

In the final analysis of OS, which occurred after a median follow-up of 73 months, an improvement in OS was observed for the DVd arm compared to the Vd arm. The hazard ratio was 0.74 (95% CI: 0.59, 0.92; p=0.0075), in favour of DVd, representing a 26% reduction in the risk of death. The median OS was 49.6 months in the DVd arm and 38.5 months in the Vd arm (Figure 9).

Figure 9: Kaplan-Meier Plot for OS in Study MMY3004 (ITT population)



Darzalex SC (daratumumab injection) is indicated in combination with pomalidomide and dexamethasone for the treatment of patients with multiple myeloma who have received at least one prior line of therapy, including lenalidomide and a proteasome inhibitor.

Table 44: Summary of clinical trials in patients with relapsed or refractory multiple myeloma who were administered Darzalex SC 1800 mg

Study # Trial design	Dosage, route of administration and duration	Number of subjects
Study MMY3013 (APOLLO Study) Phase 3, randomized, open-label, active-controlled study comparing treatment with Darzalex SC in combination treatment with pomalidomide and dexamethasone (DPd) versus pomalidomide and dexamethasone (Pd) alone in patients with relapsed or refractory multiple myeloma who have received at least one prior therapy with both lenalidomide and a proteasome inhibitor (PI).	Darzalex SC 1800 mg (SC): Cycles* 1-2: weekly; Cycles 3-6: every 2 weeks; Cycle ≥7: every 4 weeks Pomalidomide (4 mg p.o): Days 1-21 of each cycle Dexamethasone (40 mg p.o): Once weekly (reduced dose of 20 mg per week for patients ≥75 years) * Cycle = 4 weeks.	N=304 DPd arm: 151 Pd arm: 153

Study MMY3013: Darzalex SC in combination with pomalidomide and dexamethasone

DPd was compared to Pd in Study MMY3013. Table 44 summarizes the study design and dosing regimen. Patients were randomized 1:1 to DPd or Pd. Randomization was stratified by number of lines of prior therapy and ISS stage (I, II or III). Key eligibility criteria included: age at least 18 years, measurable multiple myeloma, receipt of at least 1 prior treatment regimen, and prior treatment with both lenalidomide and a PI. Patients must have experienced a response to prior treatment and had subsequent documented disease progression based on International Myeloma Working Group (IMWG) criteria. Subjects who received only 1 line of prior treatment must have demonstrated progressive disease within 60 days of completion of the lenalidomide-containing regimen (i.e., lenalidomide refractory). Subjects must have had an ECOG performance status score of 0, 1, or 2. Patients were ineligible for the study if they had received a previous allogeneic stem cell transplant or an autologous stem cell transplant that occurred within 12 weeks prior to cycle 1 day 1 of the study.

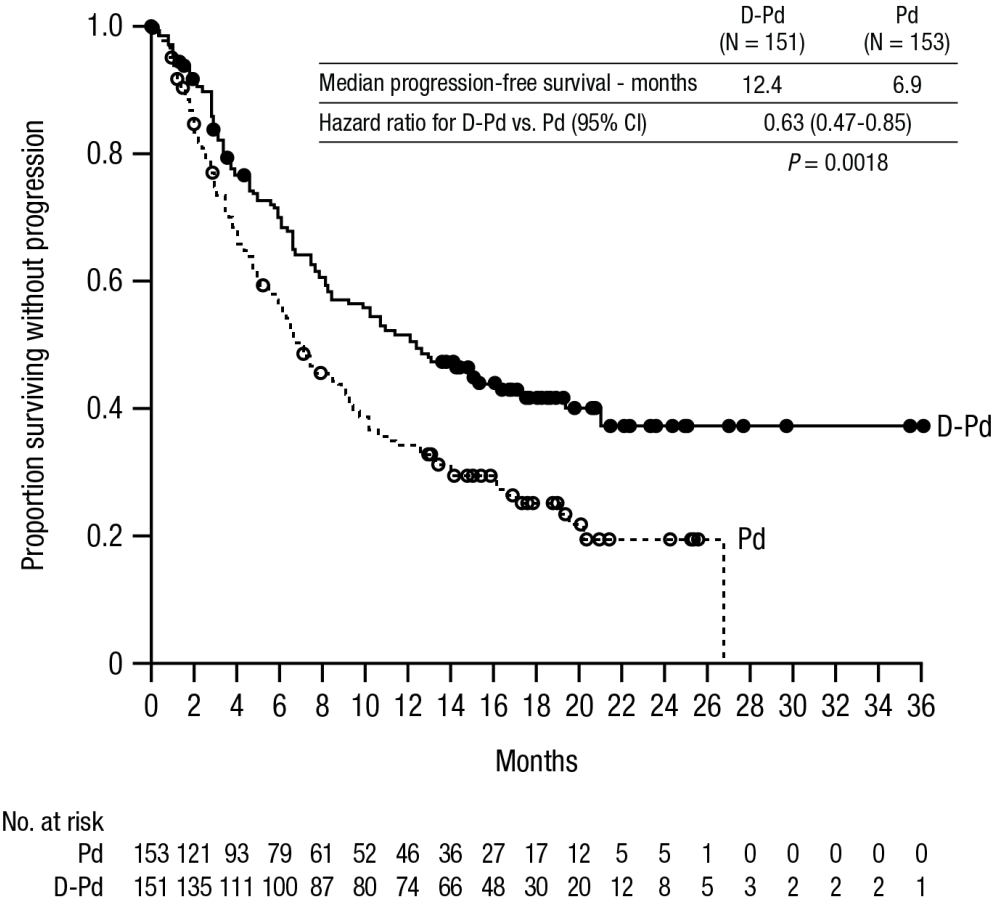
On Darzalex SC administration days, dexamethasone served as the treatment dose of steroid for that day, as well as the required pre-infusion medication. Treatment was continued in both arms until disease progression or unacceptable toxicity.

A total of 304 patients were randomized: 151 to DPd and 153 to Pd. The median age was 67 years (range: 35 to 90); 53% were male; 89% were White; <1% were Black or African American; <1% were Asian; 45% had ISS Stage I, 33% had ISS Stage II, and 22% had ISS Stage III disease. Ninety-two percent (92%) of patients had an ECOG performance status of 0 – 1, and 8% had an ECOG performance status of 2. Patients had received a median of 2 prior lines of therapy (range: 1-5). All patients had received prior treatment that included a PI and lenalidomide, and 56% of patients received prior ASCT. The majority of patients were refractory to lenalidomide (80%), a PI (48%), or both an immunomodulatory agent and a PI (42%). Of the 211 patients who had baseline cytogenetic data reported, 38% in the DPd arm and 32% in the Pd arm had high-risk cytogenetics abnormalities which included del17p (16%), t(4;14) (17%) and t(14;16) (6%).

Study Results:
The primary efficacy endpoint was progression free survival (PFS) based on International Myeloma Working Group (IMWG) criteria using a computer algorithm. Key secondary endpoints were overall response rate (ORR), rate of VGPR or better, rate of CR or better, minimal residual disease (MRD) negativity rate, and overall survival (OS).

MMY3013 demonstrated an improvement in the primary endpoint of progression free survival (PFS) in the DPd treatment group as compared to the Pd treatment group; the median PFS was 12.4 months (95%CI: 8.34, 19.3) in the DPd treatment group and 6.9 months (95%CI: 5.5, 9.3) in the Pd treatment group (HR [95% CI]: 0.63 [0.47, 0.85]; p-value = 0.0018), representing a 37% reduction in the risk of disease progression or death for patients treated with DPd versus Pd. Pre-specified, exploratory subgroup analyses based on PFS hazard ratio were generally consistent across the subgroups and showed a PFS improvement for subjects in the DPd group compared to those in the Pd group. With a median follow-up time of 16.9 months, 99 deaths were observed (48 in the DPd arm, 51 in the Pd group. Median OS was not reached for either treatment group.

Figure 10: Kaplan-Meier Curve of PFS in MMY3013



Efficacy results from MMY3013 are presented in Table 45.

Table 45: Efficacy results from Study MMY3013

	D-Pd (n=151)	Pd (n=153)
PFS		
Number of events (%)	84 (55.6)	106 (69.3)
Hazard Ratio [95% CI][a]	0.63 (0.47, 0.85)	
Stratified log-rank test p-value[b]	0.0018	
Median PFS in months [95% CI]	12.4 (8.3, 19.3)	6.9 (5.5, 9.3)
Overall response (sCR+CR+VGPR+PR) n(%)[c]	104 (68.9%)	71 (46.4%)
P-value[d]	<0.0001	
Stringent complete response (sCR)	14 (9.3%)	2 (1.3%)
Complete response (CR)	23 (15.2%)	4 (2.6%)
Very good partial response (VGPR)	40 (26.5%)	24 (15.7%)
Partial response (PR)	27 (17.9%)	41 (26.8%)
MRD negativity rate[e] n (%)	13 (8.7%)	3 (2.0%)
95% CI (%)	(4.7%, 14.3%)	(0.4%, 5.6%)
P-value[f]	0.0102	

D-Pd=daratumumab-pomalidomide-dexamethasone; Pd=pomalidomide-dexamethasone; MRD=minimal residual disease; CI=confidence interval

[a] Hazard ratio and 95% CI from a Cox proportional hazards model with treatment as an explanatory variable and stratified with ISS staging (I, II, III), and number of prior lines of therapy. A hazard ratio <1 indicates an advantage for DPd.

[b] P-value is obtained from the two-sided log-rank test stratified with ISS (1, 2, 3), and number of lines of prior therapy (1, 2-3, ≥ 4).

[c] based on intent-to-treat population

[d] p-value from Cochran Mantel-Haenszel Chi-Squared test adjusted for stratification factors

[e] MRD Negative rate is based on the intent-to-treat population and a threshold of 10^{-5} using a next generation sequencing assay.

[f] p-value from Fisher's exact test.

In responders, the median time to response was 1 month (range: 0.9 to 9.1 months) in the DPd group and 1.9 months (range: 0.9 to 17.3 months) in the Pd group. The median duration of response had not been reached in the DPd group (range: 1 to 34.9+ months) and was 15.9 months (range: 1+ to 24.8 months) in the Pd group.

With a median follow-up of 16.9 months, 99 deaths were observed; 48 in the DPd group and 51 in the Pd group.

Darzalex SC (daratumumab injection) is indicated in combination with carfilzomib and dexamethasone for the treatment of patients with relapsed multiple myeloma who have received 1 to 3 prior lines of therapy

The clinical efficacy and safety of Darzalex in combination with carfilzomib and dexamethasone for the treatment of patients with relapsed or refractory multiple myeloma was demonstrated in the CANDOR Study (with twice-weekly carfilzomib) using the intravenous formulation (Table 46).

Table 46: Summary of clinical trials in patients with multiple myeloma who have received 1 to 3 prior lines of therapy

Study # Trial design	Dosage, route of administration and duration	Number of subjects
CANDOR Study, Phase 3, randomized, open-label, multicenter superiority trial of Darzalex with carfilzomib and dexamethasone (DKd) vs. carfilzomib and dexamethasone (Kd) in patients with relapsed or refractory multiple myeloma who had received 1 to 3 prior lines of therapy.	Darzalex 16 mg/kg (IV; 28-day cycles): Cycle 1: Split dose (8 mg/kg) on Days 1 and 2; thereafter, 16 mg/kg once weekly on Days 8, 15, and 22. Cycle 2: once weekly dosing on Days 1, 8, 15 and 22 Cycles 3 to 6: every two-week dosing Cycle 7 and subsequent cycles: every four-week dosing until disease progression or unacceptable toxicity. Carfilzomib 20/56 mg/m^2 (IV): Administered at a dose of 20 mg/m^2 in Cycle 1 on Days 1 and 2; at a dose of 56 mg/m^2 in Cycle 1 on Days 8, 9, 15, and 16; and at a dose 56 mg/m^2 on Days 1, 2, 8, 9, 15, and 16 of each 28-day cycle thereafter. Dexamethasone 20 mg was administered orally or intravenously on Days 1, 2, 8, 9, 15 and 16 and then 40 mg orally or intravenously on Day 22 of each 28-day cycle.	N=466 DKd arm: 312 Kd arm: 154

<u>CANDOR Study: Darzalex in combination with carfilzomib (20/56 mg/m^2) and dexamethasone (DKd)</u>

See Table 46 above for study design and dosing. Patients were excluded if they had known moderate or severe persistent asthma within the past 2 years, known chronic obstructive pulmonary disease (COPD) with a FEV1 <50% of predicted normal, and active congestive heart failure. A total of 466 patients were enrolled and randomized in a 2:1 randomization (312 in DKd arm and 154 in Kd arm). Randomization was stratified by the ISS (stage 1 or 2 vs stage 3) at screening, prior proteasome inhibitor exposure (yes vs no), number of prior lines of therapy (1 vs ≥ 2), and prior cluster differentiation antigen 38 (CD38) antibody therapy (yes vs no).

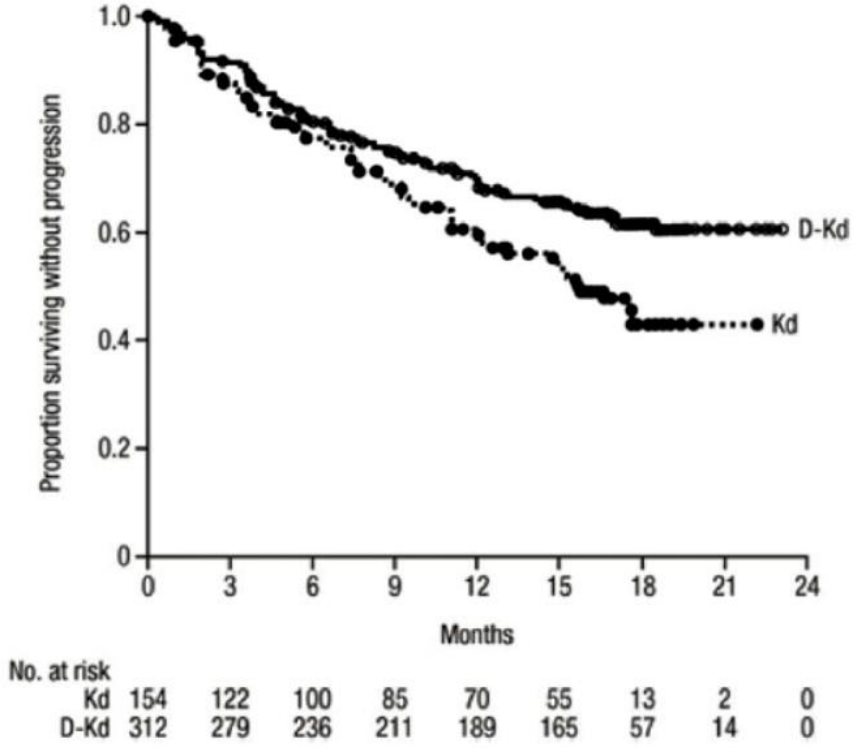
The baseline demographic and disease characteristics were similar between arms. In the study population, the median age was 64 years (range 29 to 84 years), 9% were ≥75 years, 58% were male; 79% White, 14% Asian, and 2% Black. Patients had received a median of 2 prior lines of therapy and 58% of patients had received prior autologous stem cell transplantation (ASCT). The majority of patients (92%) received a prior PI and of those 34% were refractory to PI including regimen. Forty-two percent (42%) of patients had received prior lenalidomide and of those, 33% were refractory to a lenalidomide containing regimen.

Patients received treatment with any study drug for a median duration of 70 weeks in the DKd arm and 40 weeks in the Kd arm. Patients in the DKd group received a median of 68 weeks of treatment with daratumumab. Patients received a median of 58 weeks of treatment with carfilzomib in the DKd arm and 40 weeks in the Kd arm.

Study Results:

The primary efficacy endpoint of the CANDOR study was PFS determined by a Blinded Independent Review Committee using IMWG Uniform Response Criteria. Key secondary efficacy endpoints were overall response rate, minimal residue disease-negative complete response (MRD [-] CR) rate at 12 months and overall survival. The trial demonstrated an improvement in PFS in the DKd arm as compared to the Kd arm; the median PFS has not been reached in the DKd arm vs. 15.8 months in the Kd arm (hazard ratio [HR]=0.630; 95% CI: 0.464, 0.854; p=0.0014) representing a 37% reduction in the risk of disease progression or death in patients treated with DKd (Figure 11).

Figure 11: Kaplan-Meier Curve of PFS in CANDOR



Efficacy results from CANDOR are presented in Table 47.

Table 47: Efficacy Results From CANDOR (Intent-to-Treat Population)

	DKd (N=312)	Kd (N=154)
PFS[a]		
Number of events, n (%)	110 (35.3)	68 (44.2)
Median, Months (95% CI)	NE (NE, NE)	15.8 (12.1, NE)
Hazard Ratio (95% CI)	0.630 (0.46, 0.85)	
p-value (1-sided)	0.0014	
Overall response[b] (sCR+CR+VGPR+PR)		
N with Response	263	115
ORR, (%) (95% CI)	84.3 (79.8, 88.1)	74.7 (67.0, 81.3)
Odds Ratio (95% CI)	1.925 (1.18, 3.13)	
p-value (1-sided)	0.0040	
CR, n (%)	89 (28.5)	16 (10.4)
VGPR, n (%)	127 (40.7)	59 (38.3)
PR, n (%)	47 (15.1)	40 (26.0)
MRD [-] CR at 12 months (at a 10^{-5} level)[b, c]		
MRD[-]CR rate (%) (95% CI)	12.5 (9.0, 16.7)	1.3 (0.2, 4.6)
Odds Ratio (95% CI)	11.329 (2.70, 47.48)	
p-value (1-sided)	<0.0001	

	DKd (N=312)	Kd (N=154)

CI = confidence interval; CR = complete response; Kd = carfilzomib and dexamethasone; DKd = Darzalex, carfilzomib, dexamethasone; MRD[-]CR = minimal residual disease negative-complete response; NE = not estimable; ORR = overall response rate; PR = partial response; PFS = progression-free survival; VGPR = very good partial response
Stratification factors used in the analyses include (as assessed at randomization): International Staging System (ISS) stage (Stage 1 or 2 vs Stage 3) at screening; prior proteasome inhibitor exposure (yes vs no); number of prior lines of therapy (1 vs ≥ 2).

[a] Hazard ratio and 95% CI were estimated using stratified Cox proportional hazards model; 1-sided p-value was calculated using log-rank test stratified by the randomization stratification factors at level of 0.025 (1-sided); medians were estimated using the Kaplan-Meier method. 95% CIs for medians were estimated using the method by Klein and Moeschberger (1997) with log-log transformation.

[b] Odds ratio and 95% CI were estimated by a stratified analysis using the Mantel-Haenszel method; 1-sided p-values were calculated using Cochran-Mantel-Haenszel Chi-Square test controlling for the stratification factors at level of 0.025(1-sided); 95% CIs for proportions were estimated using the Clopper-Pearson method.

[c] MRD[-]CR at 12-month is defined as achievement of CR or better per IMWG-URC and MRD[-] status as assessed by NGS at 12 months landmark (from 8 months to 13 months window).

Overall survival data were not mature. The median duration of response was not estimable for the DKd arm and was 16.6 months (13.9, NE) for the Kd arm. The median time to response was 1 (range: 1, 14) months for the DKd arm and 1 (range: 1,10) months for the Kd arm.

Darzalex SC (daratumumab injection) is indicated for the treatment of patients with multiple myeloma who have received at least three prior lines of therapy including a proteasome inhibitor (PI) and an immunomodulatory agent (IMiD), or who are refractory to both a PI and an IMiD.

Table 48: Summary of clinical trials in patients with multiple myeloma who were administered Darzalex SC 1800 mg

Study # Trial design	Dosage, route of administration and duration	Number of subjects
Study MMY3012 (COLUMBA Study), Phase 3, randomized, open-label, active-controlled, multicenter study to demonstrate that the efficacy and PK for Darzalex SC (subcutaneous) are non-inferior to those for Darzalex (intravenous) in terms of ORR and the maximum trough concentration (C_{trough}) in patients with multiple myeloma who have received at least 3 prior lines of therapy including a proteasome inhibitor (PI) and an immunomodulatory drug (IMiD), or whose disease is double refractory to both a PI and an IMiD.	Darzalex SC 1800 mg (SC): Cycles** 1-2: weekly; Cycles 3-6: every 2 weeks; Cycle ≥7: every 4 weeks; Darzalex 16 mg/kg (intravenous): Cycles 1-2: weekly; Cycles 3-6: every 2 weeks; Cycle ≥7: every 4 weeks; ** Cycle = 4 weeks.	N=522 SC arm: 263 IV arm: 259

Study MMY3012

MMY3012, an open-label, randomized, Phase 3 non-inferiority study, compared the efficacy and safety of treatment with Darzalex SC (1800 mg) vs. intravenous (16 mg/kg) daratumumab. Key inclusion criteria included 1) patients must have relapsed or refractory multiple myeloma and received ≥3 prior lines of therapy including a PI and an IMiD or are refractory to both a PI and an IMiD; 2) patients must have achieved evidence of response to ≥1 prior treatment regimen; and 3) patients must have an ECOG status of 0-2. See Table 48 for a summary of study design and dosing. Treatment continued until unacceptable toxicity or disease progression.

A total of 522 patients were randomized; 263 to the Darzalex SC arm and 259 to the intravenous Darzalex arm. Randomization was stratified by body weight at baseline (≤65 kg, 66 to 85 kg, and >85 kg), number of prior lines of therapy (≤4 prior lines versus >4 prior lines), and type of myeloma (IgG versus non-IgG). The baseline demographic and disease characteristics were similar between the two treatment groups. The median patient age was 67 years (range: 33-92 years), 55% were male and 78% were Caucasian. The median patient weight was 73 kg

(range: 29 – 138 kg); 29% had an ECOG Performance score of 0, 54% had a score of 1, and 16% had a score of 2; patients had IgG/IgA/Light chain myeloma in 57%/17%/22% of instances; 34% of subjects had ISS Stage I, 36% had ISS stage II, and 30% had ISS stage III disease. Of 400 subjects who had baseline cytogenetic data reported, 22% had high-risk cytogenetic abnormalities, with 26% in the SC group and 17% in the IV group, which included del17p (14%), t(4;14) (9%), t(14;16) (3%). Patients had received a median of 4 prior lines of therapy. A total of 51% of patients had prior autologous stem cell transplant (ASCT). Prior therapies included bortezomib (99%), carfilzomib (22%), lenalidomide (86%), thalidomide (57%), and pomalidomide (32%). All subjects were previously treated with both PI(s) and IMiD(s) and most patients were refractory to a prior systemic therapy, including both PI and IMiD (49%).

Study Results:

The study was designed to demonstrate non-inferiority of treatment with Darzalex SC versus intravenous Darzalex based on co-primary endpoints of ORR by computer algorithm using the IMWG response criteria and maximum C_{trough} at pre-dose Cycle 3 Day 1 (see 10.3 Pharmacokinetics).

The ORR was 41.1% (95% CI: 35.1%, 47.3%) in the Darzalex SC arm and 37.1% (95% CI: 31.2%, 43.3%) in the intravenous Darzalex arm.

Efficacy results from Study MMY3012 are presented in Table 49 below.

Table 49: Efficacy results from Study MMY3012

	Darzalex SC (N=263)	**Darzalex (N=259)**
Primary Endpoint		
Overall response (sCR+CR+VGPR+PR), n (%)[a]	108 (41.1%)	96 (37.1%)
95% CI (%)	(35.1%, 47.3%)	(31.2%, 43.3%)
Ratio of response rates (95% CI)[b]		1.11 (0.89, 1.37)
CR or better, n (%)	5 (1.9%)	7 (2.7%)
Very good partial response (VGPR)	45 (17.1%)	37 (14.3%)
Partial response (PR)	58 (22.1%)	52 (20.1%)

[a] Based on intent-to-treat population.
[b] p-value <0.0001 from Farrington-Manning test for non-inferiority hypothesis that Darzalex SC retains at least 60% of ORR in Darzalex (intravenous formulation).

The PK evaluation portion of maximum C_{trough} (Cycle 3 Day 1 pre-dose) included 149/263 (56.7%) patients from the Darzalex SC arm and 146/259 (56.4%) patients from the Darzalex (intravenous formulation) arm. A total of 227 patients were excluded from the PK evaluation (N=114 Darzalex SC and N=113 Darzalex). The main reasons for exclusion were: patients did not receive full protocol specified doses in Cycle 1 and Cycle 2 (N=161), Cycle 1 and Cycle 2

doses were not all within dosing window (N=35), and Cycle 3 Day 1 predose sample was not within sampling window (N=20).

The PK results demonstrated that Darzalex SC yields non-inferior maximum C_{trough} levels at Cycle 3 Day 1 pre-dose as compared with Darzalex (intravenous formulation) as the lower bound of the two-sided 90% Confidence Interval (90% CI) of the geometric mean ratio (GMR) for C_{trough}(SC)/C_{trough}(IV) was above the pre-specified non-inferior boundary of 80% (GMR of 107.93%; 90% CI: 95.74-121.67).

The study met its co-primary objectives to show that Darzalex SC is non-inferior to intravenous Darzalex in terms of ORR (Table 49) and maximum trough concentration.

Median progression-free survival was 5.6 months in the Darzalex SC arm and 6.1 months in the intravenous Darzalex arm.

After a median follow-up of 29.3 months, the median overall survival (OS) was 28.2 months (95% CI: 22.8, NE) in the Darzalex SC arm and was 25.6 months (95% CI: 22.1, NE) in the intravenous Darzalex arm.

The clinical efficacy and safety of Darzalex for the treatment of patients with relapsed and refractory multiple myeloma was also demonstrated in two open-label studies using the intravenous formulation (Table 50).

Table 50: Summary of clinical trials in patients with relapsed and refractory multiple myeloma treated with Darzalex (intravenous formulation), 16 mg/kg

Study # Trial design	Dosage, route of administration and duration	Number of subjects
MMY2002 (SIRIUS Study) Phase 2, open-label, 2-part, single arm study in patients with multiple myeloma who have received at least three prior lines of therapy including a proteasome inhibitor (PI) and an immunomodulatory agent (IMiD), or who are double-refractory to a PI and an IMiD.	16 mg/kg (IV) on Days 1, 8, 15, and 22 of Cycles 1 and 2 (weekly dosing), on Days 1 and 15 of Cycles 3 to 6 (every two week dosing), and on Day 1 of Cycle 7 and subsequent cycles (every four week dosing).	106 subjects treated with 16 mg/kg
GEN501 Phase 1/2, open-label, 2-part, single arm study in patients with multiple myeloma whose disease was relapsed or refractory to at least 2 prior lines of therapies.	16 mg/kg (IV): first dose followed by three week resting period, then weekly for eight weeks, then every two weeks for sixteen weeks, then every four weeks.	42 subjects treated with 16 mg/kg

Study MMY2002: Darzalex monotherapy

Study MMY2002 was a Phase 2, open-label, 2-part, single arm study in patients with multiple myeloma who had received at least three prior lines of therapy including a PI and an IMiD, or who were refractory to both a PI and an IMiD. The selected dose from Part 1 was 16 mg/kg. Part 1 of the study was to establish an optimal dose schedule, and Part 2 was an expansion cohort. A total of 106 patients received 16 mg/kg Darzalex monotherapy weekly for 8 weeks, then every two weeks for 16 weeks, and every four weeks thereafter until disease progression or unacceptable toxicity. The primary efficacy endpoint was objective response rate (ORR) according to the International Myeloma Working Group (IMWG) criteria (2011) as assessed by an Independent Review Committee (IRC). Tumour assessment was performed every 28 days (± 3 days) until disease progression. Key secondary endpoints included duration of response.

The median patient age was 63.5 years (range: 31-84), 49% were male, and 79% were white. Twenty-seven percent of patients had a baseline ECOG score of 0 while 65% and 7.5% of patients had an ECOG baseline of 1 and 2, respectively. Based on the International Staging System (ISS), 24.5%, 37.7% and 37.7% of the patients had disease stage I, II and III, respectively.

Patients had received a median of 5 (range: 2-14) prior lines of therapy. Eighty percent of patients had received prior autologous stem cell transplantation (ASCT). Prior therapies included proteasome inhibitors (bortezomib [99%] and carfilzomib [50%]), and immunomodulatory drugs (lenalidomide [99%], and pomalidomide [63%]). At baseline, 97% of patients were refractory to the last line of treatment, 95% were refractory to both a PI and an IMiD, 77% were refractory to alkylating agents, 63% were refractory to pomalidomide and 48% of patients were refractory to carfilzomib. Patient cytogenetic profiles included t(4;14) (9.5%), del17p (16.8%), del13q (31.6%) and amp1q21 (24.2%).

Study Results:

Efficacy results based on the Independent Review Committee (IRC) assessment are presented in Table 51.

Table 51: IRC assessed efficacy results for Study MMY2002

Efficacy Endpoint	Darzalex 16 mg/kg N=106
Overall response rate[1] (ORR: sCR+CR+VGPR+PR) [n (%)] 95% CI (%)	31 (29.2) (20.8, 38.9)
Stringent complete response[2] (sCR) [n (%)]	3 (2.8)
Complete response (CR) [n (%)]	0
Very good partial response (VGPR) [n (%)]	10 (9.4)
Partial response (PR) [n (%)]	18 (17.0)
Median Duration of Response [months (95% CI)]	7.4 (5.5, NE)

[1] Primary efficacy endpoint (International Myeloma Working Group criteria)
[2] Defined as negative immunofixation on the serum and urine and disappearance of any soft tissue plasmacytomas and < 5% plasma cells in bone marrow plus normal FLC ratio and absence of clonal cells in bone marrow by immunohistochemistry or immunofluorescence (International Myeloma Working Group criteria). Clearance of plasma cells from bone marrow was demonstrated in 3 subjects with a stringent CR.

CI = confidence interval; NE = not estimable

The median time to response was 1 month (range: 0.9-5.6).

Study GEN501: Darzalex monotherapy

Study GEN501 was a Phase 1/2, open-label, 2-part, single arm study in patients with multiple myeloma whose disease was relapsed or refractory to at least 2 prior lines of therapy. Part 1 of the study was to establish the optimal dose schedule and Part 2 was an expansion cohort. In Study GEN501, 42 patients received 16 mg/kg Darzalex until disease progression. Patients received the first full infusion with a 3-week resting period, followed by weekly dosing for 7 weeks and then biweekly (every 2 weeks) infusions for 14 additional weeks. Patients then received monthly infusions for up to 72 weeks or until disease progression or unmanageable toxicity. Tumour assessment was performed on weeks 2, 4, 6 (±1 day), and 9 (±4 days), followed by assessment every 4 weeks (±4 days) until disease progression. The primary efficacy endpoint was ORR according to the IMWG criteria (2011) as assessed by an IRC. The key secondary endpoints included duration of response.

The median patient age was 64 years (range, 44 to 76 years), 64% were male and 76% were white. Patients in the study had received a median of 4 prior lines of therapy. Seventy-four percent of patients had received prior ASCT. Prior therapies included bortezomib (100%), lenalidomide (95%), pomalidomide (36%) and carfilzomib (19%). At baseline, 76% were refractory to the last line of treatment, 64% of patients were refractory to both a PI and IMiD, 60% were refractory to alkylating agents, 36% were refractory to pomalidomide and 17% were refractory to carfilzomib.

Study Results:

Treatment with daratumumab at 16 mg/kg led to a 36% ORR (95% CI: 21.6, 52.0) with 1 CR and 3 VGPR. The median time to response was 1 month (range: 0.5 to 3.2 months). The median duration of response was not reached (95% CI: 5.55 months, not estimable).

Darzalex SC (daratumumab injection) is indicated in combination with bortezomib, cyclophosphamide, and dexamethasone, for the treatment of adult patients with newly diagnosed light chain (AL) amyloidosis.

Table 52: Summary of clinical trials in patients with newly diagnosed AL amyloidosis who were administered Darzalex SC 1800 mg

Study # Trial design	Dosage, route of administration and duration	Number of subjects
Study AMY3001 (ANDROMEDA Study) Phase 3 randomized, open-label, active-controlled, multicenter study in subjects with newly diagnosed AL amyloidosis comparing the combination treatment of Darzalex SC plus bortezomib, cyclophosphamide and dexamethasone (D-VCd) to bortezomib, cyclophosphamide and dexamethasone alone (VCd).	**Darzalex SC** 1800 mg (SC): Cycles* 1-2: weekly; Cycles 3-6: every 2 weeks; Cycle ≥7: every 4 weeks; (Darzalex SC is given until disease progression or start of subsequent therapy, or for a maximum of 24 cycles) **Bortezomib**** 1.3 mg/m^2 BSA (SC): Cycles 1-6: weekly **Cyclophosphamide** 300 mg/m^2 BSA (PO or IV): Cycles 1-6: weekly (maximum cyclophosphamide weekly dose of 500 mg, irrespective of BSA) **Dexamethasone***** 40 mg (PO or IV): Weekly * Cycle = 4 weeks. ** For subjects whose bortezomib was discontinued because of a bortezomib-related toxicity (eg, peripheral neuropathy), doses of daratumumab, cyclophosphamide, and dexamethasone were continued unless criteria existed to hold these medications as well. *** D-VCd arm: subjects received 20 mg on the day of daratumumab dosing as premedication and 20 mg on the day after daratumumab dosing. VCd arm: on weeks that daratumumab was not administered, subjects were given 40 mg weekly on a single day or divided into 2 days. For subjects who were older than 70 years, underweight (BMI <18.5), had hypervolemia, poorly controlled diabetes mellitus, or prior intolerance/AE to steroid therapy, dexamethasone was administered at a dose of 20 mg weekly. For subjects receiving dexamethasone 20 mg weekly, on days of daratumumab treatment, it was recommended that dexamethasone 20 mg was administered as premedication.	N=388 D-VCd arm: 195 VCd arm: 193

Study AMY3001, an open-label, randomized, active-controlled Phase 3 study, compared treatment with Darzalex SC subcutaneous formulation (1800 mg) in combination with bortezomib, cyclophosphamide and dexamethasone (D-VCd) to treatment with bortezomib, cyclophosphamide and dexamethasone (VCd) alone in patients with newly diagnosed AL amyloidosis. Key inclusion criteria included 1) histopathological diagnosis of amyloidosis; 2) measurable disease of AL amyloidosis based on serum M-protein ≥0.5 g/dL by protein electrophoresis, or serum free light chain ≥50 mg/L with abnormal kappa:lambda ratio or the difference between involved and uninvolved free light chains (dFLC) ≥50 mg/L; 3) one or more organs impacted by AL amyloidosis according to consensus guidelines; patients must have an ECOG status of 0-2. Patients with NYHA classification IIIB or IV heart failure were excluded from the study. See Table 52 for a summary of study design.

A total of 388 patients were randomized: 195 to the D-VCd arm and 193 to the VCd arm. Randomization was stratified by AL amyloidosis Cardiac Staging System, countries that typically offer autologous stem cell transplant (ASCT) for patients with AL amyloidosis, and renal function. The baseline demographic and disease characteristics were similar between the two treatment groups. The majority (79%) of patients had lambda free light chain disease. The median patient age was 64 years (range: 34 to 87); 47% were ≥ 65 years; 58% were male; 76% Caucasian, 17% Asian, and 3% African American; 23% had AL amyloidosis Clinical Cardiac Stage I, 40% had Stage II, 35% had Stage IIIA, and 2% had Stage IIIB. The median number of organs involved was 2 (range: 1-6) and 66% of patients had 2 or more organs involved. Vital organ involvement was: 71% cardiac, 59% renal and 8% hepatic. The median treatment duration of was 9.6 months (range: 0.03 to 21.16 months) for the D-VCd arm and 5.3 months (range: 0.03; 7.33 months) for the VCd arm.

Study Results:

The primary endpoint was hematologic complete response (HemCR) rate, as determined by the Independent Review Committee assessment based on International Consensus Criteria. Key secondary endpoints included major organ deterioration progession-free survival (MOD-PFS).

Efficacy results are summarized in Table 53.

Table 53: Efficacy results from Study AMY3001[a]

	D-VCd (n=195)	**VCd (n=193)**	**P value**
Hematologic complete response (HemCR), n (%)	104 (53.3%)	35 (18.1%)	<0.0001[b]
Very good partial response (VGPR), n (%)	49 (25.1%)	60 (31.1%)	
Partial response (PR), n (%)	26 (13.3%)	53 (27.5%)	
Hematologic VGPR or better (HemCR + VGPR), n (%)	153 (78.5%)	95 (49.2%)	<0.0001[b]

Major organ deterioration progression-free survival (MOD-PFS), Hazard ratio with 95% CI[c]	0.58 (0.36, 0.93)[d]

D-VCd=daratumumab-bortezomib-cyclophosphamide-dexamethasone; VCd=bortezomib-cyclophosphamide-dexamethasone

[a] Based on intent-to-treat population

[b] p-value from Cochran Mantel-Haenszel Chi-Squared test.

[c] MOD-PFS defined as hematologic progression, major organ (cardiac or renal) deterioration or death

[d] Based on interim analysis; boundary not crossed (nominal p-value 0.0211).

Note: A hierarchical testing procedure was used to control the overall Type I error rate for the primary and secondary endpoints. The corresponding alpha levels for HemCR and MOD-PFS were 0.0499 and 0.00136, respectively.

The median time to HemCR was 60 days (range: 8 to 299 days) in the D-VCd group and 85 days (range: 14 to 340 days) in the VCd group. The median time to VGPR or better was 17 days (range: 5 to 336 days) in the D-VCd group and 25 days (range: 8 to 171 days) in the VCd group. The median duration of HemCR had not been reached in either arm. The median follow-up for the study is 11.4 months.

14.4 Immunogenicity

In clinical studies of patients with multiple myeloma or AL amyloidosis receiving Darzalex SC as monotherapy or in combination regimens, 7/1200 patients developed treatment-emergent anti-daratumumab antibodies, of which 6 patients tested positive for neutralizing antibodies. Given the low incidence of immunogenicity, meaningful conclusions cannot be made on the impact of anti-daratumumab antibodies and neutralizing antibodies on daratumumab exposures.

In clinical studies of patients with multiple myeloma or AL amyloidosis receiving Darzalex SC as monotherapy or in combination regimens, 106/1193 patients developed treatment-emergent non-neutralizing anti-rHuPH20 antibodies, of which 1 patient tested positive for neutralizing antibodies. The clinical relevance of the development of anti-daratumumab or anti-rHuPH20 antibodies after treatment with Darzalex SC is not known.

Patients in Darzalex intravenous formulation monotherapy Study MMY2002 (n=111) and combination therapy studies (n=691) were evaluated for anti-therapeutic antibody (ATA) responses to daratumumab at multiple time points during treatment and up to 8 weeks following the end of treatment using an electrochemiluminescent (ECL) assay. Following the start of daratumumab dosing, of the 802 evaluable patients, none of the monotherapy patients and 2 (0.25%) of the combination therapy patients tested positive for anti-daratumumab antibodies; 1 of the combination therapy patients developed transient neutralizing antibodies against daratumumab. However, the immunogenicity assay used in the study has limitations in detecting anti-daratumumab antibodies in the presence of high concentrations of daratumumab; therefore, the incidence of antibody development might not have been reliably determined.

Immunogenicity data are highly dependent on the sensitivity and specificity of the test methods used. Additionally, the observed incidence of a positive result in a test method may be influenced by several factors, including assay methodology, sample handling, timing of sample collection, drug interference, concomitant medication and the underlying disease. Therefore, comparison of the incidence of antibodies to daratumumab with the incidence of antibodies to other products may be misleading.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

SUBCUTANEOUS FORMULATION (Darzalex SC)

No carcinogenicity, genotoxicity, or fertility studies were conducted for recombinant human hyaluronidase, an excipient of Darzalex SC. There were no effects on reproductive tissues and function and no systemic exposure of hyaluronidase in monkeys given 22,000 U/kg/week subcutaneously (12 times higher than the human dose) for 39 weeks and there were no effects on embryo-fetal development in pregnant mice given 330,000 U/kg hyaluronidase subcutaneously daily during organogenesis, which is 45 times higher than the human dose. There were no effects on pre- and post-natal development through sexual maturity in offspring of mice treated daily from implantation through lactation with 990,000 U/kg hyaluronidase subcutaneously, which is 134 times higher than the human doses. As hyaluronidase is a recombinant form of the endogenous human hyaluronidase, no carcinogenicity, mutagenesis, or effects on fertility are expected.

INTRAVENOUS FORMULATION (Darzalex)

Nonclinical toxicity was assessed in a 6-week repeat dose study in chimpanzees and a 2-week repeat dose study with a surrogate anti-CD38 antibody in cynomolgus monkeys.

Daratumumab targeted primarily hematopoietic and lymphatic systems with decreased red blood cells, hemoglobin, white blood cells, platelets and lymphoid depletion. Infusion reactions and cytokine release syndrome, with one fatal event, were reported in chimpanzees that did not receive pre-infusion medication. Mild spinal cord inflammation was observed in one monkey treated with 100 mg/kg of a surrogate antibody targeting monkey CD-38.

No carcinogenicity or genotoxicity studies have been conducted with daratumumab. No animal studies have been performed to evaluate the potential effects of daratumumab on reproduction or development, or to determine the potential effects on fertility in males or females.

A summary of toxicology studies is provided in Table 54.

Table 54: Summary of Toxicology Studies

Study Type, Test Article	Treatment Duration, Dose Schedule	Species, Number	Doses	Findings/Conclusions
General Toxicity				
Repeat-Dose Toxicity (GLP) Daratumumab	6 weeks, once weekly IV infusion, ~ 3 month recovery	Chimpanzee 1/sex/group	0 (vehicle predose), 5 or 25 mg/kg	Infusion-related reactions (IRRs), including the death of one 5 mg/kg female; IRRs in the 25 mg/kg were milder due to a predose of 10 mg of daratumumab on the day prior to the first infusion. Thrombocytopenia and decreased lymphocyte cell populations (recovered as daratumumab was cleared from the circulation)
Repeat-Dose Toxicity (non-GLP) HuMab CD38[d]	2 weeks, once weekly IV infusion, 2 month recovery	Cynomolgus monkey 2/sex/group	0, 20, or 100 mg/kg	Anemia, decreased lymphocyte cell populations in peripheral blood and lymph nodes, lymphoid atrophy or cell depletion of thymus, lymph nodes, and spleen. Mild multifocal inflammation in the spinal cord in one monkey in 100 mg/kg group
Other Studies				
Tissue Cross-Reactivity (GLP) Daratumumab		Human	0, 0.5, 1, or 2μg/mL	Specific daratumumab-FITC staining occurred in the lymphoid cells in the spleen, tonsil, lymph nodes, and thymus.
Tissue Cross-Reactivity (GLP) Daratumumab		Chimpanzee	0, 0.25, or 1.25μg/mL	Specific daratumumab-FITC staining occurred in the lymphoid cells and macrophages, and in hematopoietic cells in the spleen, tonsil, lymph nodes, and lamina propria of the intestinal tract.

Study Type, Test Article	Treatment Duration, Dose Schedule	Species, Number	Doses	Findings/Conclusions
Tissue Cross-Reactivity (GLP) HuMab CD38		Cynomolgus Monkey	0, 0.2, 0.5, or 1µg/mL	Specific HuMab-CD38-FITC staining was observed in the cytoplasm of blood vessels, bone marrow lymphocytes, cerebellum white matter, cerebrum white matter, cervix, colon lamina propria, fallopian tube interstitium, ileum lamina propria, lung alveolar cells, lymph node T-cells, peripheral nerve myelin, retina/choroidea glassy membrane, spinal cord white matter, spleen T-cell zone, stomach, striated muscle fibers, thymus T-cells in medulla and cortex, and tonsil T-cell zone.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PrDARZALEX® SC

daratumumab injection

1800 mg/15 mL (120 mg/mL) Solution for Subcutaneous Injection

Read this carefully before you start taking Darzalex SC (Dar'-zah-lex) and each time you get an injection. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about Darzalex SC.

Your cancer may be treated with Darzalex in combination with other medicines. Read the leaflets for the other drugs as well as this one. This will help you understand the information related to those medicines.

What is Darzalex SC used for?

Darzalex SC is used in adults 18 years or older to treat:

- A type of cancer called multiple myeloma. This is a cancer of your plasma cells which are found in your bone marrow.
- Patients newly diagnosed with a blood disorder called light chain (AL) amyloidosis. In AL amyloidosis, abnormal blood cells make excessive amounts of abnormal protein that deposit in various organs, causing these organs to not function properly.

How does Darzalex SC work?

Darzalex SC contains the active substance daratumumab. Daratumumab belongs to a group of medicines called monoclonal antibodies. Daratumumab attaches to myeloma cells and works in multiple ways to kill the cancer cells. You may be prescribed Darzalex SC with other multiple myeloma medicines, or you may have used other multiple myeloma drugs previously. Darzalex SC works differently compared to these other medicines. In AL amyloidosis, daratumumab attaches to specific abnormal blood cells in our body so your immune system can destroy them.

What are the ingredients in Darzalex SC?

Medicinal ingredients: daratumumab.

Non-medicinal ingredients: L-histidine, L-histidine hydrochloride monohydrate, L-methionine,

polysorbate 20, recombinant human hyaluronidase (rHuPH20), sorbitol, water for injection.

Darzalex SC comes in the following dosage form:

Darzalex SC is provided as a solution that is administered by subcutaneous (under the skin) injection. It comes in 15 mL vials. Each vial of solution contains 1800 mg of daratumumab (120 mg/mL).

Do not use Darzalex SC if:

- You are allergic to daratumumab or any of the other ingredients in Darzalex SC.

If you are not sure, talk to your doctor or nurse before you are given Darzalex SC.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take Darzalex SC. Talk about any health conditions or problems you may have, including if:

- You are pregnant, think you might be pregnant or are planning to have a baby. If you become pregnant while being treated with Darzalex SC, tell your doctor or nurse immediately. You and your doctor will decide if the benefit of receiving Darzalex SC is greater than the risk to your baby. Women who are being treated with Darzalex SC must use effective contraception during treatment and for at least 3 months after treatment. Darzalex SC may harm your unborn baby.
- You are producing breast milk. You and your doctor will decide if the benefit of breast-feeding is greater than the risk to your baby. This is because the medicine may pass into the mother's milk and it is not known if it will affect the baby.
- You have breathing problems, such as asthma or Chronic Obstructive Pulmonary Disease (COPD). You will be given medicines to inhale which will help if you have breathing problems after the injection:
  - medicines to help the airways in your lungs stay open (bronchodilators)
  - medicines to lower swelling and irritation in your lungs (corticosteroids)
- You had shingles (herpes zoster).
- You had or might now have a hepatitis B virus infection
- You have a history of heart problems. Darzalex SC should not be used in light chain (AL) amyloidosis patients with highly advanced heart disease outside of clinical trials.

If you need a blood transfusion, you will have a blood test first to match your blood type. Darzalex SC can affect the evaluation of the results of this blood test. Tell the person doing the test that you are taking Darzalex SC.

Other warnings you should know about:

Administration-related reactions (systemic reactions related to administration):

Before and after each injection of Darzalex SC, you will be given medicines that help to lower the chance of administration-related reactions. These reactions can happen when you are given the medication or in the 3 days after the injection. These reactions are most likely to happen at the first injection.

Tell your doctor or nurse immediately if you get any of the symptoms of an administration-related reaction. These symptoms include:

- chills
- sore throat/throat tightness
- fever
- cough
- feeling sick
- itchy, runny or blocked nose
- feeling short of breath or other breathing problems including wheezing
- increased blood pressure
- dizziness or light-headedness
- headache
- rash or hives
- nausea
- vomiting
- itchiness

Although rare, you may have a severe allergic reaction. Tell your doctor or nurse immediately if you get any of the symptoms of a severe allergic reaction, which include:

- swollen face, lips, mouth, tongue or throat
- difficulty swallowing or breathing
- an itchy rash (hives)
- eye pain
- blurred vision

Your doctor may decide not to use Darzalex SC if you have a severe administration-related reaction.

Injection site reactions:
Skin reactions at or near the injection site (local), including injection site reactions, can happen with Darzalex SC. Symptoms may include itching, swelling pain, bruising, bleeding, or redness of the skin.

Infections:
Darzalex SC may increase the occurrence of infections. These infections could be severe, life-

threatening or potentially fatal. Tell your healthcare provider if you develop fever, feel very tired, have a cough or have flu-like symptoms.

Hepatitis B Virus:
Tell your doctor if you have ever had or might now have a hepatitis B virus infection. This is because Darzalex SC could cause hepatitis B virus to become active again. Your doctor will check you for signs of this infection before, during and for some time after treatment with Darzalex SC. Tell your doctor right away if you get worsening tiredness or yellowing of your skin or white part of your eyes.

Heart problems in patients with light chain (AL) amyloidosis:
Heart problems, in some cases fatal, have occurred. Your healthcare provider will monitor you closely during treatment with Darzalex SC. Call your healthcare provider right away if any of the following symptoms occur: chest pain, feeling faint, swollen legs, shortness of breath, or abnormal heart rhythm.

Changes in blood tests:
Darzalex SC can affect the results of blood tests to match your blood type. This interference can last for up to 6 months after your final dose of Darzalex SC. Your healthcare provider should do blood tests to match your blood type before you start treatment with Darzalex SC. Tell all of your healthcare providers that you are being treated with Darzalex SC before receiving blood transfusions.

Decreased blood cell counts:
Darzalex SC can decrease white blood cell counts which help fight infections, and blood cells called platelets which help to clot blood. Tell your healthcare provider if you develop fever or if you have signs of bruising or bleeding.

Pregnancy:
Lenalidomide and pomalidomide are expected to be harmful for an unborn baby. When Darzalex SC is given in combination with either of these medications, you must also read the patient medication information for lenalidomide or pomalidomide. When lenalidomide or pomalidomide is used, you must follow the pregnancy prevention programme for these medications. Bortezomib and carfilzomib may cause harm for an unborn baby. When Darzalex SC is given in combination with bortezomib or carfilzomib, you must also read the patient medication information for these medications. Cyclophosphamide may cause harm for an unborn baby. When Darzalex SC is given in combination with cyclophosphamide, you must also read the patient medication information for cyclophosphamide.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

Interactions with other drugs, vitamins, minerals, natural supplements or alternative medicines have not been established with Darzalex SC.

How to take Darzalex SC:

- Darzalex SC will be given to you by a doctor or nurse.
- It is given as an injection under your skin ("subcutaneous injection") over approximately 3 to 5 minutes.
- It is given in the stomach area (abdomen).

Usual dose:

The usual dose of Darzalex SC is 1800 mg of daratumumab (1800 mg/15 mL). Darzalex SC may be given alone or together with other medicines used to treat multiple myeloma (i.e. bortezomib, lenalidomide, pomalidomide, carfilzomib, dexamethasone, melphalan, or prednisone).

For AL amyloidosis, Darzalex SC is given with bortezomib, cyclophosphamide and dexamethasone.

When given alone or with some medicines, Darzalex SC is given as follows:

- once a week for the first 6, 8 or 9 weeks
- then once every 2 or 3 weeks for 15, 16 or up to 48 weeks
- then once every 4 weeks after that as long as your condition does not worsen

Depending on which other medicines Darzalex SC is given together with, your doctor may change the time between doses as well as how many treatments you will receive.

Other medicines given during treatment with Darzalex SC:

Before each injection of Darzalex SC you will be given other medicines that help to lower the chance of systemic administration-related reactions. These may include:

- medicines for an allergic reaction (anti-histamines)
- medicines for inflammation (corticosteroids)
- medicines for fever (such as acetaminophen)

After each injection of Darzalex SC you will be given other medicines (such as corticosteroids) to lower the chance of a reaction after your injection.

People with breathing problems:

If you have breathing problems, such as asthma or Chronic Obstructive Pulmonary Disease

(COPD), you will be given medicines to inhale which help your breathing problems:

- medicines to help the airways in your lungs stay open (bronchodilators)
- medicines to lower swelling and irritation in your lungs (corticosteroids)

You may be given medicines to lower the chance of getting shingles.

Overdose:

This medicine will be given by your doctor or nurse. In the unlikely event that you are given too much (an overdose) your doctor will check you for side effects.

If you think you, or a person you are caring for, have taken too much Darzalex SC, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

It is very important to go to all your appointments. If you miss an appointment, tell your doctor and make another one as soon as possible.

What are possible side effects from using Darzalex SC?

Darzalex SC is generally well-tolerated, however, like all medicines, this medicine can cause side effects.

These are not all the possible side effects you may have when taking Darzalex SC. If you experience any side effects not listed here, tell your healthcare professional.

Side effects of Darzalex SC (taken alone or in combination with other drugs) that may affect more than 1 in 5 people (≥20%) include:

- feeling tired
- nausea
- diarrhea
- constipation
- back pain
- cough
- low number of white blood cells (neutropenia)
- low number of a type of blood cell called platelets (thrombocytopenia)
- fever
- swelling

- infections of the airways – such as nose, sinuses or throat
- peripheral sensory neuropathy (numbness or tingling in feet or hands)
- COVID-19

Other side effects affecting more than 1 in 20 people (≥5%) include:

- chills
- muscle spasms
- headache
- dizziness
- fainting
- loss of appetite
- feeling very weak
- difficulty falling asleep
- vomiting
- stomachache
- pain in the chest, arms, legs, muscles, joints, or bones
- pain in the mouth or throat
- rash or itchy skin
- lung infection (such as pneumonia)
- flu or flu-like illness, stuffy nose
- prickling or burning sensation on the skin (paresthesia)
- trembling or shaking hands (tremor)
- altered taste
- urinary tract infection
- low number of white blood cells (lymphopenia, leukopenia)
- decrease in levels of calcium in your blood
- decrease in levels of potassium in your blood
- increase in blood sugar
- increased (hypertension) or decreased (hypotension) blood pressure
- anxiety or depression
- kidney impairment
- shortness of breath (including due to build-up of fluid in the lungs)
- weight decrease
- blurry vision

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
VERY COMMON (more than 1 in 10)			
Low number of blood cells such as: • platelets (thrombocytopenia) • white blood cells (neutropenia) • red blood cells (anemia) (symptoms like fatigue, loss of energy, weakness, shortness of breath)		✓	
Upper respiratory tract infections (infected nose, sinuses or throat; cold)		✓	
COMMON (less than 1 in 10 but more than 1 in 100)			
Administration-related reactions. Symptoms can include: • chills • sore throat, cough • feeling sick • itchy, runny or blocked nose • feeling short of breath or other breathing problems • increased blood pressure			✓
Lung infections such as: • pneumonia • flu • bronchitis • lower respiratory tract infections (symptoms of lung infections may include congestion, cough, sore throat, body ache, tiredness and fever)		✓	
Infections such as: • sepsis or septic shock (symptoms like high fever, increased heart rate or breathing, and confusion)		✓	

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
• urinary tract infection (symptoms like pain or burning when urinating, bloody or cloudy or foul-smelling urine)			
High fever		✓	
Irregular or rapid heartbeat (atrial fibrillation)		✓	
Bleeding problems (symptoms like blood in your stools, coughing up blood)		✓	
Severe diarrhea (symptoms like increased number of bowel movements, watery or bloody stool, stomach pain and/or cramps)		✓	
Inflamed pancreas (pancreatitis; symptoms may include abdominal pain, fever, nausea, vomiting)		✓	
UNCOMMON (less than 1 in 100 but more than 1 in 1,000)			
A type of herpes virus infection called cytomegalovirus infection, which can cause fever, sore throat, fatigue or swollen glands. This virus can cause infections in other parts of the body, such as the lung (cough or breathing trouble), eyes (change in vision or eye pain), and intestines (diarrhea or stomach pain).		✓	
RARE (less than 1 in 1,000 but more than 1 in 10,000)			
Severe allergic reaction (symptoms like swollen face, lips, mouth, tongue or throat, difficulty swallowing or breathing, an itchy rash (hives), eye pain, blurred vision)			✓

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Darzalex SC will be stored in a refrigerator at 2-8˚C.

If you want more information about Darzalex SC:

- Talk to your healthcare professional
- For questions or concerns, please contact the manufacturer, Janssen Inc., at www.janssen.com/canada
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website (http://www.janssen.com/canada), or by calling 1-800-567-3331 or 1-800-387-8781.

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