PRODUCT NAME

DARZALEX® SC (daratumumab) solution for injection.

For subcutaneous use.

DOSAGE FORMS AND STRENGTHS

Daratumumab is an immunoglobulin G1 kappa (IgG1κ) human monoclonal antibody against CD38 antigen, produced in a mammalian cell line (Chinese Hamster Ovary [CHO]) using recombinant DNA technology.

Recombinant human hyaluronidase is an endoglycosidase used to increase the dispersion and absorption of co-administered drugs when administered subcutaneously. It is produced by mammalian (Chinese Hamster Ovary) cells containing a DNA plasmid encoding for a soluble fragment of human hyaluronidase (PH20). It is a glycosylated single-chain protein with an approximate molecular weight of 61 kD.

DARZALEX® SC is available as a colorless to yellow, clear to opalescent, preservative-free solution for subcutaneous administration.

15 mL vial: Each single-dose vial contains 1800 mg daratumumab (120 mg/mL).

For excipients, see *List of Excipients*.

CLINICAL INFORMATION

Indications

DARZALEX® SC is indicated for the treatment of patients with multiple myeloma:

- in combination with bortezomib, melphalan and prednisone, or in combination with lenalidomide and dexamethasone in newly diagnosed patients who are ineligible for autologous stem cell transplant.
- in combination with bortezomib, thalidomide, and dexamethasone in newly diagnosed patients who are eligible for autologous stem cell transplant.
- in combination with lenalidomide and dexamethasone, or in combination with bortezomib and dexamethasone in patients who have received at least one prior therapy.
- in combination with pomalidomide and dexamethasone in patients who have received one prior therapy including lenalidomide and a proteasome inhibitor (PI) and were lenalidomide-refractory, or who have received at least two prior therapies that included lenalidomide and a PI and have demonstrated disease progression on or after the last therapy.
- in combination with carfilzomib and dexamethasone in patients with relapsed or refractory multiple myeloma who have received one to three prior lines of therapy.
- as monotherapy, in patients who have received at least three prior lines of therapy including a PI and an immunomodulatory agent (IMiD) or who are double-refractory to a PI and an IMiD.

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

Dosage and Administration

DARZALEX® SC is for subcutaneous use only. DARZALEX® SC has different dosage and administration instructions than intravenous daratumumab. Do not administer intravenously.

For patients currently receiving daratumumab intravenous formulation, DARZALEX® SC may be used as an alternative to the intravenous daratumumab formulation starting at the next scheduled dose.

DARZALEX® SC should be administered by a healthcare professional, and the first dose should be administered in an environment where resuscitation facilities are available.

Pre- and post-injection medications should be administered (see *Recommended concomitant medications* below).

Dosage – Adults (≥18 years)

Recommended dose for multiple myeloma

The DARZALEX® SC dosing schedule in Table 1 is for combination therapy with 4-week cycle regimens (e.g. lenalidomide, pomalidomide, carfilzomib) and for monotherapy as follows:

- combination therapy with lenalidomide and low-dose dexamethasone for patients with newly diagnosed multiple myeloma ineligible for autologous stem cell transplant (ASCT)
- combination therapy with lenalidomide or pomalidomide and low-dose dexamethasone for patients with relapsed/refractory multiple myeloma
- combination therapy with carfilzomib and low-dose dexamethasone for patients with relapsed/refractory multiple myeloma
- monotherapy for patients with relapsed/refractory multiple myeloma

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

Table 1: DARZALEX® SC dosing schedule for monotherapy and in combination with 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 of medicinal products administered with DARZALEX® SC, see *Clinical Studies* and manufacturer's prescribing information.

The DARZALEX® SC dosing schedule in Table 2 is for combination therapy with bortezomib, melphalan and prednisone (6-week cycle regimen) for patients with newly diagnosed multiple myeloma ineligible for ASCT.

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

Table 2: 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. For information on the VMP dose and dosing schedule when administered with DARZALEX® SC, see *Clinical Studies.*

The DARZALEX® SC dosing schedule in Table 3 is for combination therapy with bortezomib, thalidomide and dexamethasone (4-week cycle regimens) for treatment of newly diagnosed multiple myeloma patients eligible for ASCT.

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

Table 3: DARZALEX® SC dosing schedule in combination with bortezomib, thalidomide and dexamethasone ([VTd]; 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 1 to 8[b]	every two weeks (total of 4 doses)

[a] First dose of the every-2-week dosing schedule is given at Week 9
[b] First dose of the every-2-week dosing schedule is given at Week 1 upon re-initiation of treatment following ASCT

For dosing instructions of medicinal products administered with DARZALEX® SC, see *Clinical Studies* and manufacturer's prescribing information.

The DARZALEX® SC dosing schedule in Table 4 is for combination therapy with 3-week cycle regimens (e.g. bortezomib) for patients with relapsed/refractory multiple myeloma.

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

Table 4: Dosing schedule for DARZALEX® SC with 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 with DARZALEX® SC see *Clinical Studies* and manufacturer's prescribing information.

Recommended dose for AL amyloidosis

The DARZALEX® SC dosing schedule in Table 5 is for combination therapy with bortezomib, cyclophosphamide and dexamethasone (4-week cycle regimen) for patients with AL amyloidosis.

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

Table 5: DARZALEX® SC dosing schedule for AL amyloidosis in combination with bortezomib, cyclophosphamide and dexamethasone ([VCd]; 4-week cycle dosing regimen)[a]

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

[a] In the clinical trial, DARZALEX® SC was given until disease progression or a maximum of 24 cycles (~2 years) from the first dose of study treatment.
[b] First dose of the every-2-week dosing schedule is given at Week 9
c First dose of the every-4-week dosing schedule is given at Week 25

For dosing instructions of medicinal products administered with DARZALEX® SC, see *Clinical Studies* and manufacturer's prescribing information.

Missed dose (s)

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.

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 *Warnings and Precautions*). For information concerning medicinal products given in combination with DARZALEX® SC, see manufacturer's prescribing information.

DARZALEX® SC and management of infusion-related reactions:

In clinical trials, no modification to rate or dose of DARZALEX® SC was required to manage infusion-related reactions.

Recommended concomitant medications

Pre-injection medication

Pre-injection medications (oral or intravenous) should be administered to reduce the risk of infusion-related reactions (IRRs) to all patients 1-3 hours prior to every administration of DARZALEX® subcutaneous injection as follows:

- Corticosteroid (long-acting or intermediate-acting)

  Monotherapy:

  Methylprednisolone 100 mg, or equivalent. Following the second injection, the dose of corticosteroid may be reduced to methylprednisolone 60 mg.

  Combination therapy:

  Administer 20 mg dexamethasone (or equivalent) prior to every DARZALEX® SC injection. When dexamethasone is the background-regimen specific corticosteroid, the dexamethasone treatment dose will instead serve as pre-medication on DARZALEX® SC administration days (see *Clinical Studies*).

  Additional background-regimen specific corticosteroids (e.g. prednisone) should not be taken on DARZALEX® SC administration days when patients have received dexamethasone (or equivalent) as a pre-medication.

- Antipyretics (paracetamol/acetaminophen 650 to 1000 mg)

- Antihistamine (diphenhydramine 25 to 50 mg or equivalent)

Post-injection medication

Administer post-injection medication to reduce the risk of delayed IRRs as follows:

Monotherapy:

Administer oral corticosteroid (20 mg methylprednisolone or equivalent dose of an intermediate-acting or long-acting corticosteroid in accordance with local standards) on each of the 2 days following all DARZALEX® SC injections (beginning the day after the injection).

Combination therapy:

Consider administering low-dose oral methylprednisolone (≤ 20 mg) or equivalent the day after the DARZALEX® SC injection.

However, if a background regimen-specific corticosteroid (e.g. dexamethasone, prednisone) is administered the day after the DARZALEX® SC injection, additional post-injection medications may not be needed (see *Clinical Studies*).

If the patient experiences no major IRRs 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 short and long acting bronchodilators, and inhaled corticosteroids. Following the first four injections, if the patient experiences no major IRRs, these inhaled post-injection medications may be discontinued at the discretion of the physician.

Prophylaxis for herpes zoster virus reactivation

Anti-viral prophylaxis should be considered for the prevention of herpes zoster virus reactivation. If required, anti-viral prophylaxis is recommended to be initiated within 1 week of starting DARZALEX® SC.

Special populations

Pediatrics (17 years of age and younger)

The safety and efficacy of DARZALEX® SC have not been established in pediatric patients.

Elderly (65 years of age and older)

No dose adjustments are considered necessary in elderly patients (see *Pharmacokinetic Properties, Adverse Reactions*).

Renal impairment

No formal studies of daratumumab in patients with renal impairment have been conducted. Based on population pharmacokinetic (PK) analyses, no dosage adjustment is necessary for patients with renal impairment (see *Pharmacokinetic Properties*).

Hepatic impairment

No formal studies of daratumumab in patients with hepatic impairment have been conducted. Changes in hepatic function are unlikely to have any effect on the elimination of daratumumab since IgG1 molecules such as daratumumab are not metabolized through hepatic pathways. No dosage adjustments are necessary for patients with hepatic impairment (see *Pharmacokinetic Properties*).

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.

Administration

DARZALEX® SC should be administered by a healthcare professional.

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

DARZALEX® SC is for single use only and is ready to use.

- 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 discoloration prior to administration, whenever solution and container permit. Do not use if opaque particles, discoloration or other foreign particles are present.

- Remove the DARZALEX® SC vial from refrigerated storage [2°C–8°C (36°F–46°F)] and equilibrate to ambient temperature [15°C–30°C (59°F–86°F)]. 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 controlled and validated aseptic conditions.

- To avoid needle clogging, attach the hypodermic injection needle or subcutaneous infusion set to the syringe immediately prior to injection.

<u>Storage of prepared syringe</u>

- 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 7 hours at 15°C–30°C (59°F–86°F) and ambient light. Discard if stored more than 24 hours of being refrigerated or more than 7 hours of being at 15°C–30°C (59°F–86°F), if not used. If stored in the refrigerator, allow the solution to come to ambient temperature before administration.

<u>Administration</u>

- Inject 15 mL DARZALEX® SC into the subcutaneous tissue of the abdomen approximately 3 inches [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.
- Injection sites should be rotated 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.
- Any waste material should be disposed in accordance with local requirements.

Contraindications

Patients with a history of severe hypersensitivity to daratumumab or any of the excipients.

Warnings and Precautions

Infusion-related reactions

DARZALEX® SC can cause severe and/or serious infusion-related reactions (IRRs), including anaphylactic reactions. In clinical trials, approximately 9% (77/898) of patients experienced an infusion-related reaction. Most IRRs occurred following the first injection and were Grade 1-2 (see *Adverse Reactions*). IRRs occurring with subsequent injections were seen in 1% of patients.

The median time to onset of IRRs following DARZALEX® SC was 3.2 hours (range 0.07-83 hours). The majority of IRRs occurred on the day of treatment. Delayed IRRs have 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, 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 *Adverse Reactions*).

Pre-medicate patients with antihistamines, antipyretics and corticosteroids. Patients should be monitored and counselled regarding IRRs, 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 IRRs, administer oral corticosteroids to all patients following DARZALEX® SC injections. Patients with a history of chronic obstructive pulmonary disease may require additional post-injection medications to manage respiratory complications. Consider prescribing short- and long-acting bronchodilators and inhaled corticosteroids for patients with chronic obstructive pulmonary disease. If ocular symptoms occur, interrupt DARZALEX® SC infusion and seek immediate ophthalmologic evaluation prior to restarting DARZALEX® SC (see *Dosage and Administration*).

Neutropenia/Thrombocytopenia

Daratumumab may increase neutropenia and thrombocytopenia induced by background therapy (see *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.

In lower body weight patients receiving DARZALEX® SC, higher rates of neutropenia were observed; however, this was not associated with higher rates of serious infections. No dose reduction of DARZALEX® SC is recommended. Consider supportive care with transfusions or growth factors.

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 administration. It should be recognized that daratumumab bound to RBCs may mask detection of antibodies to minor antigens in the patient's serum. The determination of a patient's ABO and Rh blood type are not impacted.

Type and screen patients prior to starting DARZALEX® SC.

In the event of a planned transfusion, notify blood transfusion centers of this interference with indirect antiglobulin tests (see *Interactions*). If an emergency transfusion is required, non-cross-matched ABO/RhD-compatible RBCs can be given per local blood bank practices.

Hepatitis B Virus (HBV) 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.

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 (see *Interactions*). This interference can impact the determination of complete response and of disease progression in some patients with IgG kappa myeloma protein.

Interactions

Drug-Drug Interactions

No formal drug-drug interaction studies have been performed.

As an IgG1κ monoclonal antibody, renal excretion and hepatic enzyme-mediated metabolism of intact daratumumab are unlikely to represent major elimination routes. As such, variations in drug-metabolizing enzymes are not expected to affect the elimination of daratumumab. Due to the high affinity to a unique epitope on CD38, daratumumab is not anticipated to alter drug-metabolizing enzymes.

Clinical pharmacokinetic assessments with daratumumab IV or SC formulations and lenalidomide, pomalidomide, thalidomide, bortezomib, melphalan, prednisolone, carfilzomib, cyclophosphamide and dexamethasone indicated no clinically-relevant drug-drug interaction between daratumumab and these small molecule medicinal products.

Effects of DARZALEX® SC on laboratory tests

Interference with indirect antiglobulin test (indirect 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, Kell-negative units should be supplied after ruling out or identifying alloantibodies using DTT-treated RBCs.

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 (CRs) by International Myeloma Working Group (IMWG) criteria. In patients with persistent very good partial response (VGPR), where daratumumab interference is suspected, consider using a validated daratumumab-specific IFE assay to distinguish daratumumab from any remaining endogenous M protein in the patient's serum, to facilitate determination of a CR (see *Clinical Studies*).

Pregnancy, Breast-feeding and Fertility

Pregnancy

There are no human or animal data to assess the risk of DARZALEX® SC use during pregnancy. IgG1 monoclonal antibodies are known to cross the placenta after the first trimester of pregnancy. Therefore DARZALEX® SC should not be used during pregnancy unless the benefit of treatment to the woman is considered to outweigh the potential risks to the fetus. If the patient becomes pregnant while taking this drug, the patient should be informed of the potential risk to the fetus.

To avoid exposure to the fetus, women of reproductive potential should use effective contraception during and for 3 months after cessation of DARZALEX® SC treatment.

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.

Maternal IgG is excreted in human milk, but does not enter the neonatal and infant circulations in substantial amounts as they are degraded in the gastrointestinal tract and not absorbed. Because the risks of DARZALEX® SC to the infant from oral ingestion 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 therapy for the woman.

Fertility

No data are available to determine potential effects of daratumumab on fertility in males or females.

Effects on Ability to Drive and Use Machines

DARZALEX® SC has no or negligible influence on the ability to drive and use machines. However, fatigue has been reported in patients taking daratumumab and this should be taken into account when driving or using machines.

Adverse Reactions

Throughout this section, adverse reactions are presented. Adverse reactions are adverse events that were considered to be reasonably associated with the use of daratumumab based on the comprehensive assessment of the available adverse event information. A causal relationship with daratumumab cannot be reliably established in individual cases. Further, because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Experience with DARZALEX® SC (subcutaneous daratumumab)

The safety data of DARZALEX® subcutaneous (SC) formulation (1800 mg) was established in 705 patients with multiple myeloma (MM) including 260 patients from a Phase 3 active-controlled trial (Study MMY3012) who received DARZALEX® SC formulation as monotherapy, 149 patients from a Phase 3 active-controlled trial (Study MMY3013) who received DARZALEX® SC formulation in combination with pomalidomide and dexamethasone (D-Pd), and three open-label, clinical trials in which patients received DARZALEX® SC formulation either as monotherapy (N=31; MMY1004 and MMY1008) and MMY2040 in which patients received DARZALEX® SC formulation in combination with either bortezomib, melphalan and prednisone (D-VMP, n=67), lenalidomide and dexamethasone (D-Rd, n=65), bortezomib, lenalidomide and dexamethasone (D-VRd, n=67) or carfilzomib and dexamethasone (D-Kd, n=66).

The safety data of DARZALEX® SC formulation (1800 mg) was established in patients with newly diagnosed AL amyloidosis from a Phase 3 active-controlled trial (Study AMY3001) in which patients received DARZALEX® SC formulation in combination with bortezomib, cyclophosphamide and dexamethasone (D-VCd, n=193).

Monotherapy – relapsed/refractory multiple myeloma

MMY3012, a Phase 3 randomized, study compared treatment with DARZALEX® SC formulation (1800 mg) vs. intravenous (16 mg/kg) daratumumab in patients with relapsed or refractory multiple myeloma. The median DARZALEX® SC formulation treatment duration was 5.5 months (range: 0.03 to 19.35 months) and 6.0 months (range: 0.03 to 16.69 months) for intravenous daratumumab. The most common adverse reactions of any grade (≥20% patients) with DARZALEX® SC formulation were upper respiratory tract infections. Pneumonia was the only serious adverse reaction occurring in ≥5% of patients (6% IV vs. 6% SC).

Table 6 below lists the adverse reactions that occurred in patients who received DARZALEX® SC formulation or intravenous daratumumab in Study MMY3012.

Table 6: Adverse reactions (≥10%) in any treatment arm in study MMY3012

System Organ Class Adverse Reactions	SC Daratumumab (N=260)			IV Daratumumab (N=258)		
	Any Grade (%)	Grade 3 (%)	Grade 4 (%)	Any Grade (%)	Grade 3 (%)	Grade 4 (%)
Infusion-related reactions[a]	13	2	0	34	5	0
Gastrointestinal disorders						
Diarrhea	15	1	0	12	<1	0
Nausea	9	0	0	12	1	0
General disorders and administration site conditions						
Pyrexia	14	<1	0	14	1	0
Fatigue	12	1	0	11	1	0
Chills	6	<1	0	12	1	0
Infections and infestations						
Upper respiratory tract infection[b]	30	1	0	25	2	0
Musculoskeletal and connective tissue disorders						
Arthralgia	11	<1	0	7	0	0
Back pain	11	2	0	14	3	0
Nervous system disorders						
Headache	5	0	0	10	<1	0
Respiratory, thoracic and mediastinal disorders						
Cough[c]	10	1	0	16	0	0
Dyspnea[d]	6	1	0	11	1	0
Vascular disorders						
Hypertension[e]	6	4	0	10	7	0

Key: SC Daratumumab=subcutaneous daratumumab; IV Daratumumab=intravenous daratumumab.

[a] Includes terms determined by investigators to be related to infusion.

[b] Acute sinusitis, Nasopharyngitis, Pharyngitis, Pharyngitis streptococcal, Respiratory syncytial virus infection, Respiratory tract infection, Rhinitis, Rhinovirus infection, Sinusitis, Upper respiratory tract infection

[c] Cough, Productive cough

[d] Dyspnea, Dyspnea exertional

[e] Blood pressure increased, Hypertension

Laboratory abnormalities worsening during treatment from baseline are listed in Table 7.

Table 7: Treatment-emergent hematology laboratory abnormalities in study MMY3012

	SC Daratumumab (N=260)			IV Daratumumab (N=258)		
	All Grade (%)	Grade 3 (%)	Grade 4 (%)	All Grade (%)	Grade 3 (%)	Grade 4 (%)
Anemia	43	15	0	41	17	0
Thrombocytopenia	45	12	4	47	8	7
Leukopenia	66	18	1	59	11	2
Neutropenia	56	17	3	47	8	3
Lymphopenia	60	28	8	56	27	9

Key: SC Daratumumab=subcutaneous daratumumab; IV Daratumumab=intravenous daratumumab.

Combination therapies in multiple myeloma

Combination treatments: D-VMP, D-Rd, D-VRd, D-Kd

MMY2040 was an open-label trial of DARZALEX® SC formulation in combination with bortezomib, melphalan, prednisone (D-VMP) in patients with newly diagnosed MM who are ineligible for transplant, in combination with lenalidomide and dexamethasone (D-Rd) in patients with relapsed or refractory MM, in combination with bortezomib, lenalidomide, and dexamethasone (D-VRd) in patients with newly diagnosed MM who are transplant eligible, and in combination with carfilzomib and dexamethasone (D-Kd) in patients with relapsed or refractory MM. The median treatment duration was as follows: 10.6 months (0.36 to 13.17

months) for D-VMP; 11.1 months (0.49 to 13.57 months) for D-Rd; 2.6 months (0.46 to 3.91 months) for D-VRd; 8.3 months (0 to 17 months) for D-Kd.

The most common adverse reactions of any grade (≥20% patients) with DARZALEX® SC formulation were constipation, diarrhea, nausea, vomiting, pyrexia, fatigue, asthenia, upper respiratory tract infection, pneumonia, back pain, muscle spasms, peripheral sensory neuropathy, insomnia, cough, hypertension, headache, edema peripheral and dyspnea. Serious adverse reactions reported in ≥5% of patients included pneumonia (D-VMP 9%; D-Rd 12%; D-VRd 1%; D-Kd 3%); pyrexia (D-VMP 6%; D-Rd 5%; D-VRd 6%; D-Kd 3%), influenza (D-VMP 1%; D-Rd 6%; D-VRd 0%; D-Kd 2%), and diarrhea (D-VMP 1%; D-Rd 6%; D-VRd 0%; D-Kd 0%).

Table 8 below lists the adverse reactions that occurred in patients who received DARZALEX® subcutaneous formulation in Study MMY2040.

Table 8: Adverse reactions (≥10%) in any treatment arm in study MMY2040

System Organ Class Adverse Reactions	**D-VMP (N=67)**		**D-Rd (N=65)**		**D-VRd (N=67)**		**D-Kd (N=66)**	
	Any Grade (%)	**Grade 3-4 (%)**	**Any Grade (%)**	**Grade 3-4 (%)**	**Any Grade (%)**	**Grade 3-4 (%)**	**Any Grade (%)**	**Grade 3-4 (%)**
Gastrointestinal disorders								
Constipation	37	0	26	2	39	0	9	0
Nausea	36	0	12	0	18	1	21	0
Diarrhea	33	3	45	5	24	1	29	0
Vomiting	21	0	11	0	12	1	15	0
General disorders and administration site conditions								
Pyrexia	34	0	23	2	36	1	21	2
Asthenia	24	3	29	3	15	0	21	0
Fatigue	13	0	25	2	28	4	20	2
Edema peripheral[a]	13	1	18	3	19	0	20	0
Injection site erythema	7	0	0	0	13	0	6	0
Chills	4	0	5	0	12	0	3	0
Infections and infestations								
Upper respiratory tract infection[b]	39	0	43	3	13	0	52	0
Bronchitis[c]	16	0	14	2	3	0	12	2
Pneumonia[d]	13	7	20	14	6	3	6	3
Urinary tract infection	9	1	11	0	1	1	3	2
Metabolism and nutrition disorders								
Decreased appetite	15	1	6	0	3	0	6	0
Hypocalcemia	7	1	11	0	7	0	6	0
Hyperglycemia	1	1	12	9	1	1	9	2
Musculoskeletal and connective tissue disorders								
Back pain	21	3	14	0	10	0	17	2
Musculoskeletal chest pain	12	0	6	0	3	0	11	0
Muscle spasms	3	0	31	2	6	0	9	0
Nervous system disorders								
Peripheral sensory neuropathy	34	1	17	2	42	3	11	0
Dizziness	10	0	9	0	9	0	5	0
Headache	9	0	6	0	10	0	23	0
Psychiatric disorders								
Insomnia	22	3	17	5	18	0	33	6
Respiratory, thoracic and mediastinal disorders								
Cough[e]	24	0	14	0	7	0	24	0
Dyspnea[f]	4	0	22	3	16	1	23	2
Skin and subcutaneous tissue disorders								

Rash	13	0	9	0	13	0	8	0
Pruritus	12	0	3	0	6	1	6	0
Vascular disorders								
Hypertension	13	6	2	2	1	1	32	21

Key: D-VMP=SC Daratumumab-bortezomib-melphalan-prednisone; D-Rd=SC Daratumumab-lenalidomide-dexamethasone; D-VRd=SC Daratumumab-bortezomib-lenalidomide-dexamethasone; D-Kd=SC Daratumumab-carfilzomib-dexamethasone ; SC Daratumumab=subcutaneous daratumumab.

[a] Generalized edema, Edema, Edema peripheral, Peripheral swelling

[b] Nasopharyngitis, Pharyngitis, Respiratory syncytial virus infection, Respiratory tract infection, Respiratory tract infection viral, Rhinitis, Rhinovirus infection, Sinusitis, Tonsillitis, Upper respiratory tract infection, Upper respiratory tract infection bacterial, Viral pharyngitis, Viral upper respiratory tract infection

[c] Bronchitis, Bronchitis viral

[d] Lung infection, Pneumocystis jirovecii pneumonia, Pneumonia, Pneumonia bacterial

[e] Cough, Productive cough

[f] Dyspnea, Dyspnea exertional

[g] Blood pressure increased, Hypertension

Laboratory abnormalities worsening during treatment from baseline are listed in Table 9.

Table 9: Treatment-emergent hematology laboratory abnormalities in MMY2040

	D-VMP (N=67)			D-Rd (N=65)			D-VRd (N=67)			D-Kd (N=66)		
	All Grade (%)	**Grade 3 (%)**	**Grade 4 (%)**	**All Grade (%)**	**Grade 3 (%)**	**Grade 4 (%)**	**All Grade (%)**	**Grade 3 (%)**	**Grade 4 (%)**	**All Grade (%)**	**Grade 3 (%)**	**Grade 4 (%)**
Anemia	48	19	0	45	8	0	37	4	0	47	6	0
Thrombocytopenia	93	28	13	86	8	2	75	10	4	88	11	8
Leukopenia	96	37	15	94	25	9	84	22	3	68	18	0
Neutropenia	88	33	16	89	37	15	67	27	4	55	12	3
Lymphopenia	93	58	25	82	46	12	90	40	12	83	29	21

Key: D-VMP=SC Daratumumab-bortezomib-melphalan-prednisone; D-Rd=SC Daratumumab-lenalidomide-dexamethasone; D-VRd=SC Daratumumab-bortezomib-lenalidomide-dexamethasone; D-Kd=SC Daratumumab-carfilzomib-dexamethasone ; SC Daratumumab=subcutaneous daratumumab.

Combination treatment: D-Pd

MMY3013 was a Phase 3 randomized, open-label, active controlled study that compared treatment with DARZALEX® SC formulation in combination with pomalidomide and low-dose dexamethasone (D-Pd) with pomalidomide and low-dose dexamethasone (Pd) in patients with relapsed or refractory multiple myeloma who received at least 1 prior treatment with lenalidomide and a protease inhibitor (PI). The median treatment duration was 11.5 months (0.13 to 36.17 months) for D-Pd and 6.6 months (0.03 to 27.33 months) for Pd.

The most common adverse reactions of any grade (≥20% patients) were fatigue, upper respiratory infection, asthenia, diarrhea and pneumonia. Serious adverse reactions with a 2% greater incidence in the D-Pd arm compared to the Pd arm were pneumonia (D-Pd 26% vs Pd 17%), neutropenia (D-Pd 5% vs. Pd 3%), thrombocytopenia (D-Pd: 3% vs Pd: 1%), and syncope (D-Pd: 2% vs Pd: 0%).

Table 10 below summarizes the adverse reactions in Study MMY3013.

Table 10: Adverse reactions reported in ≥10% of patients and with at least a 5% greater frequency in the D-Pd arm in study MMY3013

System Organ Class Adverse Reactions	D-Pd (N=149)			Pd (N=150)		
	Any Grade (%)	Grade 3 (%)	Grade 4 (%)	Any Grade (%)	Grade 3 (%)	Grade 4 (%)
General disorders and administration site conditions						
Asthenia	22	5	1	16	1	0
Pyrexia	19	0	0	14	0	0
Edema peripheral[a]	15	0	0	9	0	0
Infections and infestations						
Pneumonia[b]	38	17	5	27	13	2
Upper respiratory tract infection[c]	36	1	0	22	2	0
Gastrointestinal disorders						
Diarrhea	22	5	0	14	1	0
Respiratory, thoracic and mediastinal disorders						
Cough[d]	13	0	0	8	0	0

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

[a] Edema peripheral includes edema, edema peripheral, and peripheral swelling.

[b] Pneumonia includes atypical pneumonia, lower respiratory tract infection, pneumonia, pneumonia aspiration, pneumonia bacterial, and pneumonia respiratory syncytial viral.

[c] Upper respiratory tract infection includes nasopharyngitis, pharyngitis, respiratory syncytial virus infection, respiratory tract infections, respiratory tract infection viral, rhinitis, sinusitis, tonsillitis, upper respiratory tract infection, and viral upper respiratory tract infection.

[d] Cough includes cough, and productive cough.

Laboratory abnormalities worsening during treatment from baseline are listed in Table 11.

Table 11: Treatment-emergent hematology laboratory abnormalities in study MMY3013

	D-Pd (N=149)			Pd (N=150)		
	Any Grade (%)	Grade 3 (%)	Grade 4 (%)	Any Grade (%)	Grade 3 (%)	Grade 4 (%)
Anemia	51	15	0	57	15	0
Lymphopenia	92	44	15	78	29	3
Neutropenia	96	36	48	83	43	20
Thrombocytopenia	75	9	10	59	14	5
Leukopenia	95	42	22	81	35	4

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

Combination treatment for AL Amyloidosis

The safety of DARZALEX® SC formulation (1800 mg) with bortezomib, cyclophosphamide and dexamethasone (D-VCd) compared to bortezomib, cyclophosphamide and dexamethasone (VCd) in patients with newly diagnosed AL amyloidosis was evaluated in an open-label, randomized, Phase 3 study, AMY3001. The median treatment duration was 9.6 months (range: 0.03 to 21.16 months) for D-VCd and 5.3 months (range: 0.03 to 7.33 months) for VCd. The most common adverse reactions of any grade (≥20%) were upper respiratory tract infection, diarrhea, constipation, peripheral sensory neuropathy, dyspnea and cough. Serious adverse reactions with a 2% greater incidence in the D-VCd arm compared to the VCd arm were pneumonia (D-VCd 9% vs VCd 6%) and sepsis (D-VCd 5% vs VCd 1%).

Table 12 below summarizes the adverse reactions in AMY3001.

Table 12: Adverse reactions reported in ≥10% of patients and with at least a 5% frequency greater in the D-VCd arm in study AMY3001

System Organ Class Adverse Reactions	D-VCd (N=193)			VCd (N=188)		
	Any Grade (%)	Grade 3 (%)	Grade 4 (%)	Any Grade (%)	Grade 3 (%)	Grade 4 (%)
Infections and infestations						
Upper respiratory tract infection[a]	40	1	0	21	1	0
Pneumonia[b]	15	8	2	9	5	1
Gastrointestinal disorders						
Diarrhea	36	6	0	30	3	1
Constipation	34	2	0	29	0	0
Nervous system disorders						
Peripheral sensory neuropathy	31	3	0	20	2	0
Respiratory, thoracic and mediastinal disorders						
Dyspnea[c]	26	3	1	20	4	0
Cough[d]	20	1	0	11	0	0
Musculoskeletal and connective tissue disorders						
Back pain	12	2	0	6	0	0
Arthralgia	10	0	0	5	0	0
Muscle spasms	10	1	0	5	0	0
General disorders and administration site conditions						
Injection site reactions[e]	11	0	0	0	0	0

Key: D-VCd=daratumumab-bortezomib-cyclophosphamide-dexamethasone; VCd=bortezomib-cyclophosphamide-dexamethasone.

[a] Upper respiratory tract infection includes laryngitis, nasopharyngitis, pharyngitis, respiratory syncytial virus infection, respiratory tract infection, respiratory tract infection viral, rhinitis, rhinovirus infection, sinusitis, tonsillitis, tracheitis, upper respiratory tract infection, upper respiratory tract infection bacterial, and viral upper respiratory tract infection.

[b] Pneumonia includes lower respiratory tract infection, pneumonia, pneumonia aspiration, and pneumonia pneumococcal.

[c] Dyspnea includes dyspnea, and dyspnea exertional.

[d] Cough includes cough, and productive cough.

[e] Injection site reactions includes terms determined by investigators to be related to daratumumab injection.

Laboratory abnormalities worsening during treatment from baseline are listed in Table 13.

Table 13: Treatment-emergent hematology laboratory abnormalities in study AMY3001

	D-VCd (N=193)			VCd (N=188)		
	All Grade (%)	Grade 3 (%)	Grade 4 (%)	All Grade (%)	Grade 3 (%)	Grade 4 (%)
Anemia	65	6	0	70	6	0
Thrombocytopenia	45	2	1	40	3	1
Leukopenia	58	5	3	45	4	0
Neutropenia	29	3	3	18	4	0
Lymphopenia	79	35	18	70	39	6

Key: D-VCd=daratumumab-bortezomib-cyclophosphamide-dexamethasone; VCd=bortezomib-cyclophosphamide-dexamethasone.

Experience with intravenous daratumumab combination therapies

The safety of intravenous (IV) daratumumab (16 mg/kg) has been established in 1910 patients with multiple myeloma including 1772 patients from five Phase 3 active-controlled trials who received IV daratumumab in combination with either lenalidomide and dexamethasone (D-Rd, n=283; MMY3003), bortezomib and dexamethasone (D-Vd, n=243; MMY3004), bortezomib, melphalan and prednisone (D-VMP, n=346; MMY3007), or lenalidomide and dexamethasone (D-Rd, n=364; MMY3008), or bortezomib and thalidomide and dexamethasone (D-VTd, n=536; MMY3006) and two open-label, clinical trials in which patients received IV daratumumab either

in combination with pomalidomide and dexamethasone (D-Pd, n=103; MMY1001) or in combination with lenalidomide and dexamethasone (n=35).

Adverse reactions in Table 14 reflect exposure to IV daratumumab for a median treatment duration as follows:

- MMY3008: 25.3 months (range: 0.1 to 40.44 months) for the daratumumab-lenalidomide-dexamethasone (D-Rd) group; 21.3 months (range: 0.03 to 40.64 months) for the lenalidomide-dexamethasone (Rd) group
- MMY3007: 14.7 months (range: 0 to 25.8 months) for the daratumumab-bortezomib, melphalan-prednisone (D-VMP) group; 12 months (range: 0.1 to 14.9 months) for the VMP group
- MMY3003: 13.1 months (range: 0 to 20.7 months) for the daratumumab-lenalidomide-dexamethasone (D-Rd) group; 12.3 months (range: 0.2 to 20.1 months) for the lenalidomide-dexamethasone (Rd) group
- MMY3004: 6.5 months (range: 0 to 14.8 months) for the daratumumab-bortezomib-dexamethasone (D-Vd) group; 5.2 months (range: 0.2 to 8.0 months) for the bortezomib-dexamethasone (Vd) group

Additionally, adverse reactions described in Table 14 reflect exposure to IV daratumumab up to day 100 post-transplant in a Phase 3 active-controlled study MMY3006 (see *Clinical Studies*). The median duration of induction/ASCT/consolidation treatment was 8.9 months (range: 7.0 to 12.0 months) for the D-VTd group and 8.7 months (range: 6.4 to 11.5 months) for the VTd group.

The most frequent adverse reactions (≥ 20%) were infusion-related reactions, fatigue, asthenia, nausea, diarrhea, constipation, decreased appetite, vomiting, muscle spasms, arthralgia, back pain, chills, pyrexia, dizziness, insomnia, cough, dyspnea, peripheral edema, peripheral sensory neuropathy, bronchitis, pneumonia, and upper respiratory tract infection. Serious adverse reactions with a 2% higher incidence in the IV daratumumab arms were pneumonia, bronchitis, upper respiratory tract infection, sepsis, pulmonary edema, influenza, pyrexia, dehydration, diarrhea, and atrial fibrillation.

Table 14: Adverse reactions reported in ≥10% of patients and with at least a 5% greater frequency in the IV daratumumab (16 mg/kg) arm observed in at least one randomized clinical study

System Organ Class Adverse Reactions	**MMY3008**		**MMY3007**		**MMY3006**		**MMY3003**		**MMY3004**	
	D-Rd N=364	**Rd N=365**	**D-VMP N=346**	**VMP N=354**	**D-VTd N=536**	**VTd N=538**	**D-Rd N=283**	**Rd N=281**	**D-Vd N=243**	**Vd N=237**
Infusion-related reactions[a]	41	0	28	0	35	0	48	0	45	0
Infections and infestations										
Bronchitis[b]	29	21	15	8	20	13	14	13	12	6
Pneumonia[c]	26	14	16	6	11	7	19	15	16	14
Upper respiratory tract infection[d]	52	36	38	22	27	17	60	42	38	25
Urinary tract infection	18	10	8	3	3	4	5	4	5	3
Metabolism and nutrition disorders										
Decreased appetite	22	15	12	13	7	7	11	10	9	5

Hyperglycemia	14	8	6	4	1	2	9	7	9	8
Hypocalcemia	14	9	6	5	1	2	6	4	4	5
Nervous system disorders										
Headache	19	11	7	4	8	8	13	7	10	6
Paresthesia	16	8	5	5	22	20	5	4	5	6
Peripheral sensory neuropathy	24	15	28	34	59	63	8	7	47	38
Vascular disorders										
Hypertension[e]	13	7	10	3	10	5	8	2	9	3
Respiratory, thoracic and mediastinal disorders										
Cough[f]	30	18	16	8	17	9	30	15	27	14
Dyspnea[g]	32	20	13	5	19	16	21	12	21	11
Pulmonary edema[h]	1	0	2	<1	0	<1	2	1	0	1
Gastrointestinal disorders										
Constipation	41	36	18	18	51	49	29	25	20	16
Diarrhea	57	46	24	25	19	17	43	25	32	22
Nausea	32	23	21	21	30	24	24	14	14	11
Vomiting	17	12	17	16	16	10	17	5	11	4
Musculoskeletal and connective tissue disorders										
Back pain	34	26	14	12	11	10	18	17	14	10
Muscle spasms	29	22	2	3	5	7	26	19	8	2
General disorders and administration site conditions										
Asthenia	32	25	12	12	32	29	16	13	9	16
Chills	13	2	8	2	9	4	6	3	5	1
Fatigue	40	28	14	14	13	16	35	28	21	24
Edema peripheral[i]	41	33	21	14	32	29	18	16	22	13
Pyrexia	23	18	23	21	26	21	20	11	16	11

Key: D=intravenous daratumumab, Rd=lenalidomide-dexamethasone; VMP=bortezomib-melphalan-prednisone; VTd=bortezomib-thalidomide-dexamethasone; Vd=bortezomib-dexamethasone.

[a] Includes terms determined by investigators to be related to infusion.

[b] Bronchiolitis, Bronchitis, Bronchitis bacterial, Bronchitis chronic, Bronchitis viral, Respiratory syncytial virus bronchiolitis, Respiratory syncytial virus bronchitis, Tracheobronchitis

[c] Atypical pneumonia, Bronchopneumonia, Bronchopulmonary aspergillosis, Idiopathic interstitial pneumonia, Lobar pneumonia, Lung infection, Pneumocystis jirovecii infection, Pneumocystis jirovecii pneumonia, Pneumonia, Pneumonia aspiration, Pneumonia bacterial, Pneumonia cytomegaloviral, Pneumonia hemophilus, Pneumonia influenzal, Pneumonia klebsiella, Pneumonia legionella, Pneumonia parainfluenzae viral, Pneumonia pneumococcal, Pneumonia pseudomonal, Pneumonia respiratory syncytial viral, Pneumonia staphylococcal, Pneumonia streptococcal, Pneumonia viral, Pulmonary mycosis, Pulmonary sepsis

[d] Acute sinusitis, Acute tonsillitis, Bacterial rhinitis, Epiglottitis, Laryngitis, Laryngitis bacterial, Laryngitis viral, Metapneumovirus infection, Nasopharyngitis, Oropharyngeal candidiasis, Pharyngitis, Pharyngitis streptococcal, Respiratory moniliasis, Respiratory syncytial virus infection, Respiratory tract infection, Respiratory tract infection viral, Rhinitis, Rhinovirus infection, Sinusitis, Staphylococcal pharyngitis, Tonsillitis, Tracheitis, Upper respiratory tract infection, Upper respiratory tract infection bacterial, Viral pharyngitis, Viral rhinitis, Viral upper respiratory tract infection

[e] Blood pressure increased, Hypertension

[f] Allergic cough, Cough, Productive cough

[g] Dyspnea, Dyspnea exertional

[h] Pulmonary congestion, Pulmonary edema

[i] Generalized edema, Gravitational edema, Edema, Edema peripheral, Peripheral swelling

Combination treatment with pomalidomide and dexamethasone

Adverse reactions described reflect exposure to IV daratumumab, pomalidomide and dexamethasone (D-Pd) for a median treatment duration of 6 months (range: 0.03 to 16.9 months) in Study MMY1001. The most frequent adverse reactions (>10%) were infusion-related reactions, diarrhea, nausea, vomiting, fatigue, pyrexia, peripheral edema, pneumonia, upper

respiratory tract infection, muscle spasms, headache, cough, and dyspnea. Adverse reactions resulted in discontinuations for 13% of patients.

Laboratory abnormalities worsening during IV daratumumab combination treatment trials are listed in Table 15.

Table 15: Treatment-emergent hematology laboratory abnormalities (any grade) in IV daratumumab studies

	MMY3008		MMY3007		MMY3006		MMY3003		MMY3004		MMY1001
	D-Rd N=364	Rd N=365	D-VMP N=346	VMP N=354	D-VTd N=536	VTd N=538	D-Rd N=283	Rd N=281	D-Vd N=243	Vd N=237	D-Pd N=103
Anemia	47	57	47	50	36	35	52	57	48	56	57
Thrombocytopenia	67	58	88	88	81	58	73	67	90	85	75
Neutropenia	91	77	86	87	63	41	92	87	58	40	95
Lymphopenia	84	75	85	83	95	91	95	87	89	81	94
Leukopenia	90	82	94	94	82	57	92	81	72	48	96

Key: D=intravenous daratumumab, Rd=lenalidomide-dexamethasone; VMP=bortezomib-melphalan-prednisone; VTd=bortezomib-thalidomide-dexamethasone; Vd=bortezomib-dexamethasone; Pd=pomalidomide-dexamethasone.

Infusion-related reactions

In clinical trials (monotherapy and combination treatments; N=898) with DARZALEX® SC formulation, the incidence of any grade infusion-related reactions was 8.2% with the first injection of DARZALEX® SC formulation (1800 mg, Week 1), 0.4% with the Week 2 injection, and 1.1% with subsequent injections. Grade 3 IRRs were seen in 1% of patients. No patients had Grade 4 IRRs.

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, pruritis, chills, vomiting, nausea, and hypotension. Severe reactions have occurred, including bronchospasm, hypoxia, dyspnea, hypertension and tachycardia (see *Warnings and Precautions*).

Injection site reactions (ISRs)

In clinical trials (N=898) with DARZALEX® SC formulation, the incidence of any grade injection site reaction was 7.7%. There were no Grade 3 or 4 ISRs. The most common (> 1%) ISR was erythema.

Infections

In patients with multiple myeloma receiving daratumumab monotherapy, the overall incidence of infections was similar between DARZALEX® SC formulation (52.9%) and IV daratumumab groups (50.0%). Grade 3 or 4 infections also occurred at similar frequencies between DARZALEX® SC formulation (11.7%) and IV daratumumab (14.3%). Most infections were manageable and rarely led to treatment discontinuation. Pneumonia was the most commonly reported Grade 3 or 4 infection across studies. In active-controlled studies, discontinuations from treatment due to infections occurred in 1-4% of patients. Fatal infections were primarily due to pneumonia and sepsis.

In patients with multiple myeloma receiving intravenous daratumumab combination therapy, the following infections were reported:

Grade 3 or 4 infections:

Relapsed/refractory patient studies: D-Vd: 21%, Vd: 19%; D-Rd: 28%, Rd: 23%; D-Pd: 28%; D-Kd[a]: 36%, Kd[a]: 27%; D-Kd[b]: 21%

[a] where carfilzomib 20/56 mg/m^2 was administered twice-weekly

[b] where carfilzomib 20/70 mg/m^2 was administered once-weekly

Newly diagnosed patient studies: D-VMP: 23%, VMP: 15%; D-Rd: 32%, Rd: 23%; D-VTd: 22%, VTd: 20%.

Grade 5 (fatal) infections:

Relapsed/refractory patient studies: D-Vd: 1%, Vd: 2%; D-Rd: 2%, Rd: 1%; D-Pd: 2%; D-Kd[a]: 5%, Kd[a]: 3%; D-Kd[b]: 0%

[a] where carfilzomib 20/56 mg/m^2 was administered twice-weekly

[b] where carfilzomib 20/70 mg/m^2 was administered once-weeklyNewly diagnosed patient studies: D-VMP: 1%, VMP: 1%; D-Rd: 2%, Rd: 2%; D-VTd: 0%, VTd: 0%.

In patients with multiple myeloma receiving DARZALEX® SC formulation combination therapy, the following were reported:

Grade 3 or 4 infections: D-Pd: 28%, Pd: 23%;

Grade 5 (fatal) infections: D-Pd: 5%, Pd: 3%

In patients with AL amyloidosis receiving DARZALEX® SC formulation combination therapy, the following were reported:

Grade 3 or 4 infections: D-VCd: 17%, VCd:10%;

Grade 5 (fatal) infections: D-VCd: 1%, VCd: 1%

Cardiac disorders and AL amyloidosis-related cardiomyopathy

The majority of patients in AMY3001 had AL amyloidosis-related cardiomyopathy at baseline (D-VCd 72% vs. VCd 71%). Grade 3 or 4 cardiac disorders occurred in 11% of D-VCd patients compared to 10% of VCd patients, while serious cardiac disorders occurred in 16% vs. 13% of D-VCd and VCd patients, respectively. Serious cardiac disorders occurring in ≥2% of patients included cardiac failure (D-VCd 6.2% vs. VCd 4.3%), cardiac arrest (D-VCd 3.6% vs. VCd 1.6%) and atrial fibrillation (D-VCd 2.1% vs. VCd 1.1%). All D-VCd patients who experienced serious or fatal cardiac disorders had AL amyloidosis-related cardiomyopathy at baseline. The longer median duration of treatment in the D-VCd arm compared to the VCd arm (9.6 months vs. 5.3 months, respectively) should be taken into consideration when comparing the frequency of cardiac disorders between the two treatment groups. Exposure-adjusted incidence rates (number of patients with the event per 100 patient-months at risk) of overall Grade 3 or 4 cardiac disorders (1.2 vs. 2.3), cardiac failure (0.5 vs. 0.6), cardiac arrest (0.1 vs. 0.0) and atrial fibrillation (0.2 vs. 0.1) were comparable in the D-VCd arm vs. the VCd arm, respectively.

With a median follow-up of 11.4 months, overall deaths (D-VCd 14% vs. VCd 15%) in Study AMY3001 were primarily due to AL amyloidosis-related cardiomyopathy in both treatment arms.

Haemolysis

There is a theoretical risk of haemolysis. Continuous monitoring for this safety signal will be performed in clinical studies and post-marketing safety data.

Other adverse reactions

Other adverse reactions reported in patients treated with daratumumab in clinical trials are listed in Table 16.

Table 16: Other adverse reactions reported in patients treated with daratumumab in clinical trials

System Organ Class Adverse Reaction (%)
Infections and Infestations Cytomegalovirus infection[a] (1%), Hepatitis B virus reactivation (<1%)
Gastrointestinal disorders Pancreatitis[b] (1%)
Immune system disorders Hypogammaglobulinemia[c] (2%)

[a] Cytomegalovirus chorioretinitis, Cytomegalovirus colitis, Cytomegalovirus duodenitis, Cytomegalovirus enteritis, Cytomegalovirus enterocolitis, Cytomegalovirus gastritis, Cytomegalovirus gastroenteritis, Cytomegalovirus gastrointestinal infection, Cytomegalovirus hepatitis, Cytomegalovirus infection, Cytomegalovirus mucocutaneous ulcer, Cytomegalovirus myelomeningoradiculitis, Cytomegalovirus myocarditis, Cytomegalovirus esophagitis, Cytomegalovirus pancreatitis, Cytomegalovirus pericarditis, Cytomegalovirus syndrome, Cytomegalovirus urinary tract infection, Cytomegalovirus viremia, Disseminated cytomegaloviral infection, Encephalitis cytomegalovirus, Pneumonia cytomegaloviral.

[b] Pancreatitis, Pancreatitis acute, Pancreatitis chronic, Hyperamylasemia, Obstructive pancreatitis, Lipase increased

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

Other special population

Elderly

Of the 3615 patients who received daratumumab (n=898 SC; n=2717 IV) at the recommended dose, 38% were 65 to less than 75 years of age, and 16% were 75 years of age or older. No overall differences in effectiveness were observed based on age. The incidence of serious adverse reactions was higher in older than in younger patients (see *Adverse Reactions, Clinical Studies*). Among patients with relapsed and refractory multiple myeloma (n=2042), the most common serious adverse reactions that occurred more frequently in elderly (≥65 years of age) were pneumonia and sepsis. Among patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant (n=777), the most common serious adverse reaction that occurred more frequently in elderly (≥75 years of age) was pneumonia. Among patients with newly diagnosed AL amyloidosis (n=193), the most common serious adverse reaction that occurred more frequently in elderly (≥65 years of age) was pneumonia.

Postmarketing data

In addition to the above, adverse reactions identified during postmarketing experience with daratumumab are included in Table 17. The frequencies are provided according to the following convention:

Very common	≥1/10
Common	≥1/100 to <1/10
Uncommon	≥1/1000 to <1/100
Rare	≥1/10000 to <1/1000
Very rare	<1/10000, including isolated reports
Not known	frequency cannot be estimated from the available data

In Table 17, adverse reactions are presented by frequency category based on spontaneous reporting rates, as well as frequency category based on precise incidence in a clinical trial, when known.

Table 17: Postmarketing adverse reactions identified with daratumumab

System Organ Class Adverse Reaction	**Frequency Category based on Spontaneous Reporting Rate**
Immune System disorders	
Anaphylactic reaction	Rare
Infections and Infestations	
COVID-19	Uncommon

Overdose

Symptoms and signs

There has been no experience of overdosage in clinical studies with DARZALEX® subcutaneous formulation.

Treatment

There is no known specific antidote for DARZALEX® SC 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.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic Properties

Pharmacotherapeutic group: Antineoplastic agents, monoclonal antibodies, ATC code: L01FC01

DARZALEX® subcutaneous formulation 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.

Mechanism of action

Daratumumab is an IgG1κ human monoclonal antibody (mAb) that binds to 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 complement-dependent cytotoxicity (CDC), antibody-dependent cell-mediated cytotoxicity (ADCC), and antibody-dependent cellular phagocytosis (ADCP) in malignancies expressing CD38. 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 DARZALEX® SC treatment in peripheral whole blood and bone marrow. T-cell receptor DNA sequencing verified that T-cell clonality was increased with DARZALEX® SC treatment, indicating immune modulatory effects that may contribute to clinical response.

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.

Pharmacodynamic effects

Natural killer (NK) cell and T-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 DARZALEX® SC treatment. However, baseline levels of NK cells did not show an association with clinical response.

Immunogenicity

In multiple myeloma and AL amyloidosis patients treated with DARZALEX® subcutaneous formulation in monotherapy and combination clinical trials, less than 1% of patients developed treatment-emergent anti-daratumumab antibodies.

In multiple myeloma and AL amyloidosis patients, the incidence of treatment-emergent non-neutralizing anti-rHuPH20 antibodies was 7.1% (58/812) in monotherapy and combination DARZALEX® clinical trials. The anti-rHuPH20 antibodies did not appear to impact daratumumab exposures. The clinical relevance of the development of anti-daratumumab or anti-rHuPH20 antibodies after treatment with DARZALEX® subcutaneous formulation is not known.

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 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.

Clinical studies

Clinical experience with DARZALEX® subcutaneous formulation

Monotherapy – relapsed/refractory multiple myeloma

MMY3012, an open-label, randomized, Phase 3 non-inferiority study, compared efficacy and safety of treatment with DARZALEX® subcutaneous formulation (1800 mg) vs. intravenous (16 mg/kg) daratumumab in patients with relapsed or refractory multiple myeloma who had received at least 3 prior lines of therapy including a PI and an IMiD or who were double-refractory to a PI and an IMiD. Treatment continued until unacceptable toxicity or disease progression.

A total of 522 patients were randomized: 263 to the DARZALEX® SC formulation arm and 259 to the IV daratumumab arm. 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). Patients had received a median of 4 prior lines of therapy. A total of 51% of patients had prior ASCT, 100% of patients 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%).

The study was designed to demonstrate non-inferiority of treatment with DARZALEX® SC formulation versus IV daratumumab based on co-primary endpoints of overall response rate (ORR) by the IMWG response criteria and maximum C_{trough} at pre-dose Cycle 3 Day 1 (see *Pharmacokinetic Properties*). The ORR, defined as the proportion of patients who achieve partial response (PR) or better, was 41.1% (95% CI: 35.1%, 47.3%) in the DARZALEX® SC formulation arm and 37.1% (95% CI: 31.2%, 43.3%) in the IV daratumumab arm.

This study met its primary objectives to show that DARZALEX® SC formulation is non-inferior to IV daratumumab in terms of ORR and maximum trough concentration. The results are provided in Table 18.

Table 18: Key results from Study MMY3012

	SC Daratumumab (N=263)	IV Daratumumab (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%)
Secondary Endpoint		
Rate of Infusion-related Reaction, n (%)[c]	33 (12.7%)	89 (34.5%)
Progression-free Survival, months		
Median (95% CI)	5.59 (4.67, 7.56)	6.08 (4.67, 8.31)
Hazard ratio (95% CI)		0.99 (0.78, 1.26)

SC Daratumumab=subcutaneous daratumumab; IV Daratumumab=intravenous daratumumab.

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

[b] p-value <0.0001 from Farrington-Manning test for non-inferiority hypothesis.

[c] Based on safety population. P-value <0.0001 from Cochran-Mantel-Haenszel Chi-Squared test.

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 formulation arm and was 25.6 months (95% CI: 22.1, NE) in the IV daratumumab arm.

Safety and tolerability results, including in lower weight patients, were consistent with the known safety profile for DARZALEX® SC formulation and IV daratumumab.

Results from the modified-CTSQ, a patient reported outcome questionnaire that assesses patient satisfaction with their therapy, demonstrated that patients receiving DARZALEX® subcutaneous formulation had greater satisfaction with their therapy compared with patients receiving IV daratumumab.

Combination treatments in multiple myeloma

MMY2040 was an open-label trial evaluating the efficacy and safety of DARZALEX® SC formulation 1800 mg:

D-VMP arm: In combination with bortezomib, melphalan, and prednisone (D-VMP) in patients with newly diagnosed multiple myeloma (MM) who are ineligible for transplant. Bortezomib was administered by subcutaneous injection at a dose of 1.3 mg/m^2 body surface area twice weekly at Weeks 1, 2, 4 and 5 for the first 6-week cycle (Cycle 1; 8 doses), followed by once weekly administrations at Weeks 1, 2, 4 and 5 for eight more 6-week cycles (Cycles 2-9; 4 doses per cycle). Melphalan at 9 mg/m^2, and prednisone at 60 mg/m^2 were orally administered on Days 1 to 4 of the nine 6-week cycles (Cycles 1-9). DARZALEX® SC formulation was continued until

disease progression or unacceptable toxicity. The median duration of follow-up for patients was 6.9 months.

The median age was 75 years and approximately 51% were ≥75 years of age. The sex of the patients was evenly distributed. Most patients were white (69%). 33% had ISS Stage I, 45% had ISS Stage II, and 22% had ISS Stage III disease at screening.

D-Rd arm: In combination with lenalidomide and dexamethasone (D-Rd) in patients with relapsed or refractory MM. Lenalidomide (25 mg once daily orally on Days 1-21 of repeated 28-day [4-week] cycles) was given with low dose dexamethasone 40 mg/week (or a reduced dose of 20 mg/week for patients >75 years or BMI <18.5). DARZALEX® subcutaneous formulation was continued until disease progression or unacceptable toxicity. The median duration of follow-up for patients was 7.1 months.

The median age was 69 years. The majority of patients were male (69%). Most patients were white (69%). 42% had ISS Stage I, 30% had ISS Stage II, and 28% had ISS Stage III disease at screening. Patients had received a median of 1 prior line of therapy, 52% of patients received prior ASCT. The majority of patients (95%) received prior PI, 59% received a prior IMiD including 22% who received prior lenalidomide. 54% of patients received both a prior PI and IMiD.

D-VRd arm: In combination with bortezomib, lenalidomide, and dexamethasone (D-VRd) in patients with newly diagnosed MM who are transplant eligible. Bortezomib was administered by SC injection at a dose of 1.3 mg/m^2 body surface area twice weekly at Weeks 1 and 2. Lenalidomide was administered orally at 25 mg once daily on Days 1-14; low dose dexamethasone was administered 40 mg/week in 3-week cycles. Total treatment duration was 4 cycles.

The median age was 59 years of age. The majority of patients (81%) fell in the range of 18 to <65 years of age and were male (72%). Most patients were white (57%); 45% had ISS Stage I, 34% had ISS Stage II, and 21% had ISS Stage III disease at screening.

D-Kd arm: In combination with carfilzomib and dexamethasone (D-Kd) for patients in first relapse or refractory MM after initial treatment with a lenalidomide-containing regimen. Carfilzomib was administered by IV infusion at a dose of 20 mg/m^2 on Cycle 1 Day 1. If a dose of 20 mg/m^2 was tolerated, carfilzomib was administered at a dose of 70 mg/m^2 as a 30-minute IV infusion, on Cycle 1 Day 8 and Day 15, and then Day 1, 8 and 15 of each cycle. This was given with low dose dexamethasone 40 mg per week (or a reduced dose of 20 mg per week for patients ≥75 years or BMI <18.5). TRADENAME SC formulation was continued until disease progression or unacceptable toxicity. The median duration of follow-up for patients was 9.2 months.

The median age was 61 years and 52% were male. Most patients were white (73%). 68% had ISS Stage I, 18% had ISS Stage II, and 14% had ISS Stage III disease at screening. A total of 79% of patients had received prior ASCT; 91% of patients received prior PI. All patients received 1 prior line of therapy with exposure to lenalidomide and 62% of patients were refractory to lenalidomide.

A total of 265 patients (D-VMP: 67; D-Rd: 65; D-VRd: 67; D-Kd: 66) were enrolled. Efficacy results were determined by computer algorithm using IMWG response criteria during the study. Primary endpoints ORR for D-VMP, D-Rd and D-Kd and VGPR or better for D-VRd were met (see Table 19). The minimal residual disease (MRD) negativity rate for patients in the D-Kd arm was 24%, based on all treated population and a threshold of 10.

Table 19: Efficacy results from Study MMY2040

	D-VMP (n=67)	**D-Rd (n=65)**	**D-VRd (n=67)**	**D-Kd (n=66)**
Overall response (sCR+CR+VGPR+PR), n (%)[a]	59 (88.1%)	59 (90.8%)	65 (97.0%)	56 (84.8%)
90% CI(%)	(79.5%, 93.9%)	(82.6%, 95.9%)	(90.9%, 99.5%)	(75.7%, 91.5%)
Stringent complete response (sCR)	5 (7.5%)	4 (6.2%)	6 (9.0%)	11 (16.7%)
Complete response (CR)	7 (10.4%)	8 (12.3%)	5 (7.5%)	14 (21.2%)
Very good partial response (VGPR)	31 (46.3%)	30 (46.2%)	37 (55.2%)	26 (39.4%)
Partial response (PR)	16 (23.9%)	17 (26.2%)	17 (25.4%)	5 (7.6%)
VGPR or better (sCR + CR + VGPR)	43 (64.2%)	42 (64.6%)	48 (71.6%)	51 (77.3%)
90% CI(%)	(53.5%, 73.9%)	(53.7%, 74.5%)	(61.2%, 80.6%)	(67.2%, 85.4%)

D-VMP=SC Daratumumab-bortezomib-melphalan-prednisone; D-Rd=SC Daratumumab-lenalidomide-dexamethasone; D-VRd=SC Daratumumab-bortezomib-lenalidomide-dexamethasone; D-Kd=SC Daratumumab-carfilzomib-dexamethasone; SC Daratumumab=subcutaneous daratumumab; CI=confidence interval

[a] Based on treated subjects

Combination treatment with pomalidomide and dexamethasone in patients with multiple myeloma

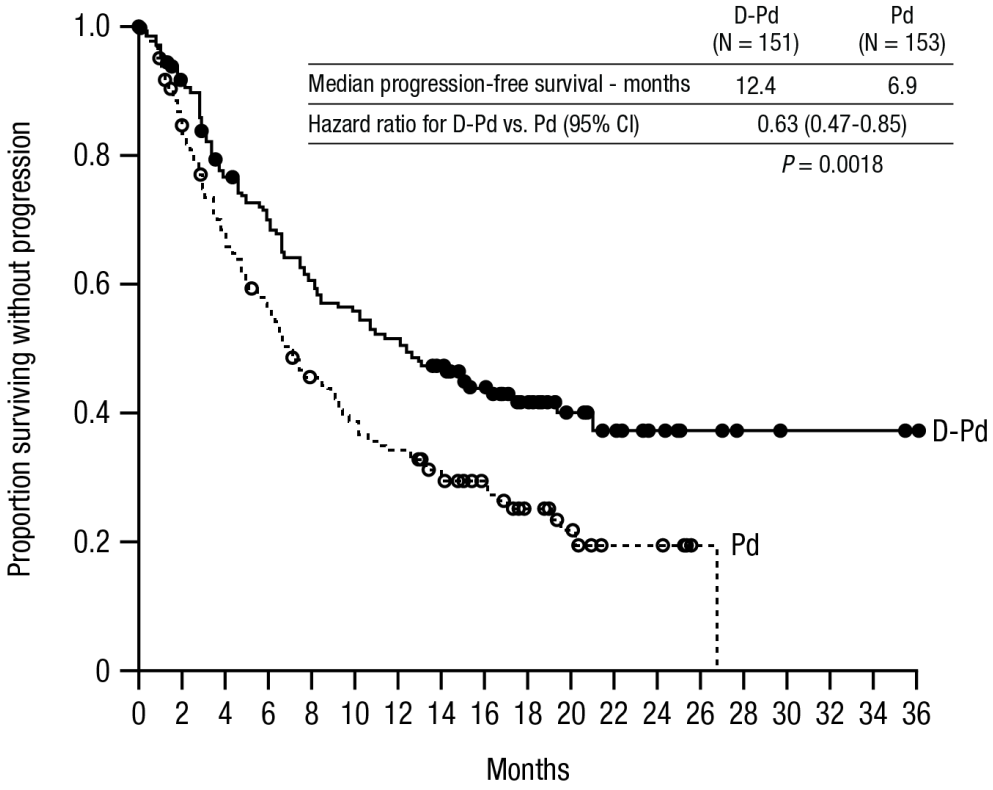
Study MMY3013 was an open-label, randomized, active-controlled Phase 3 trial that compared treatment with DARZALEX® SC formulation (1800 mg) in combination with pomalidomide and low-dose dexamethasone (D-Pd) to treatment with pomalidomide and low-dose dexamethasone (Pd) in patients with multiple myeloma who had received at least one prior therapy with lenalidomide and a protease inhibitor (PI). Pomalidomide (4 mg once daily orally on Days 1-21 of repeated 28-day [4-week] cycles) was given with low dose oral or intravenous dexamethasone 40 mg/week (or a reduced dose of 20 mg/week for patients >75 years). On DARZALEX® SC formulation administration days, 20 mg of the dexamethasone dose was given as a pre-administration medication and the remainder given the day after the administration. For patients on a reduced dexamethasone dose, the entire 20 mg dose was given as a DARZALEX® SC formulation pre-administration medication. Dose adjustments for pomalidomide and dexamethasone were applied according to manufacturer's prescribing information. Treatment was continued in both arms until disease progression or unacceptable toxicity.

A total of 304 patients were randomized: 151 to the D-Pd arm and 153 to the Pd arm. Patients with documented evidence of disease progression on or after the last regimen were included in the study. Patients who had ongoing ≥ Grade 2 peripheral neuropathy or ≥ Grade 3 rash during

prior therapy were excluded. The baseline demographic and disease characteristics were similar between the two treatment groups. The median patient age was 67 years (range 35 to 90 years), 18% were ≥ 75 years, 53% were male, and 89% Caucasian. Patients had received a median of 2 prior lines of therapy, with 11% of patients having received one prior line of therapy; all were refractory to lenalidomide and 32.4% were refractory to both lenalidomide and a PI. All patients received a prior treatment with a proteasome inhibitor (PI) and lenalidomide, and 56% of patients received prior stem cell transplantation (ASCT). Ninety-six (96%) of patients received prior treatment with bortezomib. The majority of patients were refractory to lenalidomide (80%), a PI (48%), or both an immunomodulator and a PI (42%). Efficacy was evaluated by PFS based on IMWG criteria.

With a median follow-up of 16.9 months, the primary analysis of PFS in Study MMY3013 demonstrated a statistically significant improvement in the D-Pd arm as compared to the Pd arm; the median PFS was 12.4 months in the D-Pd arm and 6.9 months in the Pd arm (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 D-Pd versus Pd. Median OS was not reached for either treatment group.

Figure 1: Kaplan-Meier Curve of PFS in Study MMY3013



Additional efficacy results from Study MMY3013 are presented in Table 20 below.

Table 20: Efficacy results from Study MMY3013[a]

	D-Pd (n=151)	Pd (n=153)
Overall response (sCR+CR+VGPR+PR) n(%)[a]	104 (68.9%)	71 (46.4%)
P-value[b]	<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[c] n(%)	13 (8.7%)	3 (2.0%)
95% CI (%)	(4.7%, 14.3%)	(0.4%, 5.6%)
P-value[d]	0.0102	

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

[a] Based on intent-to-treat population

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

[c] MRD Negative rate is based on the intent-to-treat population and a threshold of 10^{-5}

[d] 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 D-Pd 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 D-Pd group (range: 1 to 34.9+ months) and was 15.9 months (range: 1+ to 24.8 months) in the Pd group.

Combination treatment with bortezomib, cyclophosphamide and dexamethasone in patients with AL amyloidosis

Study AMY3001, an open-label, randomized, active-controlled Phase 3 study, compared treatment with DARZALEX® 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. 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.

Eligible patients were required to have newly diagnosed light chain (AL) amyloidosis with at least one affected organ, measurable hematologic disease, Cardiac Stage I-IIIA (based on European Modification of Mayo 2004 Cardiac Stage), and NYHA Class I-IIIA. Patients with NYHA Class IIIB and IV were excluded.

Bortezomib (SC; 1.3 mg/m^2 body surface area), cyclophosphamide (oral or IV; 300 mg/m^2 body surface area; max dose 500 mg), and dexamethasone (oral or IV; 40 mg or a reduced dose of 20 mg for patients >70 years or body mass index [BMI] <18.5 or those who have hypervolemia, poorly controlled diabetes mellitus or prior intolerance to steroid therapy) were administered

weekly on Days 1, 8, 15, and 22 of repeated 28-day [4-week] cycles. On the days of DARZALEX® dosing, 20 mg of the dexamethasone dose was given as a pre-injection medication and the remainder given the day after DARZALEX® administration. Bortezomib, cyclophosphamide and dexamethasone were given for six 28-day [4-week] cycles in both treatment arms, while DARZALEX® treatment was continued until disease progression, start of subsequent therapy, or a maximum of 24 cycles (~2 years) from the first dose of study treatment. Dose adjustments for bortezomib, cyclophosphamide and dexamethasone were applied according to manufacturer's prescribing information.

A total of 388 patients were randomized: 195 to the D-VCd arm and 193 to the VCd arm. 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 major efficacy outcome measure was hematologic complete response (HemCR) rate as determined by the Independent Review Committee assessment based on International Concensus Criteria. Study AMY3001 demonstrated an improvement in HemCR in the D-VCd arm as compared to the VCd arm. Efficacy results are summarized in Table 21.

Table 21: 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)		0.0211[d]
Cardiac response rate at 6 months, n/N (%)[e]	49/118 (42%)	26/117 (22%)	
Renal response rate at 6 months, n/N (%)[f]	63/117 (54%)	31/113 (27%)	

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

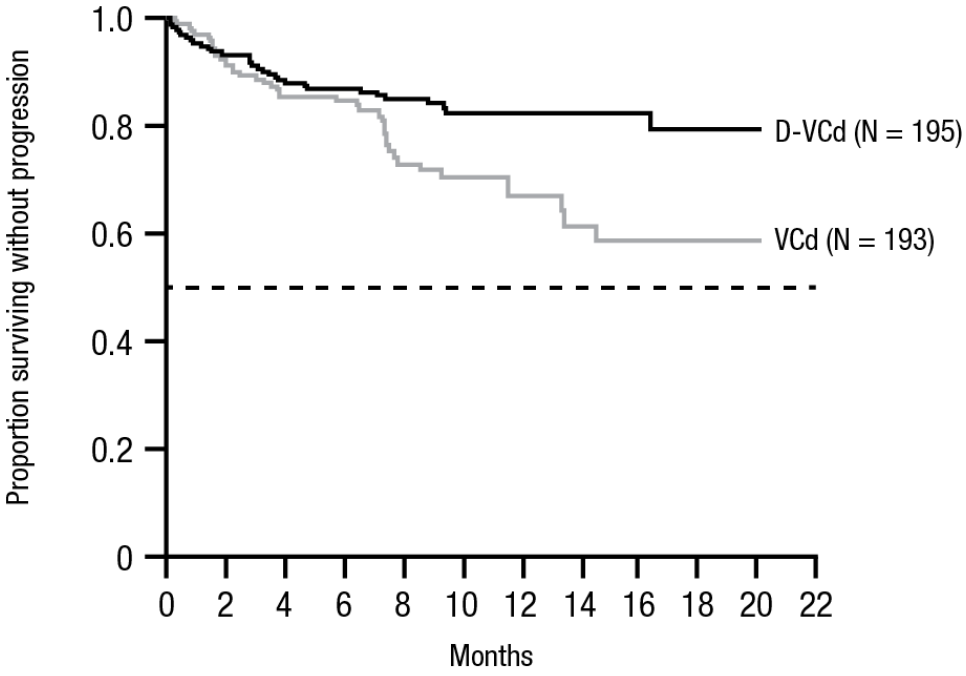
[d] Nominal p-value from inverse probability censoring weighted log-rank test

[e] n = number of subjects who had cardiac response at 6 months; N = number of subjects who were cardiac-evaluable for response

[f] n = number of subjects who had kidney response at 6 months; N = number of subjects who were renal-evalauble for response.

In responders, 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.

Figure 2: Weighted Kaplan-Meier Curve of MOD-PFS in Study AMY3001



The median follow-up for the study is 11.4 months. The median major organ deterioration progression-free survival (MOD-PFS) was not reached for patients in either arm. The median major organ deterioration event-free survival (MOD-EFS) was not reached for patients receiving D-VCd and was 8.8 months for patient receiving VCd. The hazard ratio for MOD-EFS was 0.39 (95 CI: 0.27, 0.56) and the nominal p-value was <0.0001. Overall survival (OS) data were not mature. A total of 56 deaths were observed [N=27 (13.8%) D-VCd vs. N=29 (15%) VCd group].

Patients treated with D-VCd reported clinically meaningful improvement in fatigue and Global Health Status compared with VCd at week 16 of treatment, assessed using EORTC QLQ-C30 (European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30-items). After 6 cycles of treatment, there were meaningful improvements in patients HRQoL (health-related quality of life) outcomes with continued daratumumab treatment. No adjustments were made for multiplicity.

Clinical experience with daratumumab intravenous formulation

Newly Diagnosed Multiple Myeloma Eligible for ASCT

Combination with bortezomib, thalidomide and dexamethasone in patients eligible for autologous stem cell transplant (ASCT)

Study MMY3006, an open-label, randomized, active-controlled Phase 3 study compared induction and consolidation treatment with IV daratumumab 16 mg/kg in combination with

bortezomib, thalidomide and dexamethasone (D-VTd) to treatment with bortezomib, thalidomide and dexamethasone (VTd) in patients with newly diagnosed multiple myeloma eligible for ASCT. The consolidation phase of treatment began a minimum of 30 days post-ASCT, when the patient had recovered sufficiently, and engraftment was complete.

Bortezomib was administered by subcutaneous (SC) injection or intravenous (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 28-day (4-week) induction treatment cycles (Cycles 1-4) and two consolidation cycles (Cycles 5 and 6) following ASCT after Cycle 4. Thalidomide was administered orally at 100 mg daily during the six bortezomib cycles. Dexamethasone (oral or intravenous) was administered at 40 mg on Days 1, 2, 8, 9, 15, 16, 22 and 23 of Cycles 1 and 2, and at 40 mg on Days 1-2 and 20 mg on subsequent dosing days (Days 8, 9, 15, 16) of Cycles 3-4. Dexamethasone 20 mg was administered on Days 1, 2, 8, 9, 15, 16 in Cycles 5 and 6. On the days of IV daratumumab infusion, the dexamethasone dose was administered intravenously as a pre-infusion medication. Dose adjustments for bortezomib, thalidomide and dexamethasone were applied according to manufacturer's prescribing information.

A total of 1085 patients were randomized: 543 to the D-VTd arm and 542 to the VTd arm. The baseline demographic and disease characteristics were similar between the two treatment groups. The median age was 58 (range: 22 to 65 years). The majority were male (59%), 48% had an ECOG performance score of 0, 42% had an ECOG performance score of 1 and 10% had an ECOG performance score of 2. Forty percent had ISS Stage I, 45% had ISS Stage II and 15% had ISS Stage III disease.

Efficacy was evaluated by the stringent Complete Response (sCR) rate at Day 100 post-transplant.

Table 22: Efficacy results from Study MMY3006[a]

	D-VTd (n=543)	**VTd (n=542)**	**P value[b]**
Response assessment Day 100 post-transplant			
Stringent Complete Response (sCR)	157 (28.9%)	110 (20.3%)	0.0010
CR or better (sCR+CR)	211 (38.9%)	141 (26.0%)	<0.0001
Very Good Partial Response or better (sCR+CR+VGPR)	453 (83.4%)	423 (78.0%)	
MRD negativity[c] n(%)	346 (63.7%)	236 (43.5%)	<0.0001
95% CI (%)	(59.5%, 67.8%)	(39.3%, 47.8%)	
Odds ratio with 95% CI[d]	2.27 (1.78, 2.90)		
MRD negativity[e] n(%)	183 (33.7%)	108 (19.9%)	<0.0001
95% CI (%)	(29.7%, 37.9%)	(16.6%, 23.5%)	
Odds ratio with 95% CI[d]	2.06 (1.56, 2.72)		

D-VTd=daratumumab-bortezomib-thalidomide-dexamethasone; VTd=bortezomib-thalidomide-dexamethasone; MRD=minimal residual disease; CI=confidence interval

[a] Based on intent-to-treat population

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

[c] Based on threshold of 10^{-5}

[d] Mantel-Haenszel estimate of the common odds ratio for stratified tables is used.

[e] Only includes patients who achieved MRD negativity (threshold of 10^{-5}) and CR or better

With a median follow-up of 18.8 months, the primary analysis of PFS in study MMY3006 demonstrated an improvement in PFS in the D-VTd arm as compared to the VTd arm; the median PFS had not been reached in either arm. Treatment with D-VTd resulted in a reduction in the risk of progression or death by 53% compared to VTd alone (HR=0.47; 95% CI: 0.33, 0.67; p<0.0001). Results of an updated PFS analysis after a median follow-up of 44.5 months continued to show an improvement in PFS for patients in the D-VTd arm compared with the VTd arm. Median PFS was not reached in the D-VTd arm and was 51.5 months in the VTd arm (HR=0.58; 95% CI: 0.47, 0.71; p<0.0001), representing a 42% reduction in the risk of disease progression or death in patients treated with D-VTd.

Newly Diagnosed Multiple Myeloma Ineligible for ASCT

Combination treatment with lenalidomide and dexamethasone in patients ineligible for autologous stem cell transplant

Study MMY3008 an open-label, randomized, active-controlled Phase 3 study, compared treatment with IV daratumumab 16 mg/kg in combination with lenalidomide and low-dose dexamethasone (D-Rd) to treatment with lenalidomide and low-dose dexamethasone (Rd) in patients with newly diagnosed multiple myeloma. Lenalidomide (25 mg once daily orally on Days 1-21 of repeated 28-day [4-week] cycles) was given 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). On IV daratumumab infusion days, the dexamethasone dose was given as a 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.

A total of 737 patients were randomized: 368 to the D-Rd arm and 369 to the Rd arm. The baseline demographic and disease characteristics were similar between the two treatment groups. The median age was 73 (range: 45-90) years, with 44% of the patients ≥75 years of age. The majority were white (92%), male (52%), 34% had an Eastern Cooperative Oncology Group (ECOG) performance score of 0, 50% had an ECOG performance score of 1 and 17% had an ECOG performance score of ≥2. Twenty-seven percent had International Staging System (ISS) Stage I, 43% had ISS Stage II and 29% had ISS Stage III disease. Efficacy was evaluated by progression free survival (PFS) based on IMWG criteria and overall survival (OS).

With a median follow-up of 28 months, the primary analysis of PFS in study MMY3008 demonstrated an improvement in the D-Rd arm as compared to the Rd arm; the median PFS had not been reached in the D-Rd 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 44% reduction in the risk of disease progression or death in patients treated with D-Rd. Results of an updated PFS analysis after a median follow-up of 56 months continued to show an improvement in PFS for patients in the DRd arm compared with the Rd arm. Median PFS was not reached in the DRd arm and 34.4 months in the Rd arm (HR=0.53; 95% CI: 0.43, 0.66; p<0.0001).

After a median follow-up of 56 months, D-Rd has shown an OS advantage over the Rd arm (HR=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 D-Rd arm. Median OS was not reached for either arm. The 60-month survival rate was 66% (95% CI: 61, 71) in the D-Rd arm and was 53% (95% CI: 47, 59) in the Rd arm.

In responders, the median time to response was 1.05 months (range: 0.2 to 12.1 months) in the D-Rd group and 1.05 months (range: 0.3 to 15.3 months) in the Rd group. The median duration of response had not been reached in the D-Rd group and was 34.7 months (95% CI: 30.8, not estimable) in the Rd group.

Additional efficacy results from Study MMY3008 are presented in Table 23 below.

Combination treatment with bortezomib, melphalan and prednisone (VMP) in patients ineligible for autologous stem cell transplant

Study MMY3007, an open-label, randomized, active-controlled Phase 3 study, compared treatment with IV daratumumab 16 mg/kg in combination with bortezomib, melphalan and prednisone (D-VMP), to treatment with VMP in patients with newly diagnosed multiple myeloma. Bortezomib was administered by subcutaneous injection at a dose of 1.3 mg/m^2 body surface area twice weekly at Weeks 1, 2, 4 and 5 for the first 6-week cycle (Cycle 1; 8 doses), followed by once weekly administrations at Weeks 1, 2, 4 and 5 for eight more 6-week cycles (Cycles 2-9; 4 doses per cycle). Melphalan at 9 mg/m^2, and prednisone at 60 mg/m^2 were orally administered on Days 1 to 4 of the nine 6-week cycles (Cycles 1-9). IV daratumumab treatment was continued until disease progression or unacceptable toxicity.

A total of 706 patients were randomized: 350 to the D-VMP arm and 356 to the VMP arm. The baseline demographic and disease characteristics were similar between the two treatment groups. The median age was 71 (range: 40-93) years, with 30% of the patients ≥75 years of age. The majority were white (85%), female (54%), 25% had an ECOG performance score of 0, 50% had an ECOG performance score of 1 and 25% had an ECOG performance score of 2. Patients had IgG/IgA/Light chain myeloma in 64%/22%/10% of instances, 19% had ISS Stage I, 42% had ISS Stage II and 38% had ISS Stage III disease. Efficacy was evaluated by PFS based on IMWG criteria and overall survival (OS).

With a median follow-up of 16.5 months, the primary analysis of PFS in study MMY3007 demonstrated an improvement 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 (HR=0.5; 95% CI: 0.38, 0.65; p<0.0001), representing 50% reduction in the risk of disease progression or death

in patients treated with D-VMP. Results of an updated PFS analysis after a median follow-up of 40 months continued to show an improvement in PFS for patients in the D-VMP arm compared with the VMP arm. Median PFS was 36.4 months in the D-VMP arm and 19.3 months in the VMP arm (HR=0.42; 95% CI: 0.34, 0.51; p<0.0001), representing a 58% reduction in the risk of disease progression or death in patients treated with D-VMP.

After a median follow-up of 40 months, D-VMP has shown an OS advantage 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 in the D-VMP arm. Median OS was not reached for either arm.

In responders, the median time to response was 0.79 months (range: 0.4 to 15.5 months) in the D-VMP group and 0.82 months (range: 0.7 to 12.6 months) in the VMP group. The median duration of response had not been reached in the D-VMP group and was 21.3 months (range: 18.4, not estimable) in the VMP group.

Additional efficacy results from Study MMY3007 are presented in Table 23 below.

Relapsed/Refractory Multiple Myeloma

Combination treatment with lenalidomide and dexamethasone

Study MMY3003, an open-label, randomized, active-controlled Phase 3 trial, compared treatment with IV daratumumab 16 mg/kg in combination with lenalidomide and low-dose dexamethasone (D-Rd) to treatment with lenalidomide and low-dose dexamethasone (Rd) in patients with multiple myeloma who had received at least one prior therapy. Lenalidomide (25 mg once daily orally on Days 1-21 of repeated 28-day [4-week] cycles) was given with low dose oral or intravenous dexamethasone 40 mg/week (or a reduced dose of 20 mg/week for patients >75 years or BMI <18.5). On IV daratumumab 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 IV daratumumab 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.

A total of 569 patients were randomized; 286 to the D-Rd arm and 283 to the Rd arm. The baseline demographic and disease characteristics were similar between the IV daratumumab 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 ASCT. The majority of patients (86%) received a prior PI, 55% of patients had received a prior IMiD, including 18% of patients who had received prior lenalidomide, and 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. Efficacy was evaluated by PFS based on IMWG criteria and overall survival (OS).

With a median follow-up of 13.5 months, the primary analysis of PFS in study MMY3003 demonstrated an improvement in the D-Rd arm as compared to the Rd arm; the median PFS had not been reached in the D-Rd arm and was 18.4 months in the Rd arm (HR=0.37; 95% CI: 0.27, 0.52; p<0.0001) representing 63% reduction in the risk of disease progression or death in patients treated with D-Rd. Results of an updated PFS analysis after a median follow-up of 55 months continued to show an improvement in PFS for patients in the D-Rd arm compared with the Rd arm. Median PFS was 45.0 months in the D-Rd arm and 17.5 months in the Rd arm (HR=0.44; 95% CI: 0.35, 0.54; p<0.0001), representing a 56% reduction in the risk of disease progression or death in patients treated with D-Rd.

After a median follow-up of 80 months, D-Rd has shown an OS advantage over the Rd arm (HR=0.73; 95% CI: 0.58, 0.91; p=0.0044), representing a 27% reduction in the risk of death in patients treated in the D-Rd arm. The median OS was 67.6 months in the D-Rd arm and 51.8 months in the Rd arm. The 78-month survival rate was 47% (95% CI: 41, 52) in the DRd arm and was 35% (95% CI: 30, 41) in the Rd arm.

Additional efficacy results from Study MMY3003 are presented in Table 23 below.

Combination treatment with bortezomib and dexamethasone

Study MMY3004, an open-label, randomized, active-controlled Phase 3 trial, compared treatment with IV daratumumab 16 mg/kg in combination with bortezomib and dexamethasone (D-Vd), to treatment with bortezomib and dexamethasone (Vd) in patients with multiple myeloma who had received at least one prior therapy. Bortezomib was administered by SC 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 was administered 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. On the days of IV daratumumab 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 IV daratumumab pre-infusion medication. Bortezomib and dexamethasone were given for 8 three-week cycles in both treatment arms; whereas IV daratumumab was given until treatment progression. However, dexamethasone 20 mg was continued as a IV daratumumab pre-infusion medication in the D-Vd arm. Dose adjustments for bortezomib and dexamethasone were applied according to manufacturer's prescribing information.

A total of 498 patients were randomized; 251 to the D-Vd arm and 247 to the Vd arm. The baseline demographic and disease characteristics were similar between the IV daratumumab 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 ASCT. Sixty-nine percent (69%) of patients had received a prior PI (66% received bortezomib) and 76%

of patients received an IMiD (42% received lenalidomide). 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, and 28% were refractory to lenalidomide. Efficacy was evaluated by PFS based on IMWG criteria and overall survival (OS).

With a median follow-up of 7.4 months, the primary analysis of PFS in study MMY3004 demonstrated an improvement in the D-Vd arm as compared to the Vd arm; the median PFS had not been reached in the D-Vd arm and was 7.2 months in the Vd arm (HR [95% CI]: 0.39 [0.28, 0.53]; p-value < 0.0001), representing a 61% reduction in the risk of disease progression or death for patients treated with D-Vd versus Vd. Results of an updated PFS analysis after a median follow-up of 50 months continued to show an improvement in PFS for patients in the D-Vd arm compared with the Vd arm. Median PFS was 16.7 months in the D-Vd arm and 7.1 months in the Vd arm (HR [95% CI]: 0.31 [0.24, 0.39]; p-value < 0.0001), representing a 69% reduction in the risk of disease progression or death in patients treated with D-Vd versus Vd.

After a median follow-up of 73 months, D-Vd has shown an OS advantage over the Vd arm (HR=0.74: 95% CI: 0.59, 0.92; p=0.0075), representing a 26% reduction in the risk of death in patients treated in the D-Vd arm. The median OS was 49.6 months in the D-Vd arm and 38.5 months in the Vd arm. The 72-month survival rate was 39% (95% CI: 33, 45) in the D-Vd arm and was 25% (95% CI: 20, 31) in the Vd arm.

Additional efficacy results from Study MMY3004 are presented in Table 23 below.

Table 23: Summary of efficacy result of randomized studies with IV daratumumab in multiple myeloma

	MMY3008		MMY3007		MMY3003		MMY3004	
	D-Rd n=368	**Rd n=369**	**D-VMP n=350**	**VMP n=356**	**D-Rd n=281[h]**	**Rd n=276[h]**	**D-Vd n=240[h]**	**Vd n=234[h]**
Progression-free survival (PFS) months								
Median[a]	NE	31.87	NE	18.14	NE	18.43	NE	7.16
Hazard ratio (95% CI)[b]	0.56 (0.43, 0.73)		0.50 (0.38, 0.65)		0.37 (0.27, 0.52)		0.39 (0.28, 0.53)	
P-value[c]	<0.0001		<0.0001		<0.0001		<0.0001	
Overall response (sCR+CR+VGPR+PR) n(%)[d]	342 (92.9%)	300 (81.3%)	318 (90.9%)	263 (73.9%)	261 (92.9%)	211 (76.4%)	199 (82.9%)	148 (63.2%)
P-value[e]	<0.0001		<0.0001		<0.0001		<0.0001	
Stringent complete response (sCR)	112 (30.4%)	46 (12.5%)	63 (18.0%)	25 (7.0%)	51 (18.1%)	20 (7.2%)	11 (4.6%)	5 (2.1%)
Complete response (CR)	63 (17.1%)	46 (12.5%)	86 (24.6%)	62 (17.4%)	70 (24.9%)	33 (12.0%)	35 (14.6%)	16 (6.8%)
Very good partial response (VGPR)	117 (31.8%)	104 (28.2%)	100 (28.6%)	90 (25.3%)	92 (32.7%)	69 (25.0%)	96 (40.0%)	47 (20.1%)
Partial response (PR)	50 (13.6%)	104 (28.2%)	69 (19.7%)	86 (24.2%)	48 (17.1%)	89 (32.2%)	57 (23.8%)	80 (34.2%)
MRD negative rate (95% CI)[f] (%)	89 (24.2%)	27 (7.3%)	78 (22.3%)	22 (6.2%)	60 (21.0%)	8 (2.8%)	22 (8.8%)	3 (1.2%)
95% CI	(19.9%, 28.9%)	(4.9%, 10.5%)	(18.0%, 27.0%)	(3.9%, 9.2%)	(16.4%, 26.2%)	(1.2%, 5.5%)	(5.6%, 13.0%)	(0.3%, 3.5%)
P-value[g]	<0.0001		<0.0001		<0.0001		0.0001	

Key: NE=not estimable; D=intravenous daratumumab, Rd=lenalidomide-dexamethasone; VMP=bortezomib-melphalan-prednisone; Vd=bortezomib-dexamethasone. MRD=minimal residual disease; CI=confidence interval

[a] Kaplan-Meier estimate based on intent-to-treat population

[b] Hazard ratio estimate is based on a Cox proportional-hazard model adjusted for stratification factors

[c] p-value based on the stratified log-rank test adjusted for stratification factors

[d] Based on intent-to-treat population for MMY3008 and MMY3007 studies. Based on response evaluable population for MMY3003 and MMY3004 studies.

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

[f] MRD Negative rate is based on the intent-to-treat population and a threshold of 10^{-5}

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

[h] Response evaluable population

Combination treatment with pomalidomide and dexamethasone

Study MMY1001 was an open-label trial in which 103 patients with multiple myeloma who had received a prior PI and an IMiD, received IV daratumumab 16 mg/kg in combination with pomalidomide and low-dose dexamethasone until disease progression. Pomalidomide (4 mg once daily orally on Days 1-21 of repeated 28-day [4-week] cycles) was given with low dose oral or intravenous dexamethasone at 40 mg/week (reduced dose of 20 mg/week for patients >75 years or BMI <18.5). On IV daratumumab 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 IV daratumumab pre-infusion medication.

The median patient age was 64 years (range: 35 to 86 years) with 8% of patients ≥75 years of age. Patients in the study had received a median of 4 prior lines of therapy. Seventy-four percent (74%) of patients had received prior ASCT. Ninety eight percent (98%) of patients received prior bortezomib treatment, and 33% of patients received prior carfilzomib. All patients received prior lenalidomide treatment, with 98% of patients previously treated with the combination of bortezomib and lenalidomide. Eighty nine percent (89%) of patients were refractory to lenalidomide and 71% refractory to bortezomib; 64% of patients were refractory to bortezomib and lenalidomide.

Overall response rate was 59% (95% CI: 49.1%, 68.8%); VGPR or better was achieved in 42% of patients, CR or better was achieved in 14% of patients and stringent CR was achieved in 8% of patients. The Clinical Benefit Rate (ORR+ MR [Minimal response]) was 62% (95% CI: 52.0, 71.5). The median time to response was 1 month (range: 0.9 to 2.8 months). The median duration of response was 13.6 months (95% CI: 10.0, not estimable). After a median duration of follow-up of 9.8 months, the median OS was not reached. The 12-month survival rate was 72%.

Pharmacokinetic Properties

Daratumumab exposure in a monotherapy study (MMY3012) in patients with multiple myeloma following the recommended 1800 mg administration of DARZALEX® SC formulation (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 ± 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).

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 formulation as monotherapy, 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 formulation are typically observed at the end of the weekly dosing regimens for both monotherapy and combination therapy.

In patients with multiple myeloma, the simulated trough concentrations following 6 weekly doses of 1800 mg DARZALEX® SC for combination therapy were similar to 1800 mg DARZALEX® SC monotherapy.

In patients with multiple myeloma, daratumumab exposure in a combination study with pomalidomide and dexamethasone (MMY3013) was similar to that in monotherapy, with the maximum C_{trough} (Cycle 3 Day 1 pre-dose) mean ± SD of 537±277 µg/mL following the recommended 1800 mg administration of DARZALEX® SC formulation (weekly for 8 weeks, biweekly for 16 weeks, monthly thereafter).

In a combination study, AMY3001, in patients with AL amyloidosis, the maximum C_{trough} (Cycle 3 Day 1 pre-dose) was similar to that in multiple myeloma with mean ± SD of 597 ± 232 µg/mL following the recommended 1800 mg administration of DARZALEX® SC formulation (weekly for 8 weeks, biweekly for 16 weeks, monthly thereafter).

Absorption and Distribution

At the recommended dose of 1800 mg in multiple myeloma patients, the absolute bioavailability of DARZALEX® SC formulation 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 was not estimated, the absorption rate constant was 0.77 day^{-1} (8.31% CV) and peak concentrations occurred at 3 days.

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, and 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. In AL amyloidosis patients, the model estimated apparent volume of distribution after SC administration is 10.8L (3.1% CV). These results suggest that daratumumab is primarily localized to the vascular system with limited extravascular tissue distribution.

Metabolism and Elimination

Daratumumab is cleared by parallel linear and nonlinear saturable target mediated clearances. In multiple myeloma patients, the population PK model estimated mean clearance value of daratumumab is 4.96 mL/h (58.7% CV) in daratumumab monotherapy and 4.32 mL/h (43.5% CV) when daratumumab was administered in combination with pomalidomide and

dexamethasone. In AL amyloidosis patients, the apparent clearance after SC administration is 210mL/day (4.1% CV)..

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 and 19.7 days (15.3% CV) when daratumumab was administered in combination with pomalidomide and dexamethasone. In AL amyloidosis patients, the model-based geometric mean post hoc estimate for half-life associated with linear elimination is 27.5 days (74.0% CV). 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).

A population PK analysis, using data from DARZALEX® SC formulation monotherapy and combination therapy in multiple myeloma patients, was conducted with data from 487 patients who received DARZALEX® SC formulation and 255 patients who received IV daratumumab. The predicted PK exposures are summarized in Table 24.

Table 24: Daratumumab exposure following administration of DARZALEX® SC (1,800 mg) or IV daratumumab (16 mg/kg) monotherapy in patients with multiple myeloma

PK parameters	Cycles	SC daratumumab Median (5^{th}; 95^{th} percentile)	IV daratumumab Median (5^{th}; 95^{th} percentile)
C_{trough} (µg/mL)	Cycle 1, 1st weekly dose	123 (36; 220)	112 (43; 168)
	Cycle 2, last weekly dose (Cycle 3 Day 1 Ctrough)	563 (177; 1063)	472 (144; 809)
C_{max} (µg/mL)	Cycle 1, 1st weekly dose	132 (54; 228)	256 (173; 327)
	Cycle 2, last weekly dose	592 (234; 1114)	688 (369; 1061)
$AUC_{0\text{-}7\ days}$ (µg/mL•day)	Cycle 1, 1st weekly dose	720 (293; 1274)	1187 (773; 1619)
	Cycle 2, last weekly dose	4017 (1515; 7564)	4019 (1740; 6370)

A population PK analysis, using data from DARZALEX® SC formulation combination therapy in AL amyloidosis patients, was conducted with data from 211 patients. At the recommended dose of 1,800 mg, predicted daratumumab concentrations were slightly higher, but generally within the same range, in comparison with multiple myeloma patients.

Table 25: Daratumumab exposure following administration of DARZALEX® (1,800 mg) in patients with AL amyloidosis

PK parameters	Cycles	SC daratumumab Median (5^{th}; 95^{th} percentile)
C_{trough} (µg/mL)	Cycle 1, 1st weekly dose	138 (86; 195)
	Cycle 2, last weekly dose (Cycle 3 Day 1 Ctrough)	662 (315; 1037)
C_{max} (µg/mL)	Cycle 1, 1st weekly dose	151 (88; 226)
	Cycle 2, last weekly dose	729 (390; 1105)
$AUC_{0\text{-}7\ days}$ (µg/mL•day)	Cycle 1, 1st weekly dose	908 (482; 1365)
	Cycle 2, last weekly dose	4855 (2562; 7522)

Special populations

Age and gender

Based on population PK analyses in patients (33-92 years) receiving monotherapy or various combination therapies, age had no statistically significant effect on the PK of daratumumab. No individualization is necessary for patients on the basis of age.

Gender had a statistically significant effect on PK parameter in patients with multiple myeloma but not in patients with AL amyloidosis. Slightly higher exposure in females were observed than males, but the difference in exposure is not considered clinically meaningful. No individualization is necessary for patients on the basis of gender.

Renal impairment

No formal studies of DARZALEX® SC formulation 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® monotherapy or various combination therapies in patients with multiple myeloma or AL amyloidosisand no clinically important differences in exposure to daratumumab were observed between patients with renal impairment and those with normal renal function.

Hepatic impairment

No formal studies of DARZALEX® SC formulation in patients with hepatic impairment have been conducted. Population PK analyses were performed in patients with multiple myeloma receiving DARZALEX® SC formulation monotherapy or various combination therapies in patients with multiple myeloma or in AL amyloidosis. No clinically important differences in the exposure to daratumumab 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.

Race

Based on the population PK analyses in patients receiving either DARZALEX® SC formulation monotherapy or various combination therapies, the daratumumab exposure was similar across races.

Body weight

The flat dose administration of DARZALEX® SC formulation 1800 mg as monotherapy achieved adequate exposure for all body-weight subgroups. In patients with multiple myeloma, the mean Cycle 3 Day 1 C_{trough} in the lower body-weight subgroup (≤65 kg) was 60% higher and in the higher body weight (>85 kg) subgroup, 12% lower than the IV daratumumab subgroup.

However, no body weight-based dose adjustments are needed, as the exposure changes are not considered clinically relevant.

In patients with AL amyloidosis, no meaningful differences were observed in C_{trough} across body weight.

NON-CLINICAL INFORMATION

Carcinogenicity and Mutagenicity

No animal studies have been performed to establish the carcinogenic potential of daratumumab. Routine genotoxicity and carcinogenicity studies are generally not applicable to biologic pharmaceuticals as large proteins cannot diffuse into cells and cannot interact with DNA or chromosomal material.

Reproductive Toxicology

No animal studies have been performed to evaluate the potential effects of daratumumab on reproduction or development.

No systemic exposure of hyaluronidase was detected in monkeys given 22,000 U/kg subcutaneously (12 times higher than the human dose) 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.

Fertility

No animal studies have been performed to determine potential effects on fertility in males or females.

PHARMACEUTICAL INFORMATION

List of Excipients

Recombinant human hyaluronidase (rHuPH20), L-histidine, L-histidine hydrochloride monohydrate, L-methionine, polysorbate 20, sorbitol, water for injection

Incompatibilities

This medicinal product should only be used with the materials mentioned in section *Dosage and Administration.*

Shelf Life

Unopened vials:
See expiry date on the outer pack.

Shelf life 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 7 hours at 15°C–30°C (59°F–86°F) and ambient light. Discard if stored more than 24 hours of being refrigerated or more than 7 hours of being at 15°C–30°C (59°F–86°F), if not used. If stored in the refrigerator, allow the solution to come to ambient temperature before administration.

Storage Conditions

Keep out of the sight and reach of children.

Store DARZALEX® SC in a refrigerator [2°C–8°C (36°F–46°F)] and equilibrate to ambient temperature [15°C–30°C (59°F–86°F)] 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. Do not freeze.

For storage conditions of the prepared syringe, see *Shelf-life*.

Nature and Contents of Container

The primary packaging consists of a 25R Type 1 glass vial closed with a fluoropolymer coated 20-mm stopper and a 20-mm aluminum seal with a flip-off cap. Pack size of 1 vial.

Batch Releaser

Cilag AG, Hochstrasse 201
8200 Schaffhausen, Switzerland

Product Registrant

Johnson & Johnson International (Singapore) Pte. Ltd.
2 Science Park Drive
#07-13, Ascent,
Singapore Science Park 1
Singapore 118222

Last Date of Revision of Text

02 March 2023 (CCDS 23 March 2022)