DARZALEX® SC

daratumumab

NEW ZEALAND DATA SHEET

1 PRODUCT NAME

DARZALEX SC (daratumumab) 1800 mg/15 mL solution for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

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 (synonyms: hyaluronidase, vorhyaluronidase alfa, rHuPH20) 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. It is a glycosylated single-chain protein with an approximate molecular weight of 61 kD.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

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

4 CLINICAL PARTICULARS

4 .1 THERAPEUTIC INDICATIONS

DARZALEX SC is indicated for the treatment of adult patients (18 years and over):

- with newly diagnosed multiple myeloma:
  - who are eligible for autologous stem cell transplant. For use in combination with:
    - bortezomib, thalidomide, and dexamethasone.
  - who are ineligible for autologous stem cell transplant. For use in combination with:
    - bortezomib, melphalan and prednisone, or
    - lenalidomide and dexamethasone.
- with multiple myeloma who have received:
  - at least one prior therapy. For use in combination with:
    - bortezomib and dexamethasone, or
    - lenalidomide and dexamethasone.

- at least three prior lines of therapy including a proteasome inhibitor (PI) and an immunomodulatory agent or who are refractory to both a PI and an immunomodulatory agent. For use as:
    - monotherapy.

4.2 DOSE AND METHOD OF ADMINISTRATION

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

DARZALEX SC should be administered by a healthcare professional.

Before DARZALEX SC therapy is commenced, clinicians should arrange for extended red cell phenotyping of patients (see 4.4 Special warnings and precautions for use – Effect on laboratory tests).

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

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

Substitution by any other biological medicinal product requires the consent of the prescribing physician.

Dose

Adults (≥ 18 years)

Recommended dose

DARZALEX SC with VTd combination therapy (4-week cycle dosing regimen)

The DARZALEX SC dosing schedule in Table 1 is for combination therapy with bortezomib, thalidomide and dexamethasone (4-week cycle regimens) for treatment of newly diagnosed 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 1: DARZALEX SC dosing schedule in combination with bortezomib, thalidomide and dexamethasone ([D-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

Bortezomib is given twice weekly in the four 4-week induction cycles (for a total of 32 doses) followed by twice weekly in the two 4-week consolidation cycles post ASCT (for a total of 16 doses). For dosing instructions of medicinal products administered with DARZALEX SC, see section 5.1 and manufacturer's Data Sheet.

DARZALEX SC with VMP combination therapy (6-week cycle dosing regimen)

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 ([D-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 (8 doses), followed by **once** weekly at Weeks 1, 2, 4 and 5 for eight additional 6-week cycles (32 additional doses for a total of 40 doses). For information on the VMP dose and dosing schedule when administered with DARZALEX SC, see section 5.1.

DARZALEX SC with Vd combination therapy (3-week cycle dosing regimen)

The DARZALEX SC dosing schedule in Table 3 is for combination therapy with 3-week cycle regimen (bortezomib and dexamethasone) 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 3: DARZALEX SC dosing schedule in combination with bortezomib and dexamethasone ([D-Vd]; 3-week cycle dosing regimen)

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 section 5.1 and manufacturer's Data Sheet.

DARZALEX SC with Rd combination therapy or DARZALEX SC monotherapy ([4-week cycle dosing regimens)

The DARZALEX SC dosing schedule in Table 4 is for combination therapy with 4-week cycle regimens (e.g. lenalidomide) 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 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 4: DARZALEX SC dosing schedule in combination with lenalidomide and low-dose dexamethasone or monotherapy ([D-Rd] or monotherapy; 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 section 5.1 and manufacturer's Data Sheet.

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 SC 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 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 section 5.1).

  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 (oral paracetamol 500 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 section 5.1).

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.

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 haematological toxicity (see section 4.4). For information concerning medicinal products given in combination with DARZALEX SC, see manufacturer's Data Sheet.

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

Special populations

Paediatrics (17 years of age and younger)

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

Elderly (65 years of age and older)

No dose adjustments are considered necessary in elderly patients (see section 4.8 and 5.2).

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 section 5.2).

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. Based on population PK analyses, no dosage adjustments are necessary for patients with hepatic impairment) (see section 5.2).

Method of 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 SC for subcutaneous injection and not intravenous daratumumab. DARZALEX SC 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) and equilibrate to ambient temperature (15°C–30°C). The unpunctured vial may be stored at ambient temperature and ambient light for a maximum of 24 hours. Keep out of direct sunlight. Do not shake.
- Prepare the dosing syringe in 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.

Storage of prepared syringe

- If the syringe containing DARZALEX SC is not used immediately, store the DARZALEX SC solution for up to 4 hours at ambient temperature and ambient light.

Instructions for use

- Inject 15 mL DARZALEX SC into the subcutaneous tissue of the abdomen approximately 7.5 cm to the right or left of the navel (umbilicus) 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.

4.3 CONTRAINDICATIONS

Patients with a history of severe hypersensitivity (e.g. anaphylactic reaction) to daratumumab or to any of the excipients listed in section 6.1.

Before starting therapy, refer to the Data Sheet for medicinal products used in combination with DARZALEX SC.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Before starting combination therapy, also refer to the Data Sheet for relevant other medicines (bortezomib, lenalidomide, thalidomide, dexamethasone, as appropriate).

Patients receiving DARZALEX SC in combination with lenalidomide and dexamethasone or thalidomide and dexamethasone should adhere to the pregnancy prevention programmes of lenalidomide or thalidomide (see also section 4.6).

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 section 4.8). IRRs occurring with subsequent injections were seen in less than 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 less than 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, and hypotension. Severe reactions have occurred, including bronchospasm, hypoxia, dyspnea, hypertension and tachycardia (see section 4.8).

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 IRRs, pre-medicate patients with antihistamines, antipyretics and corticosteroids. The risk of delayed IRRs can be reduced with the administration of post-injection 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 (see section 4.2).

Neutropenia/Thrombocytopenia

Daratumumab may increase neutropenia and thrombocytopenia induced by background therapy (see section 4.8).

Monitor complete blood cell counts periodically during treatment. This should be done as per clinical judgment but not less frequently than as prescribed in the Data Sheet 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 (≤65kg) receiving DARZALEX SC subcutaneous formulation, 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.

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.

Use in the Elderly

No overall differences in safety or effectiveness were observed between older (≥ 65 years) and younger patients.

No dose adjustments are considered necessary (see section 5.2).

Paediatric Use

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

Effect on laboratory tests

Interference with indirect antiglobulin test (indirect Coombs test)

Daratumumab binds to CD38 found at low levels on red blood cells (RBCs) and may result in a positive indirect Coombs test. Daratumumab-mediated positive indirect Coombs test may persist for up to 6 months after the last daratumumab infusion. 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 centres of this interference with indirect antiglobulin tests (see section 4.5). If an emergency transfusion is required, non-cross-matched ABO/RhD-compatible RBCs can be given per local blood bank practices.

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 section 4.5). This interference can affect the determination of complete response and of disease progression in some patients with IgG kappa myeloma protein.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

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 of daratumumab in combination with lenalidomide, pomalidomide, thalidomide, bortezomib 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 (see section 4.4).

Interference with serum protein electrophoresis and immunofixation tests

Daratumumab may be detected on serum protein electrophoresis (SPE) and immunofixation (IFE) assays used for monitoring disease monoclonal immunoglobulins (M protein). This can lead to false positive SPE and IFE assay results for patients with IgG kappa myeloma protein impacting initial assessment of complete responses by International Myeloma Working Group (IMWG) criteria. In patients with persistent very good partial response, consider other methods to evaluate the depth of response.

4.6 FERTILITY, PREGNANCY AND LACTATION

Fertility

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

Pregnancy

Category C

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 foetus. If the patient becomes pregnant while taking this drug, the patient should be informed of the potential risk to the foetus.

To avoid exposure to the foetus, women of reproductive potential should use effective contraception during and for 3 months after cessation of DARZALEX SC treatment. However, when DARZALEX SC is used in combination with lenalidomide and dexamethasone or thalidomide and dexamethasone, patients must also follow advice about use in pregnancy of those products – see below.

Use of DARZALEX SC with lenalidomide or thalidomide

Lenalidomide and thalidomide (both Pregnancy Category X) are associated with risk of foetal harm, including severe life-threatening human birth defects. Refer to the lenalidomide and thalidomide Data Sheets for additional information. Patients (both male and female) receiving DARZALEX SC in combination with lenalidomide and dexamethasone, or thalidomide and dexamethasone, should adhere to the pregnancy prevention programme of these medicines.

Use in lactation

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.

4.7 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.

4.8 UNDESIRABLE EFFECTS

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.

The safety data of DARZALEX SC (subcutaneous 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 (subcutaneous formulation) as monotherapy and three open-label, clinical trials in which patients received DARZALEX SC (subcutaneous formulation) either as monotherapy (N=31; MMY1004 and MMY1008) and MMY2040 in which patients received DARZALEX SC (subcutaneous formulation) in combination with either bortezomib, melphalan and prednisone (D-VMP, n=67), lenalidomide and dexamethasone (D-Rd, n=65) or bortezomib, lenalidomide and dexamethasone (D-VRd, n=67) or carfilzomib and dexamethasone (D-Kd, n=66).

MMY3012, a Phase 3 randomized, study compared treatment with DARZALEX SC (subcutaneous formulation 1800 mg) vs. intravenous (16 mg/kg) daratumumab in patients with relapsed or refractory multiple myeloma. The median DARZALEX SC (subcutaneous formulation) treatment duration was 5.5 months (range: 0.03 to 19.35 months) and 6.0 months (range: 0.03 to16.69 months) for intravenous daratumumab. The most common adverse reactions of any grade (≥20% patients) with DARZALEX SC (subcutaneous formulation) were upper respiratory tracts infections. Pneumonia was the only serious adverse reaction occurring in ≥ 5% of patients (6% IV vs. 6% SC).

Table 5 below lists the adverse reactions that occurred in patients who received DARZALEX SC (subcutaneous formulation) or intravenous daratumumab in Study MMY3012.

Table 5: 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						
Diarrhoea	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
Dyspnoea[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] Dyspnoea, Dyspnoea exertional

[e] Blood pressure increased, Hypertension

Laboratory abnormalities worsening during treatment from baseline are listed in Table 6.

Table 6: Treatment-emergent haematology 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 (%)
Anaemia	43	15	0	41	17	0
Thrombocytopenia	45	12	4	47	7	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.

MMY2040 was an open-label trial of DARZALEX SC (subcutaneous 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, and in combination with bortezomib, lenalidomide, 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 (subcutaneous formulation) were constipation, diarrhoea, nausea, vomiting, pyrexia, fatigue, asthenia, upper respiratory tract infection, pneumonia, back pain, muscle spasms, peripheral sensory neuropathy, insomnia, cough, hypertension, headache, oedema peripheral and dyspnoea. 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 7 below lists the adverse reactions that occurred in patients who received DARZALEX SC (subcutaneous formulation) in Study MMY2040.

Table 7: Adverse reactions (≥ 10%) in any treatment arm in studyMMY2040

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
Diarrhoea	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
Oedema 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
Hyperglycaemia	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
Dyspnoea[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] Generalised oedema,Oedema, Oedema 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] Dyspnoea, Dyspnoea exertional
[g] Blood pressure increased, Hypertension

Laboratory abnormalities worsening during treatment from baseline are listed in Table 8.

Table 8: Treatment-emergent haematology 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	86	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.

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 9 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 9 reflect exposure to IV daratumumab up to day 100 post-transplant in a Phase 3 active-controlled study MMY3006 (see section 5.1 Pharmacodynamic properties, 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, diarrhoea, constipation, decreased appetite, vomiting, muscle spasms, arthralgia, back pain, chills, pyrexia, dizziness, insomnia, cough, dyspnoea, peripheral oedema, 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 oedema, influenza, pyrexia, dehydration, diarrhoea, and atrial fibrillation.

Table 9: 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
Hyperglycaemia	14	8	6	4	1	2	9	7	9	8
Hypocalcaemia	14	9	6	5	1	2	6	4	4	5
Nervous system disorders										
Headache	19	11	7	4	8	8	13	7	10	6
Paraesthesia	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
Dyspnoea[g]	32	20	13	5	19	16	21	12	21	11
Pulmonary oedema[h]	1	0	2	<1	0	<1	2	1	0	1
Gastrointestinal disorders										
Constipation	41	36	18	18	51	49	29	25	20	16
Diarrhoea	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
Oedema 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 haemophilus, 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] Dyspnoea, Dyspnoea exertional

[h] Pulmonary congestion, Pulmonary oedema

[i] Generalized oedema, Gravitational oedema, Oedema, Oedema peripheral, Peripheral swelling

Laboratory abnormalities worsening during IV daratumumab combination treatment trials are listed in Table 10.

Table 10: Treatment-emergent haematology laboratory abnormalities (any grade) in IV daratumumab studies

	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
Anaemia	47	57	47	50	36	35	52	57	48	56
Thrombocytopenia	67	58	88	88	81	58	73	67	90	85
Neutropenia	91	77	86	87	63	41	92	87	58	40
Lymphopenia	84	75	85	83	95	91	95	87	89	81
Leukopenia	90	82	94	94	82	57	92	81	72	48

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

Infusion-related reactions

In clinical trials (monotherapy and combination treatments; N=898 with DARZALEX SC subcutaneous formulation, the incidence of any grade infusion-related reactions was 8.2% with the first injection of DARZALEX SC subcutaneous 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, dyspnoea, hypertension and tachycardia.

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 receiving daratumumab monotherapy, the overall incidence of infections was similar between DARZALEX SC subcutaneous formulation (52.9%) and IV daratumumab groups (50.0%). Grade 3 or 4 infections also occurred at similar frequencies between DARZALEX SC subcutaneous 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 4infection 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 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-week
- Newly 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%

Other Adverse Reactions

Other adverse reactions reported in patients treated with daratumumab in clinical trials are listed in Table 11.

Table 11: 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%)
Nervous system disorders	Syncope (2%)
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

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.

Postmarketing data

Adverse reactions identified during postmarketing experience with daratumumab are included in Table 11. 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 11, adverse reactions are presented by frequency category based on spontaneous reporting rates.

Table 11: 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 Hepatitis B virus reactivation	Rare

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/.

4.9 OVERDOSE

Symptoms and signs

There has been no experience of overdosage in clinical studies with DARZALEX SC.

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.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Antineoplastic agents, monoclonal antibodies, ATC code: L01XC24.

DARZALEX SC subcutaneous formulation contains hyaluronidase. Hyaluronidase 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 at a high level on the surface of cells in a variety of haematological malignancies, including multiple myeloma tumour cells, as well as other cell types and tissues at various levels. CD38 protein has multiple functions such as receptor mediated adhesion, signalling and enzymatic activity.

Daratumumab has been shown to inhibit the *in vivo* growth of CD38-expressing tumour cells. Based on *in vitro* studies, daratumumab may utilize multiple effector functions, resulting in immune mediated tumour cell death. These studies suggest that daratumumab can induce tumour 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 tumour 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

The incidence of treatment-emergent anti-daratumumab antibodies for DARZALEX SC subcutaneous formulation treatment was low, with 1 out of 451 patients (0.2%) testing positive for anti-drug antibodies. The 1 patient in monotherapy that was positive for anti-daratumumab antibody also had transient neutralizing antibodies. There were no treatment-emergent anti-daratumumab antibody positive patients in the combination therapies study. The anti-daratumumab antibodies and neutralizing antibodies did not appear to impact daratumumab exposures.

The incidence of treatment-emergent non-neutralizing anti-rHuPH20 antibodies was 7.8% (35/447); with 7.5% (19/255) in the monotherapy DARZALEX SC groups, and 8.3% (16/187192) in the pooled combination DARZALEX SC groups. 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 SC 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.

Cardiac electrophysiology

Daratumumab as a large protein has a low likelihood of direct ion channel interactions. The effect of daratumumab on the QTc interval was evaluated in an open-label study for 83 patients (Study GEN501) with relapsed and refractory multiple myeloma following daratumumab infusions (4 to 24 mg/kg). Linear mixed PK-PD analyses indicated no large increase in mean QTcF interval (i.e., greater than 20ms) at daratumumab C_{max}. The mean time-averaged QTcF interval increase was 10.1 ms (n=3) and 4.3 ms (n=42) in the 16 mg/kg cohorts from these analyses.

Clinical efficacy and safety

Clinical experience with DARZALEX SC 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 SC 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 proteasome inhibitor (PI) and an immunomodulatory agent (IMiD) or who were double-refractory to a proteasome inhibitor and an immunomodulatory agent. Treatment continued until unacceptable toxicity or disease progression.

A total of 522 patients were randomized: 263 to the DARZALEX SC subcutaneous 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 autologous stem cell transplant (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 subcutaneous 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 section 5.2 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 subcutaneous 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 subcutaneous formulation is non-inferior to IV daratumumab in terms of ORR and maximum trough concentration. The results are provided in Table 12.

Table 12: 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.

Safety and tolerability results, including in lower weight patients, were consistent with the known safety profile for DARZALEX SC subcutaneous 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 SC subcutaneous formulation had greater satisfaction with their therapy compared with patients receiving IV daratumumab.

Combination therapies in multiple myeloma

MMY2040 was an open-label trial evaluating the efficacy and safety of DARZALEX SC subcutaneous 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 (SC) 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 subcutaneous formulation was continued until disease progression or unacceptable toxicity.

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 SC subcutaneous formulation was continued until disease progression or unacceptable toxicity.

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 autologous stem cell transplantation (ASCT). The majority of patients (95%) received prior PI, 59% received a prior Immunomodulatory Agent including 22% who received prior lenalidomide. 54% of patients received both a prior PI and Immunomodulatory Agents.

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.

A total of 199 patients (D-VMP: 67; D-Rd:65; D-VRd:67) were enrolled. Efficacy results were determined by computer algorithm using IMWG criteria. Primary endpoints ORR for D-VMP and D-Rd and VGPR or better for D-VRd were met (see Table 13).

Table 13: Efficacy results from Study MMY2040

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

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

[a] Based on treated subjects

Clinical experience with daratumumab intravenous formulation

Newly diagnosed multiple myeloma eligible for ASCT

Combination treatment with bortezomib, thalidomide and dexamethasone (VTd) 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 (DVTd) 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, 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 the manufacturer's Data Sheet.

Table 14: Dosage regimen in treatment with bortezomib, thalidomide and dexamethasone

	Induction Phase		**Consolidation Phase**
	Weeks 1-8	**Weeks 9-16**	**Weeks 1-8 (starting minimum of 30 days post-transplant)**
Daratumumab	16 mg/kg IV Weekly for two 4-week induction cycles (total of 8 doses)	16 mg/kg IV Every 2 weeks for two 4-week induction cycles (total of 4 doses)	16 mg/kg IV Every 2 weeks for two 4-week consolidation cycles (total of 4 doses)
Bortezomib	1.3 mg/m^2 SC[a] Days 1, 4, 8, 11 in each of the four 4-week cycles (total of 16 doses)		1.3 mg/m^2 SC[a] Days 1, 4, 8, 11 of the two 4-week cycles (total of 8 doses)
Thalidomide	100 mg oral Daily in each cycle		
Dexamethasone[b, c]	40 mg oral or IV Days 1, 2, 8, 9, 15, 16, 22, 23	40 mg oral or IV Days 1, 2 and 20 mg oral or IV Days 8, 9, 15, 16	20 mg oral or IV Days 1, 2, 8, 9, 15, 16

[a] Bortezomib was administered SC; or IV if injection site reactions were encountered.
[b] Dexamethasone reduced dose of 20 mg/week for patients >75 years or body mass index [BMI] <18.5
[c] On DARZALEX infusion days, 20 mg of the dexamethasone dose was given as a pre-infusion medication and the remainder given the day after the infusion. For patients on a reduced dexamethasone dose, the entire 20 mg dose was given as a DARZALEX pre-infusion medication.

A total of 1085 patients were randomized: 543 to the DVTd 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 Eastern Cooperative Oncology Group (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 15: Efficacy results from Study MMY3006[a]

	DVTd (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; HR = Hazard Ratio

[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

Study MMY3006 demonstrated an improvement in Progression Free Survival (PFS) in the DVTd arm as compared to the VTd arm; with a median follow up of 18.8 months, the median PFS had not been reached in either arm. Treatment with DVTd 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).

Newly Diagnosed Multiple Myeloma Ineligible for ASCT

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 (SC) 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 additional 6-week cycles (Cycles 2-9; 4 doses per cycle). Melphalan at 9 mg/m2, and prednisone at 60 mg/m2 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.

Table 16: Dosage regimen in combination treatment with bortezomib, melphalan and prednisone

	Weeks 1-6	**Weeks 7-54**	**Weeks 55 onwards until disease progression**
Daratumumab	16 mg/kg IV Weekly (total of 6 doses)	16 mg/kg IV Every 3 weeks (total of 16 doses)[a]	16 mg/kg IV Every 4 weeks[b]
Bortezomib	1.3 mg/m^2 SC Twice weekly Weeks 1, 2, 4 and 5 of the first 6-week cycle	1.3 mg/m^2 SC Once weekly Weeks 1, 2, 4 and 5 of each repeated 6-week cycle	-
Melphalan	9 mg/m^2 oral Days 1-4 of each repeated 6- week cycle		-
Prednisone	60 mg/m^2 oral Days 1-4 of each repeated 6- week cycle		-

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

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

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% and 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.

Study MMY3007 demonstrated an improvement in PFS in the D-VMP arm as compared to the VMP arm; the median PFS had not been reached in the D-VMP arm and was 18.1 months in the VMP arm (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.

With an overall median overall follow-up of 16.5 months, the OS data were not yet mature, consistent with what is expected in this newly diagnosed patient population. Ninety-three (93) deaths were observed (45 subjects [13%] in the D-VMP group and 48 subjects [14%] in the VMP group). The hazard ratio for OS was 0.92 (95% CI: 0.61, 1.37; p=0.6691). The median OS was not reached for either treatment group.

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 Table 20 below.

Combination treatment with lenalidomide and dexamethasone (Rd) 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 (DRd) 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 Data Sheet. Treatment was continued in both arms until disease progression or unacceptable toxicity.

Table 17: Dosage regimen in combination treatment with lenalidomide and dexamethasone

	Weeks 1-8	**Weeks 9-24**	**Weeks ≥ 25**
Daratumumab	16 mg/kg IV Weekly for two 4-week cycles (total of 8 doses)	16 mg/kg IV Every 2 weeks for four 4-week cycles (total of 8 doses)	16 mg/kg IV Every 4 weeks
Lenalidomide	25 mg oral, once daily Days 1-21 of each repeated 28 day [4-week] cycles		
Dexamethasone[a, b]	40 mg oral or IV Weekly		

[a] Dexamethasone reduced dose of 20 mg/week for patients >75 years or body mass index [BMI] <18.5
[b] On 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 daratumumab pre-infusion medication.

A total of 737 patients were randomized: 368 to the DRd 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 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 International Myeloma Working Group (IMWG) criteria.

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

In responders, the median time to response was 1.05 months (range: 0.2 to 12.1 months) in the DRd group and 1.05 months (range: 0.3 to 15.3 months) in the Rd group. The median duration of response had not been reached in the DRd 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 20 below.

Relapsed/Refractory Multiple Myeloma

Combination treatment with bortezomib and dexamethasone (Vd)

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 (DVd), 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. IV daratumumab was continued until disease progression or unacceptable toxicity. Patients refractory to bortezomib were excluded from the study. Dose adjustments for bortezomib and dexamethasone were applied according to the manufacturer's Data Sheet.

Table 18: Dosage regimen in combination treatment with bortezomib

	Weeks 1-9	**Weeks 10-24**	**Weeks ≥ 25**
Daratumumab	16 mg/kg IV Weekly	16 mg/kg IV Every 3 weeks	16 mg/kg IV Every 4 weeks
Bortezomib	1.3 mg/m^2 SC or IV Days 1,4,8,11 of each repeated 21 day [3 week] cycle		-
Dexamethasone[a, b]	20 mg oral or IV once daily Days 1, 2, 4, 5, 8, 9, 11, 12 of each repeated 21 day [3 week] cycle (ie 80 mg/week for two out of three weeks of each of the bortezomib cycle)		20 mg oral or IV (given as daratumumab pre-infusion medication)

[a] Dexamethasone reduced dose of 20 mg/week for patients >75 years, BMI <18.5, poorly controlled diabetes mellitus or prior intolerance to steroid therapy.

[b] On the days of 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 daratumumab pre-infusion medication.

A total of 498 patients were randomized; 251 to the DVd arm and 247 to the Vd arm. The baseline demographic and disease characteristics were 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 autologous stem cell transplantation (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.

Study MMY3004 demonstrated an improvement in PFS in the DVd arm as compared to the Vd arm; the median PFS had not been reached in the DVd arm and was 7.2 months in the Vd arm (HR [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 DVd versus Vd.

Additional efficacy results from Study MMY3004 are presented in Table 20 below.
Median OS was not reached for either treatment group. With an overall median follow-up of 7.4 months (95% CI: 0.0, 14.9), the hazard ratio for OS was 0.77 (95% CI: 0.47, 1.26; p=0.2975).

Combination treatment with lenalidomide and dexamethasone (Rd)

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 (DRd) 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. Dose adjustments for lenalidomide and dexamethasone were applied according to the manufacturer's Data Sheet. Treatment was continued in both arms until disease progression or unacceptable toxicity. Patients refractory to lenalidomide were excluded from the study.

Table 19: Dosage regimen in combination treatment with lenalidomide

	Weeks 1-8	**Weeks 9-24**	**Weeks ≥ 25**
Daratumumab	16 mg/kg IV Weekly for two 4-week cycles (total of 8 doses)	16 mg/kg IV Every 2 weeks for four 4-week cycles (total of 8 doses)	16 mg/kg IV Every 4 weeks
Lenalidomide	25 mg oral, once daily Days 1-21 of each repeated 28 day [4 week] cycle		
Dexamethasone[a, b]	40 mg oral or IV Weekly		

[a] Dexamethasone reduced dose of 20 mg/week for patients >75 years or body mass index [BMI] <18.5
[b] On 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 daratumumab pre-infusion medication.

A total of 569 patients were randomized; 286 to the DRd arm and 283 to the Rd arm. The baseline demographic and disease characteristics were 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 autologous stem cell transplantation (ASCT). The majority of patients (86%) received a prior proteasome inhibitor (PI), 55% of patients had received a prior immunomodulatory agent (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.

Study MMY3003 demonstrated an improvement in PFS in the DRd arm as compared to the Rd arm; the median PFS had not been reached in the DRd arm and was 18.4 months in the Rd arm (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 DRd.

Median overall survival has not yet been reached in either treatment group. With an overall median follow-up of 13.5 months, the hazard ratio for OS was 0.64 (95% CI: 0.40, 1.01; p=0.0534).
Additional efficacy results from Study MMY3003 are presented in Table 20 below.

Table 20: 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%)	83 (29.0%)	22 (7.8%)	34 (13.5%)	7 (2.8%)
95% CI	(19.9%, 28.9%)	(4.9%, 10.5%)	(18.0%, 27.0%)	(3.9%, 9.2%)	(23.8%, 34.7%)	(4.9%, 11.5%)	(9.6%, 18.4%)	(1.1%, 5.8%)

P-value[g]	<0.0001		<0.0001		<0.000001		0.000006	

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 for MMY3008 and MMY3007 studies and the intent-to-treat population and a threshold of 10-4 for MMY3003 and MMY3004 studies

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

[h] Response evaluable population

5.2 PHARMACOKINETIC PROPERTIES

Daratumumab exposure in a monotherapy study (MMY3012) following the recommended 1800 mg administration of DARZALEX SC subcutaneous 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 parallel linear and nonlinear (saturable) elimination that is characteristic of target-mediated clearance. Following the recommended dose of 1800 mg DARZALEX SC subcutaneous formulation, 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 (8^{th} dose). Highest trough concentrations for DARZALEX SC subcutaneous formulation are typically observed at the end of the weekly dosing regimens for both monotherapy and combination therapy.

The simulated trough concentrations following 6 weekly doses of 1800 mg DARZALEX SC for combination therapy were similar to 1800 mg DARZALEX SC monotherapy.

Absorption

At the recommended dose of 1800 mg, 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}).

Distribution

The modeled mean estimate of the volume of distribution for the central compartment (V1) is 5.25 L (36.9% CV) and peripheral compartment was 3.78 L, suggesting that daratumumab is primarily localized to the vascular system with limited extravascular tissue distribution.

Metabolism and Excretion

Daratumumab is cleared by parallel linear and nonlinear saturable target mediated clearances. The population PK model estimated mean clearance value of daratumumab is 4.96 mL/h (58.7% CV).

The model-based geometric mean post hoc estimate for half-life associated with linear elimination is 20.4 days (22.4% CV). For the monotherapy regimen, 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 subcutaneous formulation monotherapy and combination therapy, was conducted with data from 487 patients who received DARZALEX SC subcutaneous formulation and 255 patients who received IV daratumumab. The predicted PK exposures are summarized in Table 21.

Table 21: Daratumumab exposure following administration of DARZALEX SC (1800 mg) or IV daratumumab (16 mg/kg) Monotherapy

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)

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 DARZALEX SC. No individualization is necessary for patients on the basis of age.

In the pooled PK analysis of 421 males and 321 females, gender had a statistically significant effect on PK, with slightly higher exposure in females 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 receiving DARZALEX SC monotherapy or various combination therapies, including 220 patients with normal renal function (creatinine clearance [CRCL] ≥90 mL/min), 273 with mild renal impairment (CRCL <90 and ≥60 mL/min), 215 with moderate renal impairment (CRCL <60 and ≥30 mL/min), and 33 with severe renal impairment or end stage renal disease (CRCL <30 mL/min). No clinically important differences in exposure to daratumumab were observed between patients with renal impairment and those with normal renal function.

Hepatic impairment

No formal studies of DARZALEX SC formulation in patients with hepatic impairment have been conducted. Population PK analyses were performed in patients receiving DARZALEX SC formulation monotherapy or various combination therapies, including 655 patients with normal hepatic function (total bilirubin [TB] and aspartate aminotransferase [AST] ≤ upper limit of normal [ULN]), 82 with mild hepatic impairment [(total bilirubin ≤ ULN and AST > ULN) or (ULN < total bilirubin ≤ 1.5×ULN)] and 5 patients with moderate (1.5×ULN < total bilirubin ≤ 3×ULN) hepatic impairment. 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

The population PK analysis dataset included 526 White, 24 Black, 27 White Hispanic or Latino, 79 Asians, 1 Native Hawaiian or Pacific Islander, and 85 Other. 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. 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.

Drug interactions studies

As a monoclonal antibody (mAb) that binds with high affinity to a unique epitope on CD38, daratumumab is not anticipated to alter drug-metabolizing enzymes. Since there is no overlapping pathway of elimination, no PK interactions are expected between daratumumab and co-administered small-molecule drugs such as bortezomib, lenalidomide, dexamethasone, melphalan, prednisone. The concentrations of daratumumab and combination agents bortezomib, pomalidomide, and thalidomide were not altered when coadministered (see also section 4.5 Interactions with other medicines and other forms of interactions).

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Routine genotoxicity studies are generally not applicable to biologic pharmaceuticals as large proteins cannot diffuse into cells and cannot interact with DNA or chromosomal material.

Carcinogenicity

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

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.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

hyaluronidase (vorhyaluronidase alfa, recombinant human hyaluronidase, rHuPH20)
histidine
histidine hydrochloride monohydrate
sorbitol
methionine
polysorbate 20
water for injection

6.2 INCOMPATIBILITIES

This medicinal product should only be used with the materials mentioned in section 4.2 Dose and method of administration.

6.3 SHELF LIFE

Unopened vials

12 months. The expiry date can be found on the packaging.

Shelf life of prepared syringe

If the syringe containing DARZALEX SC is not used immediately, store the DARZALEX SC solution for up to 4 hours at ambient temperature (15°C–30°C) and ambient light. The syringe should be discarded if not used within 4 hours of storage at ambient temperature and ambient light.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

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

For storage conditions of the prepared syringe, see section 6.3 Shelf-life.

6.5 NATURE AND CONTENTS OF CONTAINER

DARZALEX SC is available in a carton containing 1 vial:

- 15 mL solution in a Type 1 glass vial with an elastomeric closure and an aluminium seal with a dark grey flip-off cap containing 1800 mg of daratumumab.

Product is for single use subcutaneous injection in one patient only.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

Any unused product or waste material should be disposed of in accordance with local requirements.

7 MEDICINE SCHEDULE

Prescription Medicine

8 SPONSOR

Janssen-Cilag (New Zealand) Ltd
Auckland
NEW ZEALAND
Telephone: 0800 800 806
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9 DATE OF FIRST APPROVAL

13 May 2021

10 DATE OF REVISION OF THE TEXT

27 May 2021

Summary table of changes

Section	Summary of changes
4.4	Update to Neutropenia Warning and Precaution. Update to patient numbers, frequencies and range in time of onset for Infusion-Related Reactions from the D-Kd arm of MMY2040.
4.8	Update to patient numbers and frequencies in Infusion-related reactions, Injection site reactions, infections and Other population section. Addition of “Cytomegalovirus infection”, “Hepatitis B virus reactivation”, “Syncope” and “Hypogammaglobulinemia” to Other Adverse Reactions. Inclusion of safety data from the D-Kd arm of Study MMY2040. Revised “Post-marketing data” to remove reference to specific formulation (IV)