PROFESSIONAL INFORMATION

SCHEDULING STATUS

Schedule 4

1. NAME OF THE MEDICINE

DARZALEX 1 800 mg solution for injection.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL contains 120 mg daratumumab.

15 mL vial of solution for injection contains 1 800 mg of daratumumab.

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

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

Excipients with known effect

Contains sugar: Each 15 mL vial of solution for injection contains 735,1 mg of sorbitol (E420).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.

The solution is a colourless to yellow, clear to opalescent.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

DARZALEX 1 800 mg solution for injection is indicated for:

Multiple Myeloma

- In combination with bortezomib, melphalan and prednisone in adult patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant (ASCT).
- In combination with lenalidomide and dexamethasone in adult patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant (ASCT).
- In combination with bortezomib, thalidomide and dexamethasone in adult patients with newly diagnosed multiple myeloma who are eligible for autologous stem cell transplant (ASCT).

- In combination with lenalidomide and dexamethasone in adult patients with multiple myeloma who have received at least one prior therapy.
- In combination with bortezomib and dexamethasone in adult patients with multiple myeloma who have received at least one prior therapy.
- in combination with pomalidomide and dexamethasone for the treatment of adult patients with multiple myeloma who have received one prior therapy containing a proteasome inhibitor and lenalidomide and have demonstrated disease progression on or after the last therapy (see section 5.1).
- as monotherapy for the treatment of adult patients with relapsed and refractory multiple myeloma, whose prior therapy included a proteasome inhibitor and an immunomodulatory agent and who have demonstrated disease progression on the last therapy.

Light chain (AL) Amyloidosis

DARZALEX 1 800 mg solution for injection is indicated in combination with cyclophosphamide, bortezomib and dexamethasone for the treatment of adult patients with newly diagnosed systemic light chain (AL) amyloidosis.

4.2 Posology and method of administration

DARZALEX 1 800 mg solution for injection is for subcutaneous use only. DARZALEX 1 800 mg solution for injection has different dosage and administration instructions than intravenous daratumumab. Do not administer intravenously.

DARZALEX 1 800 mg solution for injection should be administered by a healthcare professional, and the first dose should be administered in an environment where resuscitation facilities are available.

Pre- and post-infusion medications should be administered to reduce the risk of infusion-related reactions (IRRs) with daratumumab. See below *Recommended concomitant medications*).

For patients currently receiving daratumumab intravenous formulation, DARZALEX 1 800 mg solution for injection subcutaneous formulation may be used as an alternative to the intravenous daratumumab formulation starting at the next scheduled dose.

Posology - Adults (≥ 18 years)

Recommended dose for multiple myeloma

The DARZALEX 1 800 mg solution for injection dosing schedule in Table 1 is for combination therapy with 4 - week cycle regimens (e.g., lenalidomide, pomalidomide) and for monotherapy as follows:

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

The recommended dose is DARZALEX 1 800 mg solution for injection administered subcutaneously, over approximately 3 - 5 minutes, according to the following dosing schedule:

Table 1: DARZALEX 1 800 mg solution for injection dosing schedule for monotherapy and in combination with 4 - week cycle dosing regimens

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

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

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

For dosing instructions of medicines administered with DARZALEX 1 800 mg solution for injection, see section 5 - Clinical Studies and manufacturer's prescribing information.

The DARZALEX 1 800 mg solution for injection 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 1 800 mg administered subcutaneously, over approximately 3 - 5 minutes, according to the following dosing schedule:

Table 2: DARZALEX 1 800 mg solution for injection dosing schedule in combination with bortezomib, melphalan and prednisone ([VMP]; 6 - week cycle dosing regimen)

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

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

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

Bortezomib is given twice weekly at Weeks 1, 2, 4 and 5 for the first 6 - week cycle, followed by once weekly at Weeks 1, 2, 4 and 5 for eight more 6 - week cycles. For information on the VMP dose and dosing schedule when administered with DARZALEX 1 800 mg solution for injection, see Clinical Studies.

The DARZALEX 1 800 mg solution for injection dosing schedule in Table 3 is for combination therapy with bortezomib, thalidomide and dexamethasone (4-week cycle regimens) for treatment of newly diagnosed multiple myeloma patients eligible for ASCT.

The recommended dose is DARZALEX 1 800 mg administered subcutaneously, over approximately 3 - 5 minutes, according to the following dosing schedule:

Table 3: DARZALEX 1 800 mg solution for injection dosing schedule in combination with bortezomib, thalidomide and dexamethasone ([VTd]; 4 - week cycle dosing regimen)

Treatment phase	Weeks	Schedule
Induction	Weeks 1 to 8	weekly (total of 8 doses)
	Weeks 9 to 16a	every two weeks (total of 4 doses)
Stop for high dose chemotherapy and ASCT		
Consolidation	Weeks 1 to 8b	every two weeks (total of 4 doses)

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

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

For dosing instructions of medicines administered with DARZALEX 1 800 mg solution for injection, see section 5 - Clinical Studies and manufacturer's prescribing information.

The DARZALEX 1 800 mg solution for injection dosing schedule in Table 4 is for combination therapy with 3-week cycle regimens (e.g., bortezomib) for patients with relapsed/refractory multiple myeloma.

The recommended dose is DARZALEX 1 800 mg administered subcutaneously, over approximately 3 - 5 minutes, according to the following dosing schedule:

Table 4: Dosing schedule for DARZALEX 1 800 mg solution for injection with 3 - week cycle dosing regimens

Weeks	Schedule
Weeks 1 to 9	weekly (total of 9 doses)

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

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

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

For dosing instructions for medicines administered with DARZALEX 1 800 mg solution for injection see section 5 - Clinical Studies and manufacturer's prescribing information.

Recommended dose for AL amyloidosis

The DARZALEX 1 800 mg solution for injection dosing schedule in Table 5 is for combination therapy with bortezomib, cyclophosphamide and dexamethasone (4 - week cycle regimen) for patients with AL amyloidosis.

The recommended dose is DARZALEX 1 800 mg administered subcutaneously, over approximately 3 - 5 minutes, according to the following dosing schedule:

Table 5: DARZALEX 1 800 mg solution for injection dosing schedule for AL amyloidosis in combination with bortezomib, cyclophosphamide and dexamethasone ([VCd]; 4 - week cycle dosing regimen)[a]

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

[a] In the clinical trial, DARZALEX 1 800 mg solution for injection was given until disease progression or a maximum of 24 cycles (~2 years) from the first dose of study treatment.

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

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

For dosing instructions of medicines administered with DARZALEX 1 800 mg solution for injection, see section 5 - Clinical Studies and manufacturer's prescribing information.

Missed dose (s)

If a planned dose of DARZALEX 1 800 mg solution for injection is missed, the dose should be administered as soon as possible and the dosing schedule should be adjusted accordingly, maintaining the treatment interval.

Dose modifications

No dose reductions of DARZALEX 1 800 mg solution for injection 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 medicines given in combination with DARZALEX 1 800 mg solution for injection, see manufacturer's prescribing information.

DARZALEX and management of infusion-related reactions:

In clinical trials, no modification to rate or dose of DARZALEX 1 800 mg solution for injection was required to manage infusion-related reactions.

<u>Recommended concomitant medications</u>

Pre-injection medication

Pre-infusion 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 1 800 mg solution for injection subcutaneous injection as follows:

- Corticosteroid (long-acting or intermediate-acting)

  Monotherapy:

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

  Combination therapy:

  Administer 20 mg dexamethasone (or equivalent) prior to every DARZALEX 1 800 mg solution for injection. When dexamethasone is the background regimen specific corticosteroid, the dexamethasone treatment dose will instead serve as pre-medication on DARZALEX 1 800 mg solution for injection administration days.

  Additional background regimen specific corticosteroids (e.g. prednisone) should not be taken on DARZALEX 1 800 mg solution for injection administration days when patients have received dexamethasone (or equivalent) as a pre-medication.

- Antipyretics (oral paracetamol 650 to 1,000 mg)
- Antihistamine (oral or intravenous 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 two days following all DARZALEX 1 800 mg solution for injection, injections (beginning the day after the injection).

Combination therapy:

Consider administering low-dose oral methylprednisolone (≤ 20 mg) or equivalent the day after the DARZALEX 1 800 mg solution for injection.

However, if a background regimen-specific corticosteroid (e.g. dexamethasone, prednisone) is administered the day after the DARZALEX 1 800 mg solution for injection, additional post-injection medications may not be needed.

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 infusions, if the patient experiences no major IRRs, these inhaled post-injection medications may be discontinued at the discretion of the medical practitioner.

Prophylaxis for herpes zoster virus reactivation

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

Special populations

Renal impairment

No dosage adjustment is necessary for patients with renal impairment.

Hepatic impairment

No dosage adjustments are necessary for patients with hepatic impairment.

Elderly (65 years of age and older)

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

Paediatric population (17 years of age and younger)

The safety and efficacy of DARZALEX 1 800 mg solution for injection have not been established in paediatric patients.

Method of administration

DARZALEX 1 800 mg solution for injection should be administered by a healthcare professional.

To prevent medication errors, it is important to check the vial labels to ensure that the medicine being prepared and administered is DARZALEX 1 800 mg solution for injection for subcutaneous injection and not intravenous daratumumab. DARZALEX subcutaneous (SC)

formulation is not intended for intravenous administration and should be administered via a subcutaneous injection only.

DARZALEX 1 800 mg solution for subcutaneous injection is for single use only and is ready to use.

- DARZALEX 1 800 mg solution for injection 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 1 800 mg solution for injection should be inspected visually for particulate matter and discolouration prior to administration, whenever solution and container permit. Do not use if opaque particles, discolouration or other foreign particles are present.
- Remove the DARZALEX 1 800 mg solution for injection 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.

<u>Storage of prepared syringe</u>

- If the syringe containing DARZALEX 1 800 mg solution for injection is not used immediately, store the DARZALEX 1 800 mg solution for injection solution for up to 4 hours at ambient temperature and ambient light.

<u>Administration</u>

- Inject 15 mL DARZALEX 1 800 mg solution for injection into the subcutaneous tissue of the abdomen approximately 7,5 cm to the right or left of the navel over approximately 3 - 5 minutes. Do not inject DARZALEX 1 800 mg solution for injection at other sites of the body as no data are available.
- Injection sites should be rotated for successive injections.
- DARZALEX 1 800 mg solution for injection 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 1 800 mg solution for injection, do not administer other medications for subcutaneous use at the same site as DARZALEX 1 800 mg solution for injection.
- Any waste material should be disposed in accordance with local requirements.

4.3 Contraindications

Hypersensitivity to daratumumab or to any of the excipients of DARZALEX 1 800 mg solution for injection (see section 6.1).

Pregnancy and breastfeeding (see section 4.6).

Live attenuated vaccines should not be administered to patients receiving DARZALEX 1 800 mg solution for injection (see section 4.4).

4.4 Special warnings and precautions for use

Infusion-related reactions

DARZALEX 1 800 mg solution for injection can cause serious infusion related reactions (IRRs), including anaphylactic reactions.

In clinical trials, approximately 9 % (74/832) 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 1 % of patients.

The median time to onset of IRRs following DARZALEX 1 800 mg solution for injection was 3,2 hours (range 0,15 - 83 hours). The majority of IRRs occurred on the day of treatment. Delayed IRRs have occurred in 1 % of patients.

Signs and symptoms of IRRs may include respiratory symptoms, such as nasal congestion, cough, throat irritation, allergic rhinitis, wheezing as well as pyrexia, chest pain, pruritis, chills, vomiting, nausea, hypotension and blurred vision. Severe reactions have occurred, including bronchospasm, hypoxia, dyspnoea, hypertension, tachycardia and ocular adverse events (including choroidal effusion, acute myopia and acute angle closure glaucoma) (see Section 4.8).

Pre-medicate patients with antihistamines, antipyretics and corticosteroids. Patients should be monitored and counselled regarding IRRs, especially during and following the first and second injections. If an anaphylactic reaction or life threatening (Grade 4) reactions occur, institute appropriate emergency care and permanently discontinue DARZALEX 1 800 mg solution for injection.

To reduce the risk of delayed IRRs, administer oral corticosteroids to all patients following DARZALEX 1 800 mg solution for injections. Patients with a history of chronic obstructive

pulmonary disease may require additional post-injection medications to manage respiratory complications. Consider prescribing short- and long-acting bronchodilators and inhaled corticosteroids for patients with chronic obstructive pulmonary disease. If ocular symptoms occur, interrupt DARZALEX 1 800 mg solution for injection and seek immediate ophthalmologic evaluation prior to restarting DARZALEX 1 800 mg solution for injection (see Section 4.2).

Neutropenia/Thrombocytopenia

DARZALEX 1 800 mg solution for injection may increase neutropenia and thrombocytopenia induced by background therapy (see Section 4.8).

Monitor complete blood cell counts periodically during treatment according to manufacturer's prescribing information for background therapies. Monitor patients with neutropenia for signs of infection. DARZALEX 1 800 mg solution for injection dose delay may be required to allow recovery of blood cell counts. In lower body weight patients receiving DARZALEX 1 800 mg solution for injection subcutaneous formulation, higher rates of neutropenia were observed; however, this was not associated with higher rates of serious infections. No dose reduction of DARZALEX 1 800 mg solution for injection is recommended. Consider supportive care with transfusions or growth factors.

Interference with Indirect Antiglobulin Test (Indirect Coombs Test)

Daratumumab binds to CD38 found at low levels on red blood cells (RBCs) and may result in a positive indirect Coombs test. Daratumumab-mediated positive indirect Coombs test may persist for up to 6 months after the last DARZALEX 1 800 mg solution for injection administration. It should be recognised that DARZALEX 1 800 mg solution for injection 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 prior to starting DARZALEX 1 800 mg solution for injection.

In the event of a planned transfusion, blood transfusion centres should be notified 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.

Hepatitis B virus (HBV) Reactivation

Hepatitis B virus reactivation, in some cases fatal, has been reported in patients treated with DARZALEX 1 800 mg solution for injection. HBV screening should be performed in all patients before initiation of treatment with DARZALEX 1 800 mg solution for injection.

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 1 800 mg solution for injection 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 1 800 mg solution for injection, suspend treatment with DARZALEX 1 800 mg solution for injection and any concomitant steroids, chemotherapy and institute appropriate treatment. Resumption of DARZALEX 1 800 mg solution for injection treatment in patients whose HBV reactivation is adequately controlled should be discussed with medical practitioners with expertise in managing HBV.

Use with vaccines

Currently, there are no data regarding a potential interaction between DARZALEX 1 800 mg solution for injection and vaccines. It is recommended that live viral or live bacterial vaccines should not be given concurrently with monoclonal antibodies.

Excipients:

Sorbitol (sugar)

The additive effect of concomitantly administered products containing sorbitol and dietary intake of sorbitol should be taken into account.

4.5 Interaction with other medicines and other forms of interaction

No formal medicine-medicine interaction studies have been performed.

As an IgG1κ monoclonal antibody, renal excretion and hepatic enzyme mediated metabolism of intact daratumumab are unlikely to represent major elimination routes. As such, variations in drug metabolising 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 metabolising enzymes.

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

Interference with Indirect Antiglobulin Test (Indirect Coombs Test)

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

Interference with serum protein electrophoresis and immunofixation tests

Daratumumab may be detected on serum protein electrophoresis (SPE) and immunofixation (IFE) assays used for monitoring disease monoclonal immunoglobulins (M protein). This can lead to false positive SPE and IFE assay results for patients with IgG kappa myeloma protein impacting initial assessment of Complete Responses (CRs) by International Myeloma Working Group (IMWG) criteria. In patients with persistent very good partial response (VGPR), where daratumumab interference is suspected, consider using a validated daratumumab-specific IFE assay to distinguish daratumumab from any remaining endogenous M protein in the patient's serum, to facilitate determination of a CR (see Clinical Studies).

4.6 Fertility, pregnancy and lactation

Women of childbearing potential / Contraception

To avoid exposure to the foetus, women of child bearing potential should use effective contraception during, and for 3 months after cessation of DARZALEX 1 800 mg solution for injection treatment.

Pregnancy

DARZALEX 1 800 mg solution for injection should not be used during pregnancy (see Section 4.3).

IgG1 monoclonal antibodies are known to cross the placenta after the first trimester of pregnancy.

If the patient becomes pregnant while taking DARZALEX 1 800 mg solution for injection, the patient should be informed of the potential risk to the foetus.

Breastfeeding

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 1 800 mg solution for injection to the infant from oral ingestion are unknown, a woman receiving DARZALEX 1 800 mg solution for injection should not breastfeed her infant.

4.7 Effects on ability to drive and use machines

DARZALEX 1 800 mg solution for injection may be associated with fatigue and IRRs may impair the patient's ability to drive and use machines. Patients should determine their personal side effects profile.

4.8 Undesirable effects

Summary of the safety profile

The most frequent adverse reactions (≥ 20 %) with DARZALEX (either intravenous or subcutaneous formulations) when administered as monotherapy or combination treatment

were IRRs, fatigue, nausea, diarrhoea, constipation, pyrexia, cough, neutropenia, thrombocytopenia, anaemia, peripheral oedema, peripheral sensory neuropathy, and upper respiratory tract infection. Serious adverse reactions were sepsis, pneumonia, bronchitis, upper respiratory tract infection, pulmonary oedema, influenza, pyrexia, dehydration, diarrhoea, atrial fibrillation and syncope.

The safety profile of the DARZALEX 1 800 mg solution for injection subcutaneous formulation was similar to that of intravenous formulation with the exception of a lower rate of IRRs. In the Phase 3 study MMY3012, neutropenia was the only adverse reaction reported at ≥ 5 % higher frequency for DARZALEX 1 800 mg solution for injection subcutaneous (SC) formulation compared to intravenous (IV) daratumumab (Grade 3 or 4: 13 % vs 8 %, respectively).

Table 6 summarises the adverse reactions that occurred in patients receiving DARZALEX subcutaneous formulation or IV formulation of daratumumab. The data reflects exposure to DARZALEX SC formulation (1 800 mg) in 639 patients with multiple myeloma (MM). The data includes 260 patients from a Phase 3 active-controlled trial (Study MMY3012) who received DARZALEX SC formulation as monotherapy, and 149 patients from a Phase 3 active-controlled trial (Study MMY3013) who received daratumumab in combination with pomalidomide and dexamethasone (D-Pd). The data also reflects three open-label, clinical trials in which patients received DARZALEX SC formulation either as monotherapy (N = 31, MMY1004 and MMY1008) and MMY2040 in which patients received DARZALEX SC formulation in combination with either bortezomib, melphalan and prednisone (D-VMP, n = 67), lenalidomide and dexamethasone (D-Rd, n = 65) or bortezomib, lenalidomide and dexamethasone (D-VRd, n = 67). Additionally, data reflect exposure to 193 patients with newly diagnosed AL amyloidosis from a Phase 3 active-controlled trial (Study AMY3001) in which

patients received DARZALEX SC formulation in combination with bortezomib, cyclophosphamide and dexamethasone (D-VCd).

The safety data also reflects exposure to IV daratumumab (16 mg/kg) in 2 324 patients with multiple myeloma including 1 910 patients who received IV daratumumab in combination with background regimens and 414 patients who received IV daratumumab as monotherapy.

Tabulated list of adverse reactions

Frequencies are defined as very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000) and very rare (< 1/10,000). Within each frequency grouping, where relevant, adverse reactions are presented in order of decreasing seriousness.

Table 6: Adverse reactions in multiple myeloma and AL amyloidosis patients treated with IV daratumumab or SC daratumumab.

System Organ Class	**Adverse Reactions**	**Frequency**
		Any Grade
Infections and infestations	Upper respiratory tract infection[a]	Very Common
	Pneumonia[a]	
	Bronchitis[a]	
	Urinary tract infection	Common
	Influenza	
	Sepsis[a]	
	Cytomegalovirus infection[a]	Uncommon
	Hepatitis B virus reactivation[a]	

Blood and lymphatic system disorders	Neutropenia[a]	Very Common
	Thrombocytopenia[a]	
	Anaemia[a]	
	Lymphopenia[a]	
	Leukopenia[a]	
Immune systems disorders	Hypogammaglobulinemia[a]	Common
Metabolism and nutrition disorders	Decreased appetite	Very Common
	Hyperglycaemia	Common
	Hypocalcaemia	
	Dehydration	
Psychiatric disorders	Insomnia	Very Common
Nervous system disorders	Peripheral sensory neuropathy	Very Common
	Headache	
	Dizziness	Common
	Paresthesia	
	Syncope	
Cardiac disorders	Atrial fibrillation	Common
Vascular disorders	Hypertension[a]	Common
Respiratory, thoracic and mediastinal disorders	Cough[a]	Very Common
	Dyspnoea[a]	
	Pulmonary oedema[a]	Common
Gastrointestinal disorders	Diarrhoea	Very Common
	Constipation	
	Nausea	
	Vomiting	

	Pancreatitis[a]	Common
Skin and subcutaneous tissue disorders	Rash	Very Common
	Pruritus	Common
Musculoskeletal and connective tissue disorders	Back pain	Very Common
	Muscle spasms	
	Arthralgia	
	Musculoskeletal chest pain	Common
General disorders and administration site conditions	Fatigue	Very Common
	Peripheral oedema[a]	
	Pyrexia	
	Asthenia	
	Chills	Common
	Injection site reactions[c,d]	
Injury, poisoning and procedural complications	Infusion-related reactions[b]	
	Daratumumab IV[e]	Very Common
	Daratumumab SC[d]	Common

[#] No grade 4

[a] Indicates a grouping of terms.

[b] Infusion-related reactions includes terms determined by investigators as related to infusion/injection of daratumumab.

[c] Injection site reactions includes terms determined by investigators as related to injection of daratumumab.

[d] Frequency based on daratumumab SC studies only (N = 832).

[e] Frequency based on daratumumab IV studies only (N = 2 324).

Note: Based on 3 156 multiple myeloma and AL amyloidosis patients treated with daratumumab IV or daratumumab SC.

Postmarketing side effects

Immune System disorders

Anaphylactic reaction

Infections and Infestations

Hepatitis B virus reactivation

COVID-19

Infusion related reactions

In clinical trials (monotherapy and combination treatments; N = 898) the incidence of any grade infusion-related reaction was 8,2 % with the first injection of DARZALEX 1 800 mg solution for injection SC formulation (1 800 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 (see Section 4.4).

Injection site reactions (ISRs)

In clinical trials (N = 898) with DARZALEX 1 800 mg solution for injection SC formulation, the incidence of any grade injection site reaction was 7,7 %. There were no Grade 3 or 4 ISRs. The most common (> 1 %) ISR was erythema.

Infections

In patients with multiple myeloma receiving daratumumab monotherapy, the overall incidence of infections was similar between DARZALEX 1 800 mg solution for injection SC formulation (52,9 %) and IV daratumumab groups (50,0 %). Grade 3 or 4 infections also occurred at similar frequencies between DARZALEX 1 800 mg solution for injection SC formulation (11,7 %) and IV daratumumab (14,3 %). Most infections were manageable and rarely led to treatment discontinuation. Pneumonia was the most commonly reported Grade 3 or 4 infection across studies. In active-controlled studies, discontinuations from treatment due to infections occurred in 1 – 4 % of patients. Fatal infections were primarily due to pneumonia and sepsis.

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

- Grade 3 or 4 infections:
    - Relapsed/refractory patient studies: DVd: 21 %, Vd: 19 %; D-Rd: 28 %, Rd: 23 %; D-Pd: 28 %.
    - 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 %.
    - 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 %

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

- Grade 3 or 4 infections: D-VCd: 17 %, VCd:10 %;
- Grade 5 (fatal) infections: D-VCd: 1 %, VCd: 1 %

Cardiac disorders and AL amyloidosis-related cardiomyopathy

The majority of patients in AMY3001 had AL amyloidosis-related cardiomyopathy at baseline (D-VCd 72 % vs. VCd 71 %). Grade 3 or 4 cardiac disorders occurred in 11 % of D-VCd patients compared to 10 % of VCd patients, while serious cardiac disorders occurred in 16 % vs. 13 % of D-VCd and VCd patients, respectively. Serious cardiac disorders occurring in ≥ 2 % of patients included cardiac failure (D-VCd 6,2 % vs. VCd 4,3 %), cardiac arrest (D-VCd 3,6 % vs. VCd 1,6 %) and atrial fibrillation (D-VCd 2,1 % vs. VCd 1,1 %). All D-VCd patients who experienced serious or fatal cardiac disorders had AL amyloidosis-related cardiomyopathy at baseline. The longer median duration of treatment in the D-VCd arm compared to the VCd arm (9,6 months vs.5,3 months, respectively) should be taken into consideration when comparing the frequency of cardiac disorders between the two treatment groups. Exposure-adjusted incidence rates (number of patients with the event per 100 patient-months at risk) of overall Grade 3 or 4 cardiac disorders (1,2 vs. 2,3), cardiac failure (0,5 vs. 0,6), cardiac arrest (0,1 vs. 0,0) and atrial fibrillation (0,2 vs. 0,1) were comparable in the D-VCd arm vs. the VCd arm, respectively. With a median follow-up of 11,4 months, overall deaths (D-VCd 14 % vs. VCd 15

%) in Study AMY3001 were primarily due to AL amyloidosis-related cardiomyopathy in both treatment arms.

Other special populations

Of the 3615 patients who received daratumumab (n = 898 SC; n = 2 717 IV) at the recommended dose, 38 % were 65 to 75 years of age, and 16 % were 75 years of age or older. No overall differences in effectiveness were observed based on age. The incidence of serious adverse reactions was higher in older than in younger patients. Among patients with relapsed and refractory multiple myeloma (n = 2 042), the most common serious adverse reactions that occurred more frequently in elderly (≥ 65 years of age) were pneumonia and sepsis. Among patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant (n = 777), the most common serious adverse reaction that occurred more frequently in elderly (≥ 75 years of age) was pneumonia. Among patients with newly diagnosed AL amyloidosis (n = 193), the most common serious adverse reaction that occurred more frequently in elderly (≥ 65 years of age) was pneumonia.

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 providers are asked to report any suspected adverse reactions via "**6.04 Adverse Drug Reaction Reporting Form**" found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/index/8

Alternatively, suspected adverse reactions may be reported directly to Janssen Pharmaceutica (see section 7 for contact details or visit www.janssen.com)

4.9 Overdose

Symptoms and signs

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

Treatment

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological classification: A 26 Cytostatic agents

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

DARZALEX subcutaneous formulation contains recombinant human hyaluronidase (rHuPH20). rHuPH20 works locally and transiently to degrade hyaluronan ((HA), a naturally occurring glycoaminoglycan found throughout the body) in the extracellular matrix of the subcutaneous space by cleaving the linkage between the two sugars (N-acetylglucosamine and glucuronic acid) which comprise HA. rHuPH20 has a half-life in skin of less than 30

minutes. Hyaluronan levels in subcutaneous tissue return to normal within 24 to 48 hours because of the rapid biosynthesis of hyaluronan.

Mechanism of action

Daratumumab is an IgG1κ human monoclonal antibody (mAb) that binds to the CD38 protein expressed on the surface of cells in a variety of haematological malignancies, including clonal plasma cells in multiple myeloma and AL amyloidosis, as well as other cell types and tissues. CD38 protein has multiple functions such as receptor mediated adhesion, 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 utilise 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 treatment in peripheral whole blood and bone marrow. T-cell receptor DNA sequencing verified that T-cell clonality was increased with DARZALEX treatment, indicating immune modulatory effects that may contribute to clinical response.

Daratumumab induced apoptosis *in vitro* after Fc mediated cross linking and 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 treatment. However, baseline levels of NK cells did not show an association with clinical response.

Immunogenicity

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

In multiple myeloma and AL amyloidosis patients, the incidence of treatment-emergent non-neutralising anti-rHuPH20 antibodies was 7,1 % (58 / 812) in monotherapy and combination DARZALEX clinical trials. The anti-rHuPH20 antibodies did not appear to impact daratumumab exposures. The clinical relevance of the development of anti-daratumumab or anti-rHuPH20 antibodies after treatment with DARZALEX subcutaneous formulation is not known.

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

the incidence of antibodies to daratumumab with the incidence of antibodies to other products may be misleading.

Clinical efficacy and safety

Monotherapy – relapsed/refractory multiple myeloma

MMY3012, an open-label, randomised, Phase 3 non-inferiority study, compared efficacy and safety of treatment with DARZALEX subcutaneous formulation (1 800 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 and an immunomodulatory agent 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 randomised: 263 to the DARZALEX SC formulation arm and 259 to the IV daratumumab arm. The baseline demographic and disease characteristics were similar between the two treatment groups. The median patient age was 67 years (range: 33 - 92 years), 55 % were male and 78 % were Caucasian. The median patient weight was 73 kg (range: 29 -138 kg). Patients had received a median of 4 prior lines of therapy. A total of 51 % of patients had prior 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 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 formulation arm and 37,1 % (95 % CI: 31,2 %, 43,3 %) in the IV daratumumab arm.

This study met its primary objectives to show that DARZALEX SC formulation is non-inferior to IV daratumumab in terms of ORR and maximum trough concentration. The results are provided in Table 7.

Table 7: Key results from Study MMY3012

	SC Daratumumab (N = 263)	IV Daratumumab (N = 259)
Primary Endpoint		
Overall response (sCR+CR+VGPR+PR), n (%)[a]	108 (41,1 %)	96 (37,1 %)
95 % CI (%)	(35,1 %, 47,3 %)	(31,2 %, 43,3 %)
Ratio of response rates (95 % CI)[b]		1,11 (0,89, 1,37)
CR or better, n (%)	5 (1,9 %)	7 (2,7 %)
Very good partial response (VGPR)	45 (17,1 %)	37 (14,3 %)
Partial response (PR)	58 (22,1 %)	52 (20,1 %)
Secondary Endpoint		
Rate of Infusion-related Reaction, n (%)[c]	33 (12,7 %)	89 (34,5 %)
Progression-free Survival, months		
Median (95 % CI)	5,59 (4,67, 7,56)	6,08 (4,67, 8,31)
Hazard ratio (95 % CI)		0,99 (0,78, 1,26)

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

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

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

[c] Based on safety population. P-value < 0,0001 from Cochran-Mantel-Haenszel Chi-Squared test.

After a median follow-up of 29,3 months, the median overall survival (OS) was 28,2 months (95 % CI: 22,8, NE) in the DARZALEX SC formulation arm and was 25,6 months (95 % CI: 22,1, NE) in the IV daratumumab arm.

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

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

Combination treatments in multiple myeloma

MMY2040 was an open-label trial evaluating the efficacy and safety of DARZALEX SC formulation 1 800 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 formulation was continued until disease progression or unacceptable toxicity. The median duration of follow-up for patients was 6,9 months.

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

D-Rd arm: In combination with lenalidomide and dexamethasone (D-Rd) in patients with relapsed or refractory MM. Lenalidomide (25 mg once daily orally on Days 1 - 21 of repeated 28-day [4 - week] cycles) was given with low dose dexamethasone 40 mg/week (or a reduced dose of 20 mg/week for patients > 75 years or BMI < 18,5). DARZALEX subcutaneous formulation was continued until disease progression or unacceptable toxicity. The median duration of follow-up for patients was 7,1 months.

The median age was 69 years. The majority of patients were male (69 %). Most patients were white (69 %). 42 % had ISS Stage I, 30 % had ISS Stage II, and 28 % had ISS Stage III disease at screening. Patients had received a median of 1 prior line of therapy, 52 % of patients received prior 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 265 patients (D-VMP: 67; D-Rd: 65; D-VRd: 67) were enrolled. Efficacy results were determined by computer algorithm using IMWG response criteria during the study. Primary endpoints ORR for D-VMP and D-Rd and VGPR or better for D-VRd were met (see Table 8).

Table 8: 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

Combination treatment with pomalidomide and dexamethasone in patients with multiple myeloma

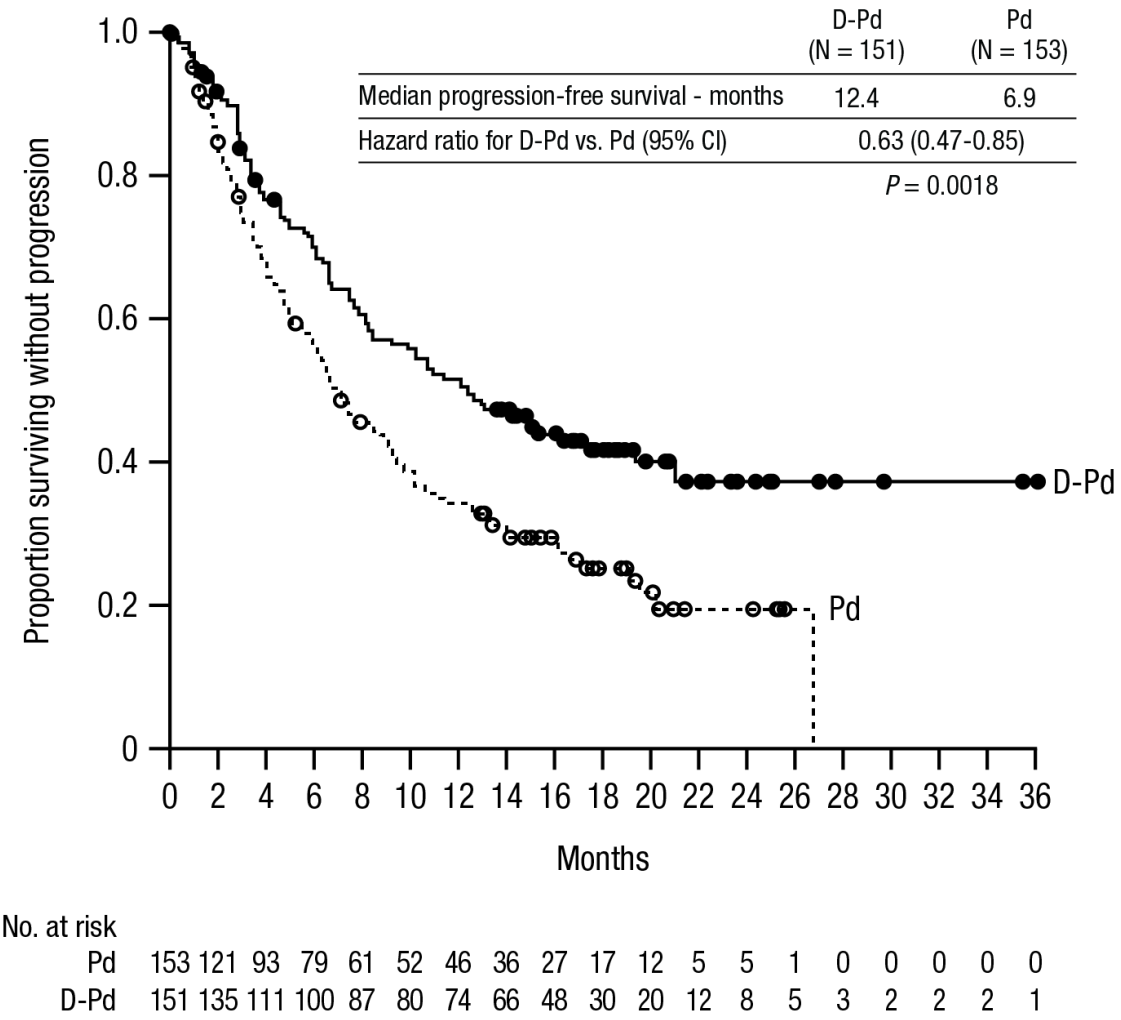
Study MMY3013 was an open-label, randomised, active-controlled Phase 3 trial that compared treatment with DARZALEX SC formulation (1 800 mg) in combination with pomalidomide and low-dose dexamethasone (D-Pd) to treatment with pomalidomide and low-dose dexamethasone (Pd) in patients with multiple myeloma who had received at least one prior therapy with lenalidomide and a protease inhibitor (PI). Pomalidomide (4 mg once daily orally on Days 1-21 of repeated 28-day [4 - week] cycles) was given with low dose oral or intravenous

dexamethasone 40 mg/week (or a reduced dose of 20 mg/week for patients > 75 years). On DARZALEX SC formulation administration days, 20 mg of the dexamethasone dose was given as a pre-administration medication and the remainder given the day after the administration. For patients on a reduced dexamethasone dose, the entire 20 mg dose was given as a DARZALEX SC formulation pre-administration medication. Dose adjustments for pomalidomide and dexamethasone were applied according to manufacturer's prescribing information. Treatment was continued in both arms until disease progression or unacceptable toxicity.

A total of 304 patients were randomised: 151 to the D-Pd arm and 153 to the Pd arm. The baseline demographic and disease characteristics were similar between the two treatment groups. The median patient age was 67 years (range 35 to 90 years), 18 % were ≥ 75 years, 53 % were male, and 89 % Caucasian. Patients had received a median of 2 prior lines of therapy, with 11 % of patients having received one prior line of therapy. All patients received a prior treatment with a proteasome inhibitor (PI) and lenalidomide, and 56 % of patients received prior stem cell transplantation (ASCT). The majority of patients were refractory to lenalidomide (80 %), a PI (48 %), or both an immunomodulator and a PI (42 %). Efficacy was evaluated by PFS based on IMWG criteria.

With a median follow-up of 16,9 months, the primary analysis of PFS in Study MMY3013 demonstrated a statistically significant improvement in the D-Pd arm as compared to the Pd arm; the median PFS was 12,4 months in the D-Pd arm and 6,9 months in the Pd arm (HR [95 % CI]: 0,63 [0,47, 0,85]; p-value = 0,0018), representing a 37 % reduction in the risk of disease progression or death for patients treated with D-Pd versus Pd. Median OS was not reached for either treatment group.

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



Additional efficacy results from Study MMY3013 are presented in Table 9 below.

Table 9: Efficacy results from Study MMY3013[a]

	D-Pd (n=151)	**Pd (n=153)**
Overall response (sCR+CR+VGPR+PR) n(%)[a]	104 (68,9 %)	71 (46,4 %)
P-value[b]	< 0,0001	
Stringent complete response (sCR)	14 (9,3 %)	2 (1,3 %)
Complete response (CR)	23 (15,2 %)	4 (2,6 %)

Very good partial response (VGPR)	40 (26,5 %)	24 (15,7 %)
Partial response (PR)	27 (17,9 %)	41 (26,8 %)
MRD negativity rate[c] n(%)	13 (8,7 %)	3 (2,0 %)
95 % CI (%)	(4,7 %, 14,3 %)	(0,4 %, 5,6 %)
P-value[d]	0,0102	

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

[a] Based on intent-to-treat population

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

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

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

In responders, the median time to response was 1 month (range: 0,9 to 9,1 months) in the D-Pd group and 1,9 months (range: 0,9 to 17,3 months) in the Pd group. The median duration of response had not been reached in the D-Pd group (range: 1 to 34,9+ months) and was 15,9 months (range: 1+ to 24,8 months) in the Pd group.

Patients treated with D-Pd reported a reduction in pain severity as measured with the EORTC QLQ-C30 and maintained baseline health-related quality of life, symptoms, and functioning for the other EORTC QLQ-C30 and EORTC QLQ-MY20 subscales. These benefits were not observed in patients treated with Pd.

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

Study AMY3001, an open-label, randomised, active-controlled Phase 3 study, compared treatment with DARZALEX subcutaneous formulation (1 800 mg) in combination with bortezomib, cyclophosphamide and dexamethasone (D-VCd) to treatment with bortezomib, cyclophosphamide and dexamethasone (VCd) alone in patients with newly diagnosed AL amyloidosis. Randomisation was stratified by AL amyloidosis Cardiac Staging System,

countries that typically offer autologous stem cell transplant (ASCT) for patients with AL amyloidosis, and renal function.

Bortezomib (SC; 1,3 mg/m^2 body surface area), cyclophosphamide (oral or IV; 300 mg/m^2 body surface area; max dose 500 mg), and dexamethasone (oral or IV; 40 mg or a reduced dose of 20 mg for patients > 70 years or body mass index [BMI] < 18,5 or those who have hypervolemia, poorly controlled diabetes mellitus or prior intolerance to steroid therapy) were administered weekly on Days 1, 8, 15, and 22 of repeated 28-day [4 - week] cycles. On the days of DARZALEX dosing, 20 mg of the dexamethasone dose was given as a pre-injection medication and the remainder given the day after DARZALEX administration. Bortezomib, cyclophosphamide and dexamethasone were given for six 28-day [4 - week] cycles in both treatment arms, while DARZALEX treatment was continued until disease progression, start of subsequent therapy, or a maximum of 24 cycles (~2 years) from the first dose of study treatment. Dose adjustments for bortezomib, cyclophosphamide and dexamethasone were applied according to manufacturer's prescribing information.

A total of 388 patients were randomised: 195 to the D-VCd arm and 193 to the VCd arm. The baseline demographic and disease characteristics were similar between the two treatment groups. The majority (79 %) of patients had lambda free light chain disease. The median patient age was 64 years (range: 34 to 87); 47 % were ≥ 65 years; 58 % were male; 76 % Caucasian, 17 % Asian, and 3 % African American; 23 % had AL amyloidosis Clinical Cardiac Stage I, 40 % had Stage II, 35 % had Stage IIIA, and 2 % had Stage IIIB. The median number of organs involved was 2 (range: 1 - 6) and 66 % of patients had 2 or more organs involved. Vital organ involvement was: 71 % cardiac, 59 % renal and 8 % hepatic. The major efficacy outcome measure was haematologic complete response (HemCR) rate as determined by the Independent Review Committee assessment based on International Concensus Criteria.

Study AMY3001 demonstrated an improvement in HemCR in the D-VCd arm as compared to the VCd arm. Efficacy results are summarised in Table 10.

Table 10: Efficacy results from Study AMY3001[a]

	D-VCd (n=195)	VCd (n=193)	P value
Haematologic complete response (HemCR), n (%)	104 (53,3 %)	35 (18,1 %)	< 0,0001[b]
Very good partial response (VGPR), n (%)	49 (25,1 %)	60 (31,1 %)	
Partial response (PR), n (%)	26 (13,3 %)	53 (27,5 %)	
Hematologic VGPR or better (HemCR + VGPR), n (%)	153 (78,5 %)	95 (49,2 %)	< 0,0001[b]
Major organ deterioration progression-free survival (MOD-PFS), Hazard ratio with 95 % CI[c]	0,58 (0,36, 0,93)		0,0211[d]
Cardiac response rate at 6 months, n/N (%)[e]	49/118 (42 %)	26/117 (22 %)	
Renal response rate at 6 months, n/N (%)[f]	63/117 (54 %)	31/113 (27 %)	

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

[a] Based on intent-to-treat population

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

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

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

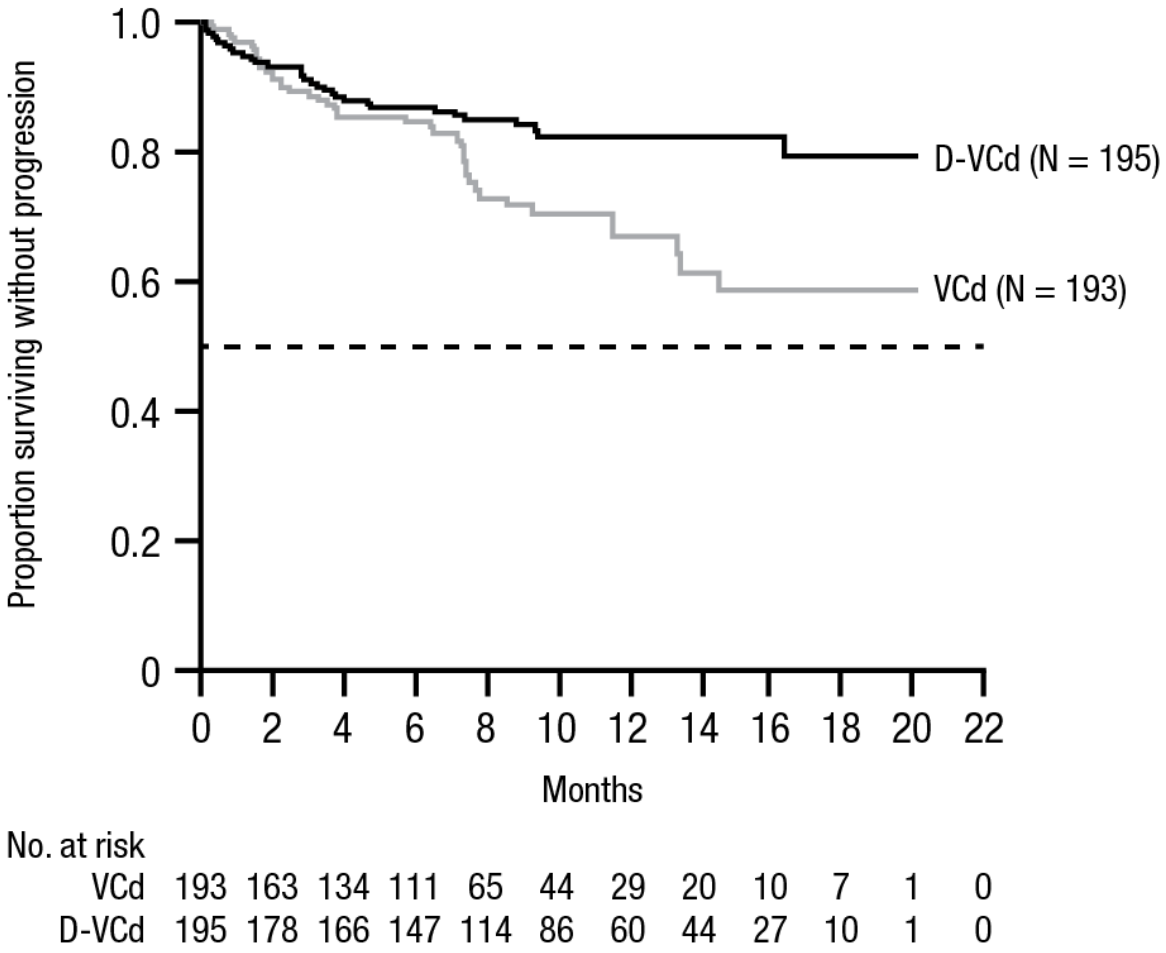
[e] n = number of subjects who had cardiac response at 6 months; N = number of subjects who were cardiac-evaluable for response

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

In responders, the median time to HemCR was 60 days (range: 8 to 299 days) in the D-VCd group and 85 days (range: 14 to 340 days) in the VCd group. The median time to VGPR or

better was 17 days (range: 5 to 336 days) in the D-VCd group and 25 days (range: 8 to 171 days) in the VCd group. The median duration of HemCR had not been reached in either arm.

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



The median follow-up for the study is 11,4 months. The median major organ deterioration progression-free survival (MOD-PFS) was not reached for patients in either arm. The median major organ deterioration event free survival (MOD-EFS) was not reached for patients receiving D-VCd and was 8,8 months for patient receiving VCd. The hazard ratio for MOD-EFS was 0,39 (95 CI: 0,27, 0,56) and the nominal p-value was < 0,0001. Overall survival (OS)

data were not mature. A total of 56 deaths were observed [N=27 (13,8 %) D-VCd vs. N=29 (15 %) VCd group].

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

Clinical experience with daratumumab intravenous formulation

Newly Diagnosed Multiple Myeloma Eligible for ASCT

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

Study MMY3006, an open-label, randomised, active-controlled Phase 3 study compared induction and consolidation treatment with IV daratumumab 16 mg/kg in combination with bortezomib, thalidomide and dexamethasone (D-VTd) to treatment with bortezomib, thalidomide and dexamethasone (VTd) in patients with newly diagnosed multiple myeloma eligible for ASCT. The consolidation phase of treatment began a minimum of 30 days post-ASCT, when the patient had recovered sufficiently, and engraftment was complete.

Bortezomib was administered by subcutaneous (SC) injection or intravenous (IV) injection at a dose of 1,3 mg/m^2 body surface area twice weekly for two weeks (Days 1, 4, 8, and 11) of repeated 28-day (4-week) induction treatment cycles (Cycles 1-4) and two consolidation cycles

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

A total of 1 085 patients were randomised: 543 to the D-VTd arm and 542 to the VTd arm. The baseline demographic and disease characteristics were similar between the two treatment groups. The median age was 58 (range: 22 to 65 years). The majority were male (59 %), 48 % had an ECOG performance score of 0, 42 % had an ECOG performance score of 1 and 10 % had an ECOG performance score of 2. Forty percent had ISS Stage I, 45 % had ISS Stage II and 15 % had ISS Stage III disease.

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

Table 11: Efficacy results from Study MMY3006[a]

	D-VTd (n=543)	**VTd (n=542)**	**P value[b]**
Response assessment Day 100 post-transplant			
Stringent Complete Response (sCR)	157 (28,9 %)	110 (20,3 %)	0,0010
CR or better (sCR+CR)	211 (38,9 %)	141 (26,0 %)	< 0,0001
Very Good Partial Response or better (sCR+CR+VGPR)	453 (83,4 %)	423 (78,0 %)	
MRD negativity[c] n(%)	346 (63,7 %)	236 (43,5 %)	< 0,0001
95% CI (%)	(59,5 %, 67,8 %)	(39,3 %, 47,8 %)	
Odds ratio with 95% CI[d]	2,27 (1,78, 2,90)		

MRD negativity[e] n(%)	183 (33,7 %)	108 (19,9 %)	< 0,0001
95% CI (%)	(29,7 %, 37,9 %)	(16,6 %, 23,5 %)	
Odds ratio with 95% CI[d]	2,06 (1,56, 2,72)		

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

[a] Based on intent-to-treat population

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

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

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

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

With a median follow-up of 18,8 months, the primary analysis of PFS in study MMY3006 demonstrated an improvement in PFS in the D-VTd arm as compared to the VTd arm; the median PFS had not been reached in either arm. Treatment with D-VTd resulted in a reduction in the risk of progression or death by 53 % compared to VTd alone (HR=0,47; 95 % CI: 0,33, 0,67; p < 0,0001). Results of an updated PFS analysis after a median follow-up of 44,5 months continued to show an improvement in PFS for patients in the D VTd arm compared with the VTd arm. Median PFS was not reached in the D VTd arm and was 51,5 months in the VTd arm (HR=0,58; 95 % CI: 0,47, 0,71; p < 0,0001), representing a 42 % reduction in the risk of disease progression or death in patients treated with D VTd.

Newly Diagnosed Multiple Myeloma Ineligible for ASCT

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

Study MMY3008 an open-label, randomised, active-controlled Phase 3 study, compared treatment with IV daratumumab 16 mg/kg in combination with lenalidomide and low-dose dexamethasone (D-Rd) to treatment with lenalidomide and low-dose dexamethasone (Rd) in

patients with newly diagnosed multiple myeloma. Lenalidomide (25 mg once daily orally on Days 1-21 of repeated 28-day [4-week] cycles) was given with low dose oral or intravenous dexamethasone 40 mg/week (or a reduced dose of 20 mg/week for patients > 75 years or body mass index [BMI] < 18,5). On IV daratumumab infusion days, the dexamethasone dose was given as a pre-infusion medication. Dose adjustments for lenalidomide and dexamethasone were applied according to manufacturer's prescribing information. Treatment was continued in both arms until disease progression or unacceptable toxicity.

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

With a median follow-up of 28 months, the primary analysis of PFS in study MMY3008 demonstrated an improvement in the D-Rd arm as compared to the Rd arm; the median PFS had not been reached in the D-Rd arm and was 31,9 months in the Rd arm (hazard ratio [HR]=0,56; 95 % CI: 0,43, 0,73; p < 0,0001), representing 44 % reduction in the risk of disease progression or death in patients treated with D-Rd. Results of an updated PFS analysis after a median follow-up of 64 months continued to show an improvement in PFS for patients in the D-Rd arm compared with the Rd arm. Median PFS was 61,9 months in the D-Rd arm and 34,4

months in the Rd arm (HR=0,55; 95 % CI: 0,45, 0,67; p < 0,0001), representing a 45% reduction in the risk of disease progression or death in patients treated with D-Rd.

After a median follow-up of 56 months, D Rd has shown an OS advantage over the Rd arm (HR=0,68; 95 % CI: 0,53, 0,86; p = 0,0013), representing a 32 % reduction in the risk of death in patients treated in the D Rd arm. Median OS was not reached for either arm. The 60 month survival rate was 66 % (95 % CI: 61, 71) in the D Rd arm and was 53 % (95 % CI: 47, 59) in the Rd arm.

In responders, the median time to response was 1,05 months (range: 0,2 to 12,1 months) in the D-Rd group and 1,05 months (range: 0,3 to 15,3 months) in the Rd group. The median duration of response had not been reached in the D-Rd group and was 34,7 months (95 % CI: 30,8, not estimable) in the Rd group.

Additional efficacy results from Study MMY3008 are presented in Table 12 below.

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

Study MMY3007, an open-label, randomised, 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 more 6-week cycles (Cycles 2 - 9; 4 doses per cycle). Melphalan at 9 mg/m^2, and prednisone at 60

mg/m^2 were orally administered on Days 1 to 4 of the nine 6-week cycles (Cycles 1 - 9). IV daratumumab treatment was continued until disease progression or unacceptable toxicity.

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

With a median follow-up of 16,5 months, the primary analysis of PFS in study MMY3007 demonstrated an improvement in the D-VMP arm as compared to the VMP arm; the median PFS had not been reached in the D-VMP arm and was 18,1 months in the VMP arm (HR=0,5; 95 % CI: 0,38, 0,65; p < 0,0001), representing 50 % reduction in the risk of disease progression or death in patients treated with D-VMP. Results of an updated PFS analysis after a median follow-up of 40 months continued to show an improvement in PFS for patients in the D VMP arm compared with the VMP arm. Median PFS was 36,4 months in the D-VMP arm and 19.3 months in the VMP arm (HR=0,42; 95 % CI: 0,34, 0,51; p < 0,0001), representing a 58 % reduction in the risk of disease progression or death in patients treated with D-VMP.

After a median follow-up of 40 months, D-VMP has shown an overall survival (OS) advantage over the VMP arm (HR=0,60; 95 % CI: 0,46, 0,80; p = 0,0003), representing a 40 % reduction in the risk of death in patients treated in the D-VMP arm. Median OS was not reached for either arm.

In responders, the median time to response was 0,79 months (range: 0,4 to 15,5 months) in the D-VMP group and 0,82 months (range: 0,7 to 12,6 months) in the VMP group. The median duration of response had not been reached in the D-VMP group and was 21,3 months (range: 18,4, not estimable) in the VMP group.

Additional efficacy results from Study MMY3007 are presented in Table 12 below.

Relapsed/Refractory Multiple Myeloma

Combination treatment with lenalidomide and dexamethasone

Study MMY3003, an open-label, randomised, active-controlled Phase 3 trial, compared treatment with IV daratumumab 16 mg/kg in combination with lenalidomide and low-dose dexamethasone (D-Rd) to treatment with lenalidomide and low-dose dexamethasone (Rd) in patients with multiple myeloma who had received at least one prior therapy. Lenalidomide (25 mg once daily orally on Days 1 - 21 of repeated 28-day [4 - week] cycles) was given with low dose oral or intravenous dexamethasone 40 mg/week (or a reduced dose of 20 mg/week for patients > 75 years or BMI < 18,5). On IV daratumumab infusion days, 20 mg of the dexamethasone dose was given as a pre-infusion medication and the remainder given the day after the infusion. For patients on a reduced dexamethasone dose, the entire 20 mg dose was given as a IV daratumumab pre-infusion medication. Dose adjustments for lenalidomide and dexamethasone were applied according to manufacturer's prescribing information. Treatment was continued in both arms until disease progression or unacceptable toxicity.

A total of 569 patients were randomised; 286 to the D-Rd arm and 283 to the Rd arm. The baseline demographic and disease characteristics were similar between the IV daratumumab

and the control arm. The median patient age was 65 years (range 34 to 89 years), 11 % were ≥ 75 years, 59 % were male; 69 % Caucasian, 18 % Asian, and 3 % African American. Patients had received a median of 1 prior line of therapy. Sixty-three percent (63 %) of patients had received prior 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 and overall survival (OS).

With a median follow-up of 13,5 months, the primary analysis of PFS in study MMY3003 demonstrated an improvement in the D-Rd arm as compared to the Rd arm; the median PFS had not been reached in the D-Rd arm and was 18,4 months in the Rd arm (HR = 0,37; 95 % CI: 0,27, 0,52; p < 0,0001) representing 63 % reduction in the risk of disease progression or death in patients treated with D-Rd. Results of an updated PFS analysis after a median follow-up of 55 months continued to show an improvement in PFS for patients in the D-Rd arm compared with the Rd arm. Median PFS was 45,0 months in the D-Rd arm and 17,5 months in the Rd arm (HR=0,44; 95 % CI: 0,35, 0,54; p < 0,0001), representing a 56 % reduction in the risk of disease progression or death in patients treated with D-Rd.

After a median follow-up of 80 months, D-Rd has shown an OS advantage over the Rd arm (HR=0,73; 95 % CI: 0,58, 0,91; p=0,0044), representing a 27 % reduction in the risk of death in patients treated in the D-Rd arm. The median OS was 67,6 months in the D-Rd arm and 51,8 months in the Rd arm. The 78 - month survival rate was 47 % (95 % CI: 41, 52) in the DRd arm and was 35 % (95 % CI: 30, 41) in the Rd arm.

Additional efficacy results from Study MMY3003 are presented in Table 12 below.

Combination treatment with bortezomib and dexamethasone

Study MMY3004, an open-label, randomised, active-controlled Phase 3 trial, compared treatment with IV daratumumab 16 mg/kg in combination with bortezomib and dexamethasone (D-Vd), to treatment with bortezomib and dexamethasone (Vd) in patients with multiple myeloma who had received at least one prior therapy. Bortezomib was administered by SC injection or IV injection at a dose of 1,3 mg/m^2 body surface area twice weekly for two weeks (Days 1, 4, 8, and 11) of repeated 21 day (3 - week) treatment cycles, for a total of 8 cycles. Dexamethasone was administered orally at a dose of 20 mg on Days 1, 2, 4, 5, 8, 9, 11, and 12 of the 8 bortezomib cycles (80 mg/week for two out of three weeks of each of the bortezomib cycle) or a reduced dose of 20 mg/week for patients > 75 years, BMI < 18,5, poorly controlled diabetes mellitus or prior intolerance to steroid therapy. On the days of IV daratumumab infusion, 20 mg of the dexamethasone dose was administered as a pre-infusion medication. For patients on a reduced dexamethasone dose, the entire 20 mg dose was given as a IV daratumumab pre-infusion medication. Bortezomib and dexamethasone were given for 8 three week cycles in both treatment arms; whereas IV daratumumab was given until treatment progression. However, dexamethasone 20 mg was continued as a IV daratumumab pre-infusion medication in the D-Vd arm. Dose adjustments for bortezomib and dexamethasone were applied according to manufacturer's prescribing information.

A total of 498 patients were randomised; 251 to the D-Vd arm and 247 to the Vd arm. The baseline demographic and disease characteristics were similar between the IV daratumumab and the control arm. The median patient age was 64 years (range 30 to 88 years); 12 % were ≥ 75 years, 57 % were male; 87 % Caucasian, 5 % Asian and 4 % African American. Patients

had received a median of 2 prior lines of therapy and 61 % of patients had received prior 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 and overall survival (OS).

With a median follow-up of 7,4 months, the primary analysis of PFS in study MMY3004 demonstrated an improvement in the D-Vd arm as compared to the Vd arm; the median PFS had not been reached in the D-Vd arm and was 7,2 months in the Vd arm (HR [95 % CI]: 0,39 [0,28, 0,53]; p-value < 0,0001), representing a 61 % reduction in the risk of disease progression or death for patients treated with D-Vd versus Vd. Results of an updated PFS analysis after a median follow-up of 50 months continued to show an improvement in PFS for patients in the D-Vd arm compared with the Vd arm. Median PFS was 16,7 months in the D-Vd arm and 7,1 months in the Vd arm (HR [95 % CI]: 0,31 [0,24, 0,39]; p-value < 0,0001), representing a 69 % reduction in the risk of disease progression or death in patients treated with D-Vd versus Vd.

After a median follow-up of 73 months, D-Vd has shown an OS advantage over the Vd arm (HR=0,74: 95 % CI: 0,59, 0,92; p=0,0075), representing a 26 % reduction in the risk of death in patients treated in the D-Vd arm. The median OS was 49,6 months in the D-Vd arm and 38,5 months in the Vd arm. The 72 - month survival rate was 39 % (95 % CI: 33, 45) in the D-Vd arm and was 25 % (95 % CI: 20, 31) in the Vd arm.

Additional efficacy results from Study MMY3004 are presented in Table 12 below.

Table 12: Summary of efficacy result of randomised studies with IV daratumumab in multiple myeloma

	MMY3008		MMY3007		MMY3003		MMY3004	
	D-Rd n=368	**Rd n=369**	**D-VMP n=350**	**VMP n=356**	**D-Rd n=281[h]**	**Rd n=276[h]**	**D-Vd n=240[h]**	**Vd n=234[h]**
Progression-free survival (PFS) months								
Median[a]	NE	31,87	NE	18,14	NE	18,43	NE	7,16
Hazard ratio (95 % CI)[b]	0,56 (0,43, 0,73)		0,50 (0,38, 0,65)		0,37 (0,27, 0,52)		0,39 (0,28, 0,53)	
P-value[c]	< 0,0001		< 0,0001		< 0,0001		< 0,0001	
Overall response (sCR+CR+VGPR+PR) n(%)[d]	342 (92,9 %)	300 (81,3 %)	318 (90,9 %)	263 (73,9 %)	261 (92,9%)	211 (76,4 %)	199 (82,9 %)	148 (63,2 %)
P-value[e]	< 0,0001		< 0,0001		< 0,0001		< 0,0001	
Stringent complete response (sCR)	112 (30,4 %)	46 (12,5 %)	63 (18,0 %)	25 (7,0 %)	51 (18,1 %)	20 (7,2 %)	11 (4,6 %)	5 (2,1 %)
Complete response (CR)	63 (17,1 %)	46 (12,5 %)	86 (24,6 %)	62 (17,4 %)	70 (24,9 %)	33 (12,0 %)	35 (14,6%)	16 (6,8 %)
Very good partial response (VGPR)	117 (31.8%)	104 (28.2%)	100 (28.6%)	90 (25.3%)	92 (32.7%)	69 (25.0%)	96 (40.0%)	47 (20.1%)
Partial response (PR)	50 (13.6%)	104 (28.2%)	69 (19.7%)	86 (24.2%)	48 (17.1%)	89 (32.2%)	57 (23.8%)	80 (34.2%)
MRD negative rate (95% CI)[f] (%)	89 (24.2%)	27 (7.3%)	78 (22.3%)	22 (6.2%)	60 (21.0%)	8 (2.8%)	22 (8.8%)	3 (1.2%)
95% CI	(19.9%, 28.9%)	(4.9%, 10.5%)	(18.0%, 27.0%)	(3.9%, 9.2%)	(16.4%, 26.2%)	(1.2%, 5.5%)	(5.6%, 13.0%)	(0.3%, 3.5%)
P-value[g]	<0.0001		<0.0001		<0.0001		0.0001	

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

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

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

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

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

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

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

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

[h] Response evaluable population

Combination treatment with pomalidomide and dexamethasone

Study MMY1001 was an open-label trial in which 103 patients with multiple myeloma who had received a prior PI and an IMiD, received IV daratumumab 16 mg/kg in combination with pomalidomide and low-dose dexamethasone until disease progression. Pomalidomide (4 mg once daily orally on Days 1-21 of repeated 28-day [4-week] cycles) was given with low dose oral or intravenous dexamethasone at 40 mg/week (reduced dose of 20 mg/week for patients > 75 years or BMI < 18,5). On IV daratumumab infusion days, 20 mg of the dexamethasone dose was given as a pre-infusion medication and the remainder given the day after the infusion. For patients on a reduced dexamethasone dose, the entire 20 mg dose was given as a IV daratumumab pre-infusion medication.

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

patients received prior lenalidomide treatment, with 98 % of patients previously treated with the combination of bortezomib and lenalidomide. Eighty nine percent (89 %) of patients were refractory to lenalidomide and 71 % refractory to bortezomib; 64 % of patients were refractory to bortezomib and lenalidomide.

Overall response rate was 59 % (95 % CI: 49,1 %, 68,8 %); VGPR or better was achieved in 42 % of patients, CR or better was achieved in 14 % of patients and stringent CR was achieved in 8 % of patients. The Clinical Benefit Rate (ORR+ MR [Minimal response]) was 62 % (95 % CI: 52,0, 71,5). The median time to response was 1 month (range: 0,9 to 2,8 months). The median duration of response was 13,6 months (95 % CI: 10,0, not estimable). After a median duration of follow up of 9,8 months, the median OS was not reached. The 12-month survival rate was 72 %.

5.2 Pharmacokinetic properties

Daratumumab exposure in a monotherapy study (MMY3012) in patients with multiple myeloma following the recommended 1 800 mg administration of DARZALEX SC formulation (weekly for 8 weeks, biweekly for 16 weeks, monthly thereafter) as_compared to 16 mg/kg IV daratumumab for the same dosing schedule, showed non-inferiority for the co-primary endpoint of maximum Ctrough (Cycle 3 Day 1 pre-dose), with mean ± SD of 593 ± 306 µg/mL compared to 522 ± 226 µg/mL for IV daratumumab, with a geometric mean ratio of 107,93 % (90 % CI: 95,74 - 121,67).

Daratumumab exhibits both concentration and time-dependent pharmacokinetics with first order absorption and parallel linear and nonlinear (saturable) elimination that is characteristic of target-mediated clearance. Following the recommended dose of 1 800 mg DARZALEX SC

formulation as monotherapy, peak concentrations (Cmax) increased 4,8 - fold and total exposure ($AUC_{0\text{-}7\ days}$) increased 5,4 - fold from first dose to last weekly dose (8th dose). Highest trough concentrations for DARZALEX SC formulation are typically observed at the end of the weekly dosing regimens for both monotherapy and combination therapy.

In patients with multiple myeloma, the simulated trough concentrations following 6 weekly doses of 1 800 mg DARZALEX for combination therapy were similar to 1 800 mg DARZALEX monotherapy.

In patients with multiple myeloma, daratumumab exposure in a combination study with pomalidomide and dexamethasone (MMY3013) was similar to that in monotherapy, with the maximum C_{trough} (Cycle 3 Day 1 pre-dose) mean ± SD of 537 ± 277 µg/mL following the recommended 1 800 mg administration of DARZALEX SC formulation (weekly for 8 weeks, biweekly for 16 weeks, monthly thereafter).

In a combination study, AMY3001, in patients with AL amyloidosis, the maximum C_{trough} (Cycle 3 Day 1 pre-dose) was similar to that in multiple myeloma with mean ± SD of 597 ± 232 µg/mL following the recommended 1 800 mg administration of DARZALEX SC formulation (weekly for 8 weeks, biweekly for 16 weeks, monthly thereafter).

Absorption and Distribution

At the recommended dose of 1 800 mg in multiple myeloma patients, the absolute bioavailability of DARZALEX SC formulation is 69 %, with an absorption rate of 0,012 hour-1, with peak concentrations occurring at 70 to 72 h (T_{max}). At the recommended dose of 1 800 mg in AL amyloidosis patients, the absolute bioavailability was not estimated, the absorption rate_constant was 0,77 day^{-1} (8,31 % CV) and peak concentrations occurred at 3 days.

In multiple myeloma patients, the modeled mean estimate of the volume of distribution for the central compartment (V1) is 5,25 L (36,9 % CV) and peripheral compartment (V2) was 3,78 L in daratumumab monotherapy, and the modeled mean estimate of the volume of distribution for V1 is 4,36 L (28,0 % CV) and V2 was 2,80 L when daratumumab was administered in combination with pomalidomide and dexamethasone. In AL amyloidosis patients, the model estimated apparent volume of distribution after SC administration is 10,8 L (3,1 % CV). These results suggest that daratumumab is primarily localised to the vascular system with limited extravascular tissue distribution.

Metabolism and Elimination

Daratumumab is cleared by parallel linear and nonlinear saturable target mediated clearances. In multiple myeloma patients, the population PK model estimated mean clearance value of daratumumab is 4,96 mL/h (58,7% CV) in daratumumab monotherapy and 4,32 mL/h (43,5 % CV) when daratumumab was administered in combination with pomalidomide and dexamethasone. In AL amyloidosis patients, the apparent clearance after SC administration is 210 mL/day (4,1 % CV).

In multiple myeloma patients, the model-based geometric mean post hoc estimate for half-life associated with linear elimination is 20,4 days (22,4 % CV) in daratumumab monotherapy and 19,7 days (15,3 % CV) when daratumumab was administered in combination with pomalidomide and dexamethasone. In AL amyloidosis patients, the model-based geometric mean post hoc estimate for half-life associated with linear elimination is 27,5 days (74,0 % CV). For the monotherapy and combination regimens, the steady state is achieved at approximately 5 months into every 4 weeks dosage at the recommended dose and schedule

(1 800 mg; once weekly for 8 weeks, every 2 weeks for 16 weeks, and then every 4 weeks thereafter).

A population PK analysis, using data from DARZALEX SC formulation monotherapy and combination therapy in multiple myeloma patients, was conducted with data from 487 patients who received DARZALEX SC formulation and 255 patients who received IV daratumumab. The predicted PK exposures are summarised in Table 13.

Table 13: Daratumumab exposure following administration of DARZALEX (1 800 mg) or IV daratumumab (16 mg/kg) monotherapy in patients with multiple myeloma

PK parameters	Cycles	SC daratumumab Median (5^{th}; 95^{th} percentile)	IV daratumumab Median (5^{th}; 95^{th} percentile)
C_{trough} (µg/mL)	Cycle 1, 1^{st} weekly dose	123 (36; 220)	112 (43; 168)
	Cycle 2, last weekly dose (Cycle 3 Day 1 C_{trough})	563 (177; 1063)	472 (144; 809)
C_{max} (µg/mL)	Cycle 1, 1^{st} 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, 1^{st} weekly dose	720 (293; 1274)	1187 (773; 1619)
	Cycle 2, last weekly dose	4017 (1515; 7564)	4019 (1740; 6370)

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

Table 14: Daratumumab exposure following administration of DARZALEX (1 800 mg) in patients with AL amyloidosis

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

Special populations

Age and gender

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

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

Renal impairment

No formal studies of DARZALEX SC formulation in patients with renal impairment have been conducted. Population PK analyses were performed based on pre-existing renal function data in patients with multiple myeloma receiving DARZALEX monotherapy or various combination therapies in patients with multiple myeloma or AL amyloidosis and no clinically important differences in exposure to daratumumab were observed between patients with renal impairment and those with normal renal function.

Hepatic impairment

No formal studies of DARZALEX SC formulation in patients with hepatic impairment have been conducted. Population PK analyses were performed in patients with multiple myeloma receiving DARZALEX SC formulation monotherapy or various combination therapies in patients with multiple myeloma or in AL amyloidosis. No clinically important differences in the exposure to daratumumab were observed between patients with normal hepatic function and mild hepatic impairment. There were very few patients with moderate and severe hepatic impairment to make meaningful conclusions for these populations.

Race

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

Body weight

The flat dose administration of DARZALEX SC formulation 1 800 mg as monotherapy achieved adequate exposure for all body-weight subgroups. In patients with multiple myeloma, the mean Cycle 3 Day 1 C_{trough} in the lower body-weight subgroup (≤ 65 kg) was 60 % higher and in the higher body weight (> 85 kg) subgroup, 12 % lower than the IV daratumumab subgroup. However, no body weight based dose adjustments are needed, as the exposure changes are not considered clinically relevant.

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

5.3 Preclinical safety data

Carcinogenicity and Mutagenicity

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

Reproductive Toxicology

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

No systemic exposure of hyaluronidase was detected in monkeys given 22,000 U/kg subcutaneously (12 times higher than the human dose) and there were no effects on embryo-foetal 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

Human hyaluronidase (rHuPH20)

L-histidine

L-histidine HCl monohydrate

Sorbitol

L-methionine

Polysorbate20

Water for injection

6.2 Incompatibilities

This medicine should only be used with the materials mentioned in Section 4.2

6.3 Shelf life

Unopened vial

18 months

See expiry date on the outer pack.

During the shelf-life, the product in unpunctured vials may be stored at room temperature (≤ 30 °C) for a single period of up to 24 hours. Once the product has been taken out of the refrigerator, it must not be returned to the refrigerator (see section 6.6).

Shelf life of prepared syringe:

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

6.4 Special precautions for storage

Store DARZALEX 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.

6.5 Nature and contents of container

15 mL solution in a type 1 glass vial with a 20 mm grey bromobutyl rubber stopper elastomer and an aluminium seal with a dark grey flip off button containing 1 800 mg of daratumumab. Pack size of 1 vial.

The DARZALEX vial is packed into an opaque paperboard carton. Each carton consists of vial and a package leaflet.

6.6 Special precautions for disposal and other handling

DARZALEX solution for subcutaneous injection is for single use only and is ready to use.

DARZALEX solution for subcutaneous injection should be a clear to opalescent and colourless to yellow solution. Do not use if opaque particles, discolouration or other foreign particles are present.

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

Remove the DARZALEX solution for subcutaneous injection 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 in the original carton to protect from light. Keep out of direct sunlight. Do not shake.

Prepare the dosing syringe in controlled and validated aseptic conditions. Once transferred from the vial into the syringe, store DARZALEX solution for subcutaneous injection for up to 4 hours at ambient temperature and ambient light (see section 6.3).

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

7. HOLDER OF CERTIFICATE OF REGISTRATION

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8. REGISTRATION NUMBER

57/26/0332

9 DATE OF FIRST AUTHORISATION

Date of registration: 12 March 2024