SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

DARZALEX 1,800 mg solution for injection.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 15 mL vial of solution for injection contains 1,800 mg of daratumumab (120 mg daratumumab per mL).

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

Excipients with known effect
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 clear to opalescent, colourless to yellow.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

DARZALEX is indicated:

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

4.2 Posology and method of administration

DARZALEX subcutaneous formulation is not intended for intravenous administration and should be given by subcutaneous injection only, using the doses specified.

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

It is important to check the vial labels to ensure that the appropriate formulation (intravenous or subcutaneous formulation) and dose is being given to the patient as prescribed.

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

Pre- and post-injection medicinal products should be administered to reduce the risk of infusion-related reactions (IRRs) with daratumumab. See below "Recommended concomitant medicinal products" and section 4.4.

Posology

Dosing schedule in combination with lenalidomide (4-week cycle regimen) and for monotherapy
The recommended dose is 1,800 mg of DARZALEX solution for subcutaneous injection administered over approximately 3-5 minutes according to the following dosing schedule in Table 1.

Table 1: DARZALEX dosing schedule in combination with lenalidomide (4-week cycle dosing regimen) and monotherapy

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 dose and schedule of medicinal products administered with DARZALEX solution for subcutaneous injection, see section 5.1 and the corresponding Summary of Product Characteristics.

Dosing schedule in combination with bortezomib, melphalan and prednisone (6-week cycle regimens)
The recommended dose is 1,800 mg of DARZALEX solution for subcutaneous injection administered over approximately 3-5 minutes according to the following dosing schedule in Table 2.

Table 2: DARZALEX 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 solution for subcutaneous injection, see section 5.1.

Dosing schedule in combination with bortezomib, thalidomide and dexamethasone (4-week cycle regimens) for treatment of newly diagnosed patients eligible for autologous stem cell transplant (ASCT)
The recommended dose is 1,800 mg of DARZALEX solution for subcutaneous injection administered over approximately 3-5 minutes according to the following dosing schedule in Table 3.

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

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

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

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

For dose and schedule of medicinal products administered with DARZALEX solution for subcutaneous injection, see section 5.1 and the corresponding Summary of Product Characteristics.

Dosing schedule in combination with bortezomib (3-week cycle regimen)
The recommended dose is 1,800 mg of DARZALEX solution for subcutaneous injection administered over approximately 3-5 minutes according to the following dosing schedule in Table 4.

Table 4: DARZALEX dosing schedule in combination with bortezomib (3-week cycle dosing regimen)

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

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

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

For dose and schedule of medicinal products administered with DARZALEX solution for subcutaneous injection, see section 5.1 and the corresponding Summary of Product Characteristics.

Missed dose
If a planned dose of DARZALEX 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 are recommended. Dose delay may be required to allow recovery of blood cell counts in the event of haematological toxicity (see section 4.4). For information concerning medicinal products given in combination with DARZALEX, see corresponding Summary of Product Characteristics.

In clinical studies, no modification to rate or dose of DARZALEX solution for subcutaneous injection was required to manage IRRs.

Recommended concomitant medicinal products

Pre-injection medicinal product
Pre-injection medicinal products (oral or intravenous) should be administered to reduce the risk of IRRs to all patients 1-3 hours prior to every administration of DARZALEX solution for 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:
    Dexamethasone 20 mg (or equivalent), administered prior to every DARZALEX solution for subcutaneous injection. When dexamethasone is the background-regimen specific corticosteroid, the dexamethasone treatment dose will instead serve as pre-injection

medicinal product on DARZALEX administration days (see section 5.1). Additional background regimen specific corticosteroids (e.g. prednisone) should not be taken on DARZALEX administration days when patients have received dexamethasone (or equivalent) as a pre-injection medicinal product.

- Antipyretics (paracetamol 650 to 1,000 mg).
- Antihistamine (oral or intravenous diphenhydramine 25 to 50 mg or equivalent).

Post-injection medicinal product
Post-injection medicinal products should be administered to reduce the risk of delayed IRRs as follows:

- Monotherapy:
  Oral corticosteroid (20 mg methylprednisolone or equivalent dose of an intermediate-acting or long-acting corticosteroid in accordance with local standards) should be administered on each of the two days following all injections (beginning the day after the injection).

- Combination therapy:
  Consider administering low-dose oral methylprednisolone (≤20 mg) or equivalent the day after the DARZALEX injection. However, if a background regimen specific corticosteroid (e.g. dexamethasone, prednisone) is administered the day after the DARZALEX injection, additional post-injection medicinal products may not be needed (see section 5.1).

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

Additionally, for patients with a history of chronic obstructive pulmonary disease, the use of post-injection medicinal products including short and long acting bronchodilators, and inhaled corticosteroids should be considered. Following the first four injections, if the patient experiences no major IRRs, these inhaled post-injection medicinal products may be discontinued at the discretion of the physician.

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

Special populations

Renal impairment
No formal studies of daratumumab in patients with renal impairment have been conducted. Based on population pharmacokinetic (PK) analyses no dosage adjustment is necessary for patients with renal impairment (see section 5.2).

Hepatic impairment
No formal studies of daratumumab in patients with hepatic impairment have been conducted.
No dosage adjustments are necessary for patients with hepatic impairment (see section 5.2).

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

Paediatric population
The safety and efficacy of DARZALEX in children aged below 18 years of age have not been established.
No data are available (see section 5.1).

Body weight (>120 kg)
Limited number of patients with body weight >120 kg have been studied using flat-dose (1,800 mg) DARZALEX solution for subcutaneous injection and efficacy in these patients has not been

established. No dose adjustment based on body weight can currently be recommended (see sections 4.4 and 5.2).

Method of administration

DARZALEX subcutaneous formulation is not intended for intravenous administration and should be given by subcutaneous injection only, using the doses specified. See section 6.6 for special precautions prior to administration.

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

Inject 15 mL DARZALEX solution for subcutaneous 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 solution for subcutaneous injection at other sites of the body as no data are available.

Injection sites should be rotated for successive injections.

DARZALEX solution for subcutaneous 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 solution for subcutaneous injection, do not administer other medicinal products for subcutaneous use at the same site as DARZALEX.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Traceability
In order to improve the traceability of biological medicinal products, the tradename and the batch number of the administered product should be clearly recorded.

Infusion-related reactions
DARZALEX solution for subcutaneous injection can cause severe and/or serious IRRs, including anaphylactic reactions. In clinical studies, approximately 11% (52/490) of patients experienced an IRR. Most IRRs occurred following the first injection and were Grade 1-2. IRRs occurring with subsequent injections were seen in less than 1% of patients (see section 4.8).

The median time to onset of IRRs following DARZALEX injection was 3.7 hours (range 0.15-83 hours). The majority of IRRs occurred on the day of treatment. Delayed IRRs have occurred in less than 1% of patients.

Signs and symptoms of IRRs may include respiratory symptoms, such as nasal congestion, cough, throat irritation, allergic rhinitis, wheezing as well as pyrexia, chest pain, pruritis, chills, vomiting, nausea, and hypotension. Severe reactions have occurred, including bronchospasm, hypoxia, dyspnoea, hypertension and tachycardia (see section 4.8).

Patients should be pre-medicated with antihistamines, antipyretics, and corticosteroids as well as 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, appropriate

emergency care should be initiated immediately. DARZALEX therapy should be discontinued immediately and permanently (see sections 4.2 and 4.3).

To reduce the risk of delayed IRRs, oral corticosteroids should be administered to all patients following DARZALEX injection (see section 4.2). Patients with a history of chronic obstructive pulmonary disease may require additional post-injection medicinal products to manage respiratory complications. The use of post-injection medicinal products (e.g. short- and long-acting bronchodilators and inhaled corticosteroids) should be considered for patients with chronic obstructive pulmonary disease (see section 4.2).

Neutropenia/Thrombocytopenia

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

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

Interference with indirect antiglobulin test (indirect Coombs test)

Daratumumab binds to CD38 found at low levels on red blood cells (RBCs) and may result in a positive indirect Coombs test. Daratumumab-mediated positive indirect Coombs test may persist for up to 6 months after the last daratumumab administration. It should be recognised that daratumumab bound to RBCs may mask detection of antibodies to minor antigens in the patient's serum. The determination of a patient's ABO and Rh blood type are not impacted.

Patients should be typed and screened prior to starting daratumumab treatment. Phenotyping may be considered prior to starting daratumumab treatment as per local practice. Red blood cell genotyping is not impacted by daratumumab and may be performed at any time.

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.

Interference with determination of complete response

Daratumumab is a human IgG kappa monoclonal antibody that can be detected on both, the serum protein electrophoresis (SPE) and immunofixation (IFE) assays used for the clinical monitoring of endogenous M-protein (see section 4.5). This interference can impact the determination of complete response and of disease progression in some patients with IgG kappa myeloma protein.

Hepatitis B virus (HBV) reactivation

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

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 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, suspend treatment with DARZALEX and institute appropriate treatment. Resumption of DARZALEX treatment in patients whose HBV reactivation is adequately controlled should be discussed with physicians with expertise in managing HBV.

Body weight (>120 kg)
There is a potential for reduced efficacy with DARZALEX solution for subcutaneous injection in patients with body weight >120 kg (see sections 4.2 and 5.2).

Excipients
This medicinal product contains sorbitol (E420). Patients with rare hereditary fructose intolerance (HFI) should not take this medicinal product (see section 2).

This medicinal product also contains less than 1 mmol (23 mg) sodium per dose, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

No 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 and lenalidomide, pomalidomide, thalidomide, bortezomib, melphalan, prednisone, carfilzomib and dexamethasone indicated no clinically-relevant drug-drug 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 (see section 4.4). Daratumumab interference mitigation methods include treating reagent RBCs with dithiothreitol (DTT) to disrupt daratumumab binding or other locally validated methods. 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. Alternatively, phenotyping or genotyping may also be considered (see section 4.4).

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

4.6 Fertility, pregnancy and lactation

Women of child-bearing potential/Contraception
Women of child-bearing potential should use effective contraception during, and for 3 months after cessation of daratumumab treatment.

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

Breast-feeding
It is not known whether daratumumab is excreted into human or animal milk.
Maternal IgG is excreted in human milk, but does not enter the neonatal and newborn/infant circulations in substantial amounts as they are degraded in the gastrointestinal tract and not absorbed.

The effect of daratumumab on newborns/infants is unknown. A decision should be made whether to discontinue breast-feeding or to discontinue DARZALEX therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility
No data are available to determine potential effects of daratumumab on fertility in males or females (see section 5.3).

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile
The most frequent adverse reactions of any grade (≥20 % patients) with daratumumab (either intravenous or subcutaneous formulations) when administered either as monotherapy or combination treatment were IRRs, fatigue, nausea, diarrhoea, constipation, pyrexia, cough, neutropenia, thrombocytopenia, anaemia, oedema peripheral, peripheral sensory neuropathy and upper respiratory tract infection. Serious adverse reactions were pneumonia, bronchitis, upper respiratory tract infection, sepsis, pulmonary oedema, influenza, pyrexia, dehydration, diarrhoea and atrial fibrillation.

With the exception of IRRs (see Table 5 below), the safety profile of DARZALEX subcutaneous formulation (evaluated in 260 and 258 patients treated with the subcutaneous and intravenous formulations respectively) from the Phase III study MMY3012 was similar to the known safety profile of the intravenous formulation. Neutropenia is the only adverse reaction reported at ≥ 5% higher frequency for DARZALEX subcutaneous formulation compared to intravenous daratumumab (Grade 3 or 4: 13% vs 8%, respectively).

Tabulated list of adverse reactions
Table 5 summarises the adverse reactions that occurred in patients receiving DARZALEX subcutaneous formulation or intravenous formulation of daratumumab.

The data reflects exposure to DARZALEX subcutaneous formulation (1,800 mg) in 490 patients with multiple myeloma (MM) including 260 patients from a Phase III active-controlled trial (Study MMY3012) who received DARZALEX solution for subcutaneous injection as monotherapy and three open-label, clinical studies in which patients received DARZALEX solution for subcutaneous injection either as monotherapy (N=31, MMY1004 and MMY1008) and MMY2040 in which patients received DARZALEX solution for subcutaneous injection 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).

The safety data also reflects exposure to intravenous daratumumab (16 mg/kg) in 2324 patients with multiple myeloma including 1910 patients who received intravenous daratumumab in combination with background regimens and 414 patients who received intravenous daratumumab as monotherapy. Post-marketing adverse reactions are also included.

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 5: Adverse reactions in multiple myeloma patients treated with intravenous daratumumab or subcutaneous daratumumab

System Organ Class	Adverse reaction	Frequency	Incidence (%)	
			Any Grade	Grade 3-4
Infections and infestations	Upper respiratory tract infection[a]	Very Common	38%	2%
	Bronchitis[a]	Very Common	14%	2%
	Pneumonia[a]	Very Common	14%	9%
	Urinary tract infection	Common	7%	1%
	Influenza	Common	4%	1%[#]
	Sepsis[a]	Common	4%	3%
	Hepatitis B reactivation[a]	Uncommon	<1%	<1%
Blood and lymphatic system disorders	Neutropenia[a]	Very Common	40%	33%
	Thrombocytopenia[a]	Very Common	30%	18%
	Anaemia[a]	Very Common	27%	12%
	Lymphopenia[a]	Very Common	13%	11%
	Leukopenia[a]	Very Common	11%	6%
Immune system disorders	Anaphylactic reaction[b]	Rare	-	-
Metabolism and nutrition disorders	Decreased appetite	Very Common	10%	1%
	Hyperglycaemia	Common	6%	3%
	Hypocalcaemia	Common	5%	1%
	Dehydration	Common	2%	1%[#]
Psychiatric disorders	Insomnia	Very Common	14%	1%[#]
Nervous system disorders	Peripheral sensory neuropathy	Very Common	26%	3%
	Headache	Very Common	11%	<1%[#]
	Dizziness	Common	9%	<1%[#]
	Paraesthesia	Common	9%	<1%
Cardiac disorders	Atrial fibrillation	Common	3%	1%
Vascular disorders	Hypertension[a]	Very Common	10%	5%
Respiratory, thoracic and mediastinal disorders	Cough[a]	Very Common	22%	<1%[#]
	Dyspnoea[a]	Very Common	18%	2%
	Pulmonary oedema[a]	Common	1%	<1%
Gastrointestinal disorders	Diarrhoea	Very Common	29%	3%
	Constipation	Very Common	28%	1%
	Nausea	Very Common	23%	1%[#]
	Vomiting	Very Common	14%	1%[#]
	Pancreatitis[a]	Common	1%	<1%
Skin and subcutaneous tissue disorders	Rash	Common	9%	<1%[#]
	Pruritus	Common	5%	<1%[#]
Musculoskeletal and connective tissue disorders	Back pain	Very Common	17%	2%
	Muscle spasms	Very Common	12%	<1%[#]
	Arthralgia	Very Common	10%	1%[#]
	Musculoskeletal chest pain	Common	6%	<1%[#]
General disorders and administration site conditions	Fatigue	Very Common	23%	3%
	Oedema peripheral[a]	Very Common	22%	1%
	Pyrexia	Very Common	22%	1%
	Asthenia	Very Common	18%	2%
	Chills	Common	9%	<1%[#]
	Injection site erythema[e]	Common	4%	0
	Injection site reactions[d,e]	Common	8%	0
Injury, poisoning and procedural complications	Infusion-related reactions[c]			
	Daratumumab intravenous[f]	Very Common	39%	5%
	Daratumumab subcutaneous[e]	Very Common	11%	1%[#]

[#] No grade 4
[a] Indicates a grouping of terms.
[b] Based on post-marketing adverse reactions.
[c] Infusion-related reactions includes terms determined by investigators as related to infusion/injection of daratumumab.
[d] Injection site reactions includes terms determined by investigators as related to injection of daratumumab.
[e] Frequency based on daratumumab subcutaneous studies only (N=490).
[f] Frequency based on daratumumab intravenous studies only (N=2324).
Note: Based on 2814 multiple myeloma patients treated with daratumumab intravenous or daratumumab subcutaneous.

Description of selected adverse reactions

Infusion-related reactions (IRRs)
In clinical studies (monotherapy and combination treatments; N=490) with DARZALEX subcutaneous formulation, the incidence of any grade IRRs was 10.2% with the first injection of DARZALEX (1,800 mg, Week 1), 0.2% with the Week 2 injection, and 0.8% with subsequent injections. Grade 3 IRRs were seen in 1.4% of patients. No patients had Grade 4 IRRs.

Signs and symptoms of IRR 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 studies (N=490) with DARZALEX subcutaneous formulation, the incidence of any grade injection site reaction was 8.2%. There were no Grade 3 or 4 ISRs. The most common (≥1%) ISRs were erythema, injection site induration, pruritis.

Infections
In patients receiving DARZALEX subcutaneous formulation as monotherapy, incidence of infections was similar between DARZALEX subcutaneous formulation (52.9%) versus intravenous daratumumab groups (50.0%). Additionally, Grade 3 or 4 infections also occurred at similar frequencies between DARZALEX subcutaneous formulation (11.7%) and intravenous daratumumab (14.3%). Most infections were manageable and rarely led to treatment discontinuation. Pneumonia was the most commonly reported severe (Grade 3 or 4) infection across studies.

In patients receiving intravenous daratumumab combination therapy, Grade 3 or 4 infections were reported as follows:
Relapsed/refractory patient studies: DVd: 21%, Vd: 19%; DRd: 27%, Rd: 23%; DPd: 28%
Newly diagnosed patient studies: D-VMP: 23%, VMP: 15%; DRd: 32%, Rd: 23%; D-VTd: 22%, VTd: 20%.
Pneumonia was the most commonly reported severe (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 receiving intravenous daratumumab combination therapy, fatal infections (Grade 5) were reported as follows:
Relapsed/refractory patient studies: DVd: 1%, Vd: 2%; DRd: 2%, Rd: 1%; DPd: 2%
Newly diagnosed patient studies: D-VMP: 1%, VMP: 1%; DRd: 2%, Rd: 2%; DVTd: 0%, VTd: 0%.
Key: D=daratumumab; Vd=bortezomib-dexamethasone; Rd=lenalidomide-dexamethasone; Pd=pomalidomide-dexamethasone; VMP=bortezomib-melphalan-prednisone; VTd=bortezomib-thalidomide-dexamethasone.

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

Other special populations
In the Phase III study MMY3007, which compared treatment with D-VMP to treatment with VMP in patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant, safety analysis of the subgroup of patients with an ECOG performance score of 2 (D-VMP: n=89, VMP: n=84), was consistent with the overall population (see section 5.1).

Elderly patients
Of the 3207 patients who received daratumumab (n=490 subcutaneous; n=2717 intravenous) at the recommended dose, 38% were 65 to 75 years of age, and 17% 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=1827), 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.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Symptoms and signs
There has been no experience of overdose in clinical studies.

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

DARZALEX solution for subcutaneous injection 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 at a high level on the surface of multiple myeloma tumour cells, as well as other cell types and tissues at various levels. CD38 protein has multiple functions such as receptor mediated adhesion, signalling and enzymatic activity.

Daratumumab has been shown to potently 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, antibody-dependent cell-mediated cytotoxicity, and antibody-dependent cellular phagocytosis 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 mediated cell lysis. T cells (CD3+, CD4+, and CD8+) are also known to express CD38 depending on the stage of development and the level of activation. Significant increases in CD4+ and CD8+ T cell absolute counts, and percentages of lymphocytes, were observed with daratumumab treatment in peripheral whole blood and bone marrow. In addition, T-cell receptor DNA sequencing verified that T-cell clonality was increased with daratumumab treatment, indicating immune modulatory effects that may contribute to clinical response.

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

Pharmacodynamic effects

Natural killer (NK) cell and T-cell count

NK cells are known to express high levels of CD38 and are susceptible to daratumumab mediated cell lysis. Decreases in absolute counts and percentages of total NK cells (CD16+CD56+) and activated (CD16+$CD56^{dim}$) NK cells in peripheral whole blood and bone marrow were observed with daratumumab treatment. However, baseline levels of NK cells did not show an association with clinical response.

Immunogenicity

In patients treated with subcutaneous daratumumab in clinical trials, less than 1% of patients developed treatment-emergent anti-daratumumab antibodies.

The incidence of treatment-emergent non-neutralizing anti-rHuPH20 antibodies was 7.8% (35/447); with 7.5% (19/255) in the monotherapy DARZALEX subcutaneous formulation groups, and 8.3% (16/192) in the pooled combination DARZALEX subcutaneous formulation groups. The anti-rHuPH20 antibodies did not appear to impact daratumumab exposures. The clinical relevance of the development of anti-daratumumab or anti-rHuPH20 antibodies after treatment with DARZALEX subcutaneous formulation is not known.

Clinical experience of DARZALEX solution for subcutaneous injection (subcutaneous formulation)

Monotherapy – relapsed/refractory multiple myeloma

MMY3012, an open-label, randomised, Phase III non-inferiority study, compared efficacy and safety of treatment with DARZALEX solution for subcutaneous injection (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 (PI) and an immunomodulatory agent (IMiD). Treatment continued until unacceptable toxicity or disease progression.

A total of 522 patients were randomised: 263 to the DARZALEX subcutaneous formulation arm and 259 to the intravenous 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 met its co-primary endpoints of overall response rate (ORR) by the IMWG response criteria (Table 6) and maximum C_{trough} at pre-dose Cycle 3 Day 1, (see section 5.2).

Table 6: Key results from Study MMY3012

	Subcutaneous Daratumumab (N=263)	Intravenous 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)

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

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

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

Safety and tolerability results, including in lower weight patients, were consistent with the known safety profile for DARZALEX subcutaneous formulation and intravenous 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 intravenous daratumumab. However, open-label studies are subject to bias.

Combination therapies in multiple myeloma
MMY2040 was an open-label trial evaluating the efficacy and safety of DARZALEX subcutaneous formulation 1,800 mg:

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

A total of 199 patients (D-VMP: 67; D-Rd: 65; D-VRd: 67) were enrolled. Efficacy results were determined by computer algorithm using IMWG criteria. The study met its primary endpoint ORR for D-VMP and D-Rd and the primary endpoint VGPR or better for D-VRd (see Table 7).

Table 7: 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]	60 (89.6%)	61 (93.8%)	65 (97.0%)
90% CI(%)	(81.3%, 95.0%)	(86.5%, 97.9%)	(90.9%, 99.5%)
Stringent complete response (sCR)	13 (19.4%)	12 (18.5%)	6 (9.0%)
Complete response (CR)	19 (28.4%)	13 (20.0%)	5 (7.5%)
Very good partial response (VGPR)	20 (29.9%)	26 (40.0%)	37 (55.2%)
Partial response (PR)	8 (11.9%)	10 (15.4%)	17 (25.4%)
VGPR or better (sCR + CR + VGPR)	52 (77.6%)	51 (78.5%)	48 (71.6%)
90% CI(%)	(67.6%, 85.7%)	(68.4%, 86.5%)	(61.2%, 80.6%)

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

[a] Based on treated subjects

Clinical experience with daratumumab concentrate for solution for infusion (intravenous formulation)

Newly diagnosed multiple myeloma

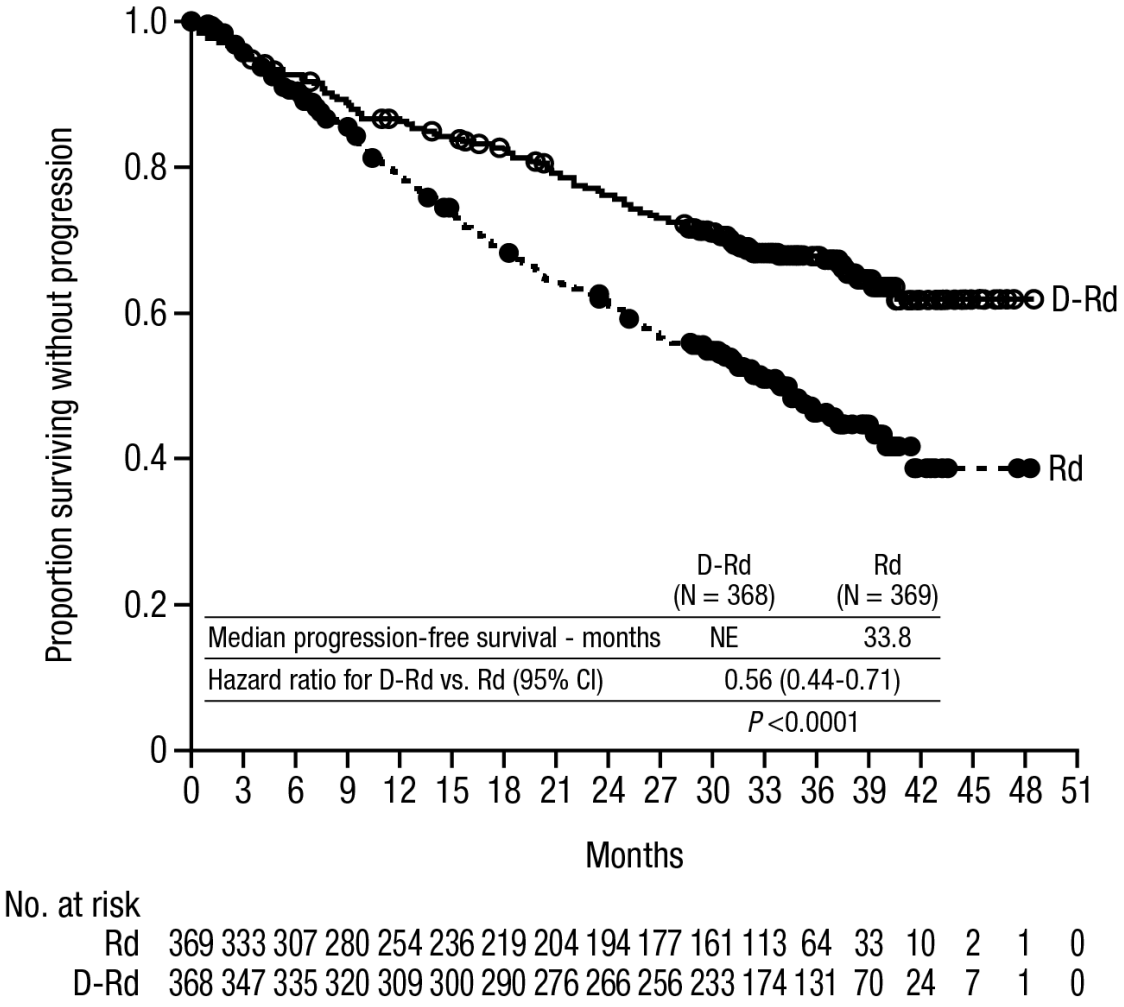
Combination treatment with lenalidomide and dexamethasone in patients ineligible for autologous stem cell transplant:

Study MMY3008, an open-label, randomised, active-controlled Phase III study, compared treatment with intravenous daratumumab 16 mg/kg in combination with lenalidomide and low-dose dexamethasone (DRd) to treatment with lenalidomide and low-dose dexamethasone (Rd) in patients with newly diagnosed multiple myeloma. Lenalidomide (25 mg once daily orally on Days 1-21 of repeated 28-day [4-week] cycles) was given with low dose oral or intravenous dexamethasone 40 mg/week (or a reduced dose of 20 mg/week for patients >75 years or body mass index [BMI] <18.5). On intravenous daratumumab infusion days, the dexamethasone dose was given as a pre-infusion medicinal product. 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 DRd arm and 369 to the Rd arm. The baseline demographic and disease characteristics were similar between the two treatment groups. The median age was 73 (range: 45-90) years, with 44% of the patients ≥75 years of age. The majority were white (92%), male (52%), 34% had an Eastern Cooperative Oncology Group (ECOG) performance score of 0, 49.5% had an ECOG performance score of 1 and 17% had an ECOG performance score of ≥2. Twenty-seven percent had International Staging System (ISS) Stage I, 43% had ISS Stage II and 29% had ISS Stage III disease. Efficacy was evaluated by progression free survival (PFS) based on International Myeloma Working Group (IMWG) criteria.

Study MMY3008 showed an improvement in Progression Free Survival (PFS) in the DRd arm as compared to the Rd arm; the median PFS had not been reached in the DRd arm and was 31.9 months in the Rd arm (hazard ratio [HR]=0.56; 95% CI: 0.43, 0.73; p<0.0001), representing 44% reduction in the risk of disease progression or death in patients treated with DRd. Results of an updated PFS analysis approximately 9 months after the original clinical cutoff, continued to show an improvement in PFS for patients in the DRd arm compared with the Rd arm. Median PFS was not reached in the DRd arm and was 33.8 months in the Rd arm (HR=0.56; 95% CI: 0.44, 0.71; p<0.0001).

Figure 1: Kaplan-Meier Curve of PFS in Study MMY3008



Additional efficacy results from Study MMY3008 are presented in Table 8 below.

Table 8: Additional efficacy results from Study MMY3008[a]

	DRd (n=368)	**Rd (n=369)**
Overall response (sCR+CR+VGPR+PR) n(%)[a]	342 (92.9%)	300 (81.3%)
p-value[b]	<0.0001	
Stringent complete response (sCR)	112 (30.4%)	46 (12.5%)
Complete response (CR)	63 (17.1%)	46 (12.5%)
Very good partial response (VGPR)	117 (31.8%)	104 (28.2%)
Partial response (PR)	50 (13.6%)	104 (28.2%)
CR or better (sCR + CR)	175 (47.6%)	92 (24.9%)
p-value[b]	<0.0001	
VGPR or better (sCR + CR + VGPR)	292 (79.3%)	196 (53.1%)
p-value[b]	<0.0001	
MRD negativity rate[a,c] n(%)	89 (24.2%)	27 (7.3%)
95% CI (%)	(19.9%, 28.9%)	(4.9%, 10.5%)
Odds ratio with 95% CI[d]	4.04 (2.55, 6.39)	
p-value[e]	<0.0001	

DRd=daratumumab-lenalidomide-dexamethasone; Rd=lenalidomide-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 odds ratio for un-stratified tables is used. An odds ratio >1 indicates an advantage for DRd.

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

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

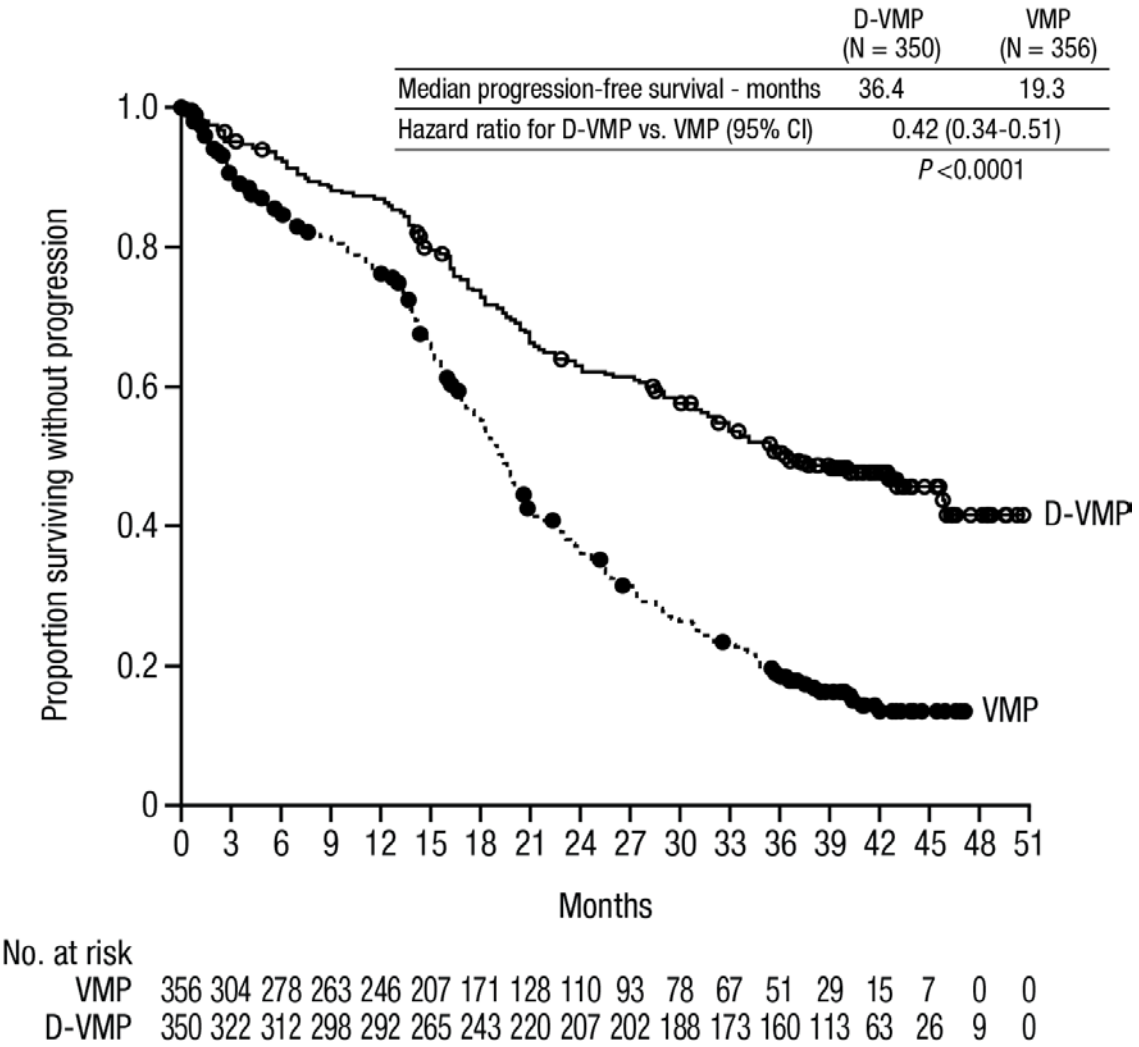
Combination treatment with bortezomib, melphalan and prednisone (VMP) in patients ineligible for autologous stem cell transplant:
Study MMY3007, an open-label, randomised, active-controlled Phase III study, compared treatment with intravenous daratumumab 16 mg/kg in combination with bortezomib, melphalan and prednisone (D-VMP), to treatment with VMP in patients with newly diagnosed multiple myeloma. Bortezomib was administered by subcutaneous injection at a dose of 1.3 mg/m^2 body surface area twice weekly at Weeks 1, 2, 4 and 5 for the first 6-week cycle (Cycle 1; 8 doses), followed by once weekly administrations at Weeks 1, 2, 4 and 5 for eight more 6-week cycles (Cycles 2-9; 4 doses per cycle). Melphalan at 9 mg/m^2, and prednisone at 60 mg/m^2 were orally administered on Days 1 to 4 of the nine 6-week cycles (Cycles 1-9). Intravenous 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, 38% had ISS Stage III disease and 84% had standard risk cytogenetics. 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 showed 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). Results of an updated PFS analysis after a median follow-up of 40 months continued to show an

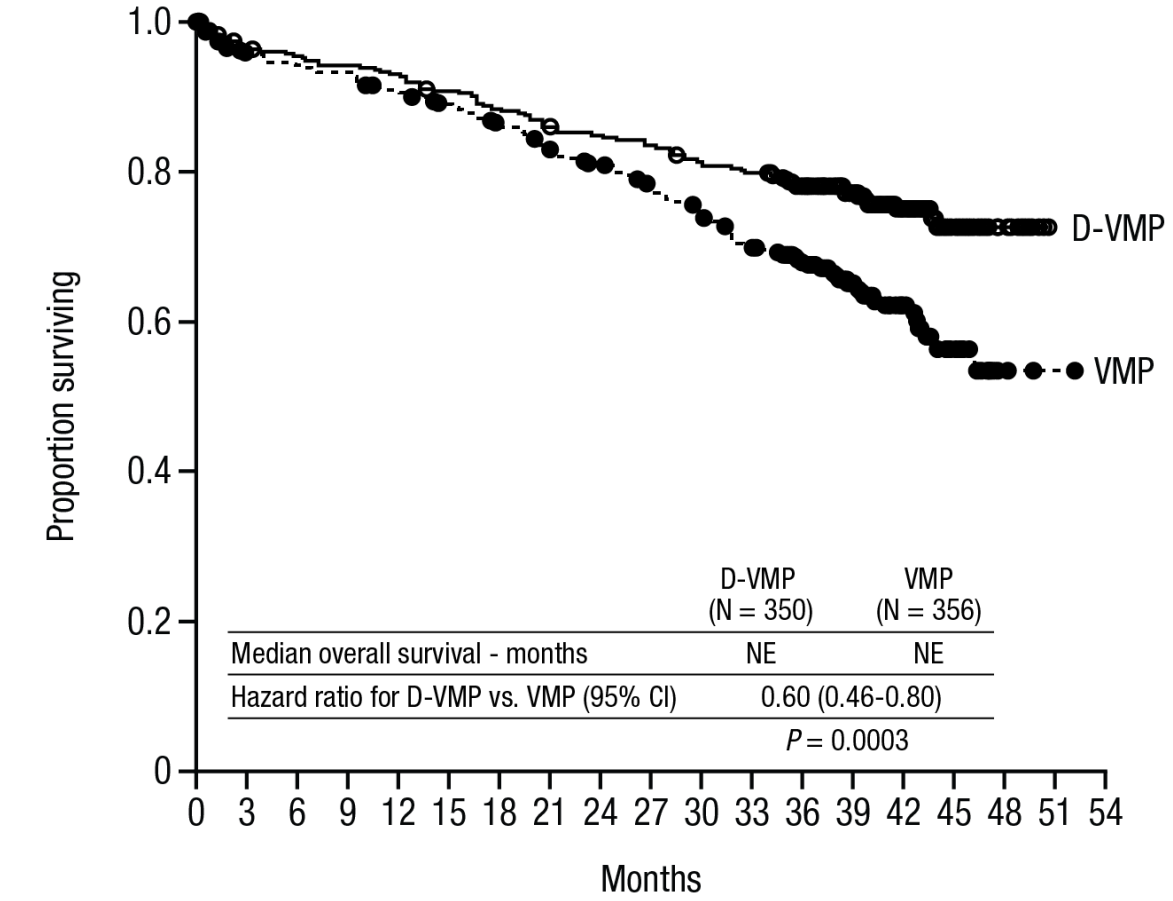
improvement in PFS for patients in the D-VMP arm compared with the VMP arm. Median PFS was 36.4 months in the D-VMP arm and 19.3 months in the VMP arm (HR=0.42; 95% CI: 0.34, 0.51; p<0.0001), representing a 58% reduction in the risk of disease progression or death in patients treated with D-VMP.

Figure 2: Kaplan-Meier Curve of PFS in Study MMY3007



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.

Figure 3: Kaplan-Meier Curve of OS in Study MMY3007



Additional efficacy results from Study MMY3007 are presented in Table 9 below.

Table 9: Additional efficacy results from Study MMY3007[a]

	D-VMP (n=350)	**VMP (n=356)**
Overall response (sCR+CR+VGPR+PR) [n(%)]	318 (90.9)	263 (73.9)
p-value[b]	<0.0001	
Stringent complete response (sCR) [n(%)]	63 (18.0)	25 (7.0)
Complete response (CR) [n(%)]	86 (24.6)	62 (17.4)
Very good partial response (VGPR) [n(%)]	100 (28.6)	90 (25.3)
Partial response (PR) [n(%)]	69 (19.7)	86 (24.2)
MRD negativity rate (95% CI) [c] (%)	22.3 (18.0, 27.0)	6.2 (3.9, 9.2)
Odds ratio with 95% CI[d]	4.36 (2.64, 7.21)	
p-value[e]	<0.0001	

D-VMP=daratumumab-bortezomib-melphalan-prednisone; VMP=bortezomib-melphalan-prednisone; 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] A Mantel-Haenszel estimate of the common odds ratio for stratified tables is used. An odds ratio >1 indicates an advantage for D-VMP.

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

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.

A subgroup analysis was performed on patients at least 70 years old, or those 65-69 years old with ECOG performance score of 2, or aged less than 65 years of age with significant comorbidity or ECOG performance score of 2 (D-VMP: n=273, VMP: n=270). The efficacy results in this subgroup were consistent with the overall population. In this subgroup, median PFS was not reached in the D-VMP group and was 17.9 months in the VMP group (HR=0.56; 95% CI: 0.42, 0.75); p<0.0001). The overall response rate was 90% in the D-VMP group and 74% in theVMP group (VGPR rate:29% in D-VMP group and 26% in VMP group; CR: 22% in D-VMP group and 18% in VMP group; sCR rate: 20% in D-VMP group and 7% in VMP group). The safety results of this subgroup were consistent with the overall population. Furthermore, safety analysis of the subgroup of patients with an ECOG performance score of 2 (D-VMP: n=89, VMP: n=84), was also consistent with the overall population.

Combination treatment with bortezomib, thalidomide and dexamethasone (VTd) in patients eligible for autologous stem cell transplant (ASCT):
Study MMY3006 is a 2 Part, open-label, randomised, active-controlled Phase III study. Part 1 compared induction and consolidation treatment with intravenous 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. In Part 2, subjects with at least a partial response (PR) by Day 100 post-transplant were re-randomised in a 1:1 ratio to daratumumab maintenance or observation only. Only results from Part 1 are described henceforth.

Bortezomib was administered by subcutaneous injection or intravenous 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 intravenous daratumumab infusion, the dexamethasone dose was administered intravenously as a pre-infusion medication. Dose adjustments for bortezomib, thalidomide and dexamethasone were applied according to manufacturer’s prescribing information.

A total of 1085 patients were 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. All patients were ≤65 years: 43% were in the age group ≥60-65 years, 41% were in the age group ≥50-60 years and 16% below age of 50 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 International Staging System (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 and Progression free survival (PFS).

Table 10: 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, d] n(%)	346 (63.7%)	236 (43.5%)	<0.0001
95% CI (%)	(59.5%, 67.8%)	(39.3%, 47.8%)	
Odds ratio with 95% CI[e]	2.27 (1.78, 2.90)		
MRD negativity in combination with CR or better[c] n(%)	183 (33.7%)	108 (19.9%)	<0.0001
95% CI (%)	(29.7%, 37.9%)	(16.6%, 23.5%)	
Odds ratio with 95% CI[e]	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] Regardless of response per IMWG

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

Results of a PFS analysis by censoring patients who were randomised to daratumumab maintenance in the second randomisation, at the date of the second randomisation showed HR=0.50; 95% CI: 0.34, 0.75; p=0.0005.

Relapsed/Refractory multiple myeloma
Monotherapy:
The clinical efficacy and safety of intravenous daratumumab 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 had demonstrated disease progression on the last therapy, was demonstrated in two open-label studies.

In Study MMY2002, 106 patients with relapsed and refractory multiple myeloma received 16 mg/kg intravenous daratumumab until disease progression. The median patient age was 63.5 years (range, 31 to 84 years), 11% of patients were ≥75 years of age, 49% were male and 79% were Caucasian. Patients had received a median of 5 prior lines of therapy. Eighty percent of patients had received prior autologous stem cell transplantation (ASCT). Prior therapies included bortezomib (99%), lenalidomide (99%), pomalidomide (63%) and carfilzomib (50%). At baseline, 97% of patients were refractory to the last line of treatment, 95% were refractory to both, a proteasome inhibitor (PI) and immunomodulatory agent (IMiD), 77% were refractory to alkylating agents, 63% were refractory to pomalidomide and 48% of patients were refractory to carfilzomib.

Efficacy results of the pre-planned interim analysis based on Independent Review Committee (IRC) assessment are presented in Table 11 below.

Table 11: IRC assessed efficacy results for study MMY2002

Efficacy endpoint	Intravenous daratumumab 16 mg/kg N=106
Overall response rate[1] (ORR: sCR+CR+VGPR+PR) [n (%)] 95% CI (%)	31 (29.2) (20.8, 38.9)
Stringent complete response (sCR) [n (%)]	3 (2.8)
Complete response (CR) [n]	0
Very good partial response (VGPR) [n (%)]	10 (9.4)
Partial response (PR) [n (%)]	18 (17.0)

Clinical Benefit Rate (ORR+MR) [n (%)]	36 (34.0)
Median Duration of Response [months (95% CI)]	7.4 (5.5, NE)
Median Time to Response [months (range)]	1 (0.9; 5.6)

[1] Primary efficacy endpoint (International Myeloma Working Group criteria)
CI=confidence interval; NE=not estimable; MR=minimal response

Overall response rate (ORR) in MMY2002 was similar regardless of type of prior anti-myeloma therapy.
At a survival update with a median duration of follow-up of 14.7 months, median Overall Survival (OS) was 17.5 months (95% CI:13.7, not estimable).

In Study GEN501, 42 patients with relapsed and refractory multiple myeloma received 16 mg/kg intravenous daratumumab until disease progression. The median patient age was 64 years (range, 44 to 76 years), 64% were male and 76% were Caucasian. Patients in the study had received a median of 4 prior lines of therapy. Seventy-four percent of patients had received prior ASCT. Prior therapies included bortezomib (100%), lenalidomide (95%), pomalidomide (36%) and carfilzomib (19%). At baseline, 76% of patients were refractory to the last line of treatment, 64% were refractory to both a PI and IMiD, 60% were refractory to alkylating agents, 36% were refractory to pomalidomide and 17% were refractory to carfilzomib.

Pre-planned interim analysis showed that treatment with daratumumab at 16 mg/kg led to a 36% ORR with 5% CR and 5% VGPR. The median time to response was 1 (range: 0.5 to 3.2) month. The median duration of response was not reached (95% CI: 5.6 months, not estimable).

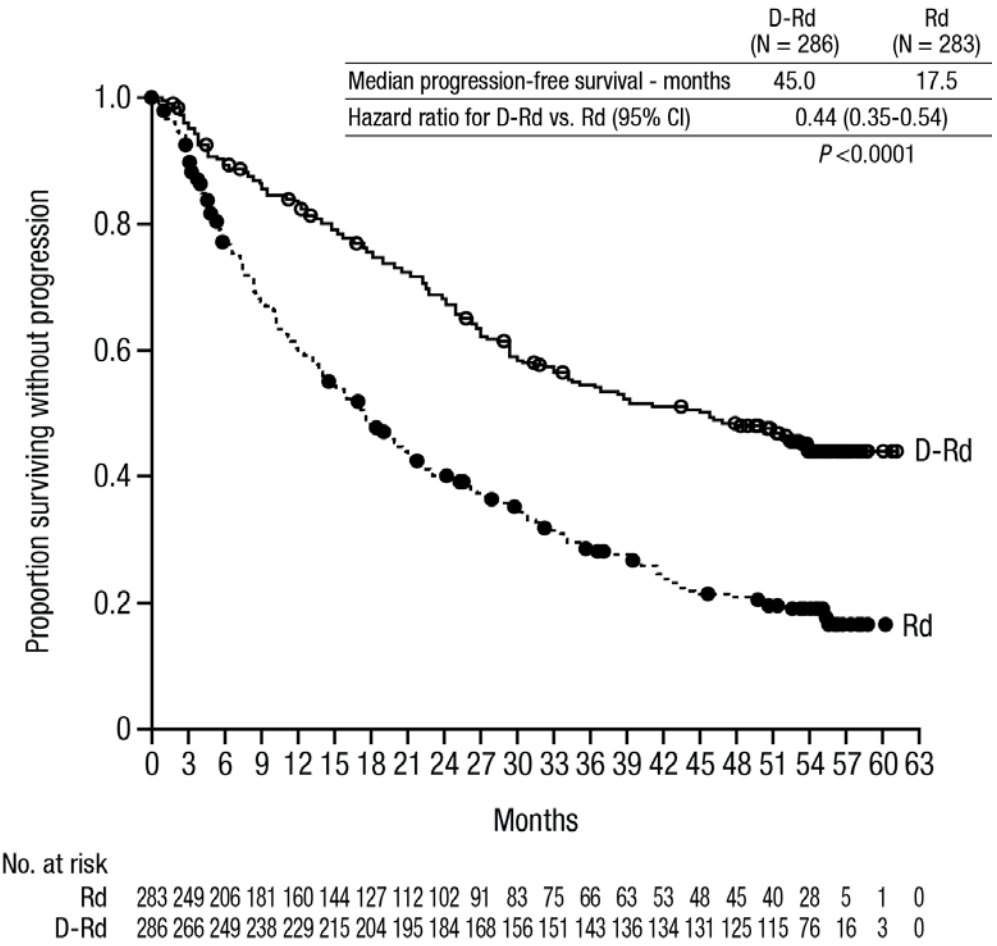
At a survival update with a median duration of follow-up of 15.2 months, median OS was not reached (95% CI: 19.9 months, not estimable), with 74% of subjects still alive.

Combination treatment with lenalidomide:
Study MMY3003, an open-label, randomised, active-controlled Phase III trial, compared treatment with intravenous daratumumab 16 mg/kg in combination with lenalidomide and low-dose dexamethasone (DRd) to treatment with lenalidomide and low-dose dexamethasone (Rd) in patients with relapsed or refractory 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 dexamethasone at 40 mg/week (or a reduced dose of 20 mg/week for patients >75 years or BMI <18.5). On intravenous 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. Treatment was continued in both arms until disease progression or unacceptable toxicity.

A total of 569 patients were randomised; 286 to the DRd arm and 283 to the Rd arm. The baseline demographic and disease characteristics were similar between the intravenous daratumumab and the control arm. The median patient age was 65 years (range 34 to 89 years) and 11% were ≥75 years. The majority of patients (86%) received a prior PI, 55% of patients had received a prior IMiD, including 18% of patients who had received prior lenalidomide; and 44% of patients had received both a prior PI and IMiD. At baseline, 27% of patients were refractory to the last line of treatment. Eighteen percent (18%) of patients were refractory to a PI only, and 21% were refractory to bortezomib. Patients refractory to lenalidomide were excluded from the study.

With a median follow-up of 13.5 months, the primary analysis of PFS in study MMY3003 demonstrated an improvement in the DRd arm as compared to the Rd arm; the median PFS had not been reached in the DRd arm and was 18.4 months in the Rd arm (HR=0.37; 95% CI: 0.27, 0.52; p<0.0001). 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 DRd arm compared with the Rd arm. Median PFS was 45.0 months in the DRd 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 DRd (see Figure 4).

Figure 4: Kaplan-Meier Curve of PFS in Study MMY3003



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

Table 12: Additional efficacy results from Study MMY3003

Response evaluable patient number	**DRd (n=281)**	**Rd (n=276)**
Overall response (sCR+CR+VGPR+PR) n(%)	261 (92.9)	211 (76.4)
p-value[a]	<0.0001	
Stringent complete response (sCR)	51 (18.1)	20 (7.2)
Complete response (CR)	70 (24.9)	33 (12.0)
Very good partial response (VGPR)	92 (32.7)	69 (25.0)
Partial response (PR)	48 (17.1)	89 (32.2)
Median Time to Response [months (95% CI)]	1.0 (1.0, 1.1)	1.3 (1.1, 1.9)
Median Duration of Response [months (95% CI)]	NE (NE, NE)	17.4 (17.4, NE)
MRD negative rate (95% CI)[b] (%)	21.0 (16.4, 26.2)	2.8 (1.2, 5.5)
Odds ratio with 95% CI[c]	9.31 (4.31, 20.09)	
P-value[d]	<0.0001	

DRd=daratumumab-lenalidomide-dexamethasone; Rd=lenalidomide-dexamethasone; MRD=minimal residual disease; CI=confidence interval; NE=not estimable.

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

[b] Based on Intent-to-treat population and threshold of 10^{-5}

[c] Mantel-Haenszel estimate of the common odds ratio is used. An odds ratio >1 indicates an advantage for DRd.

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

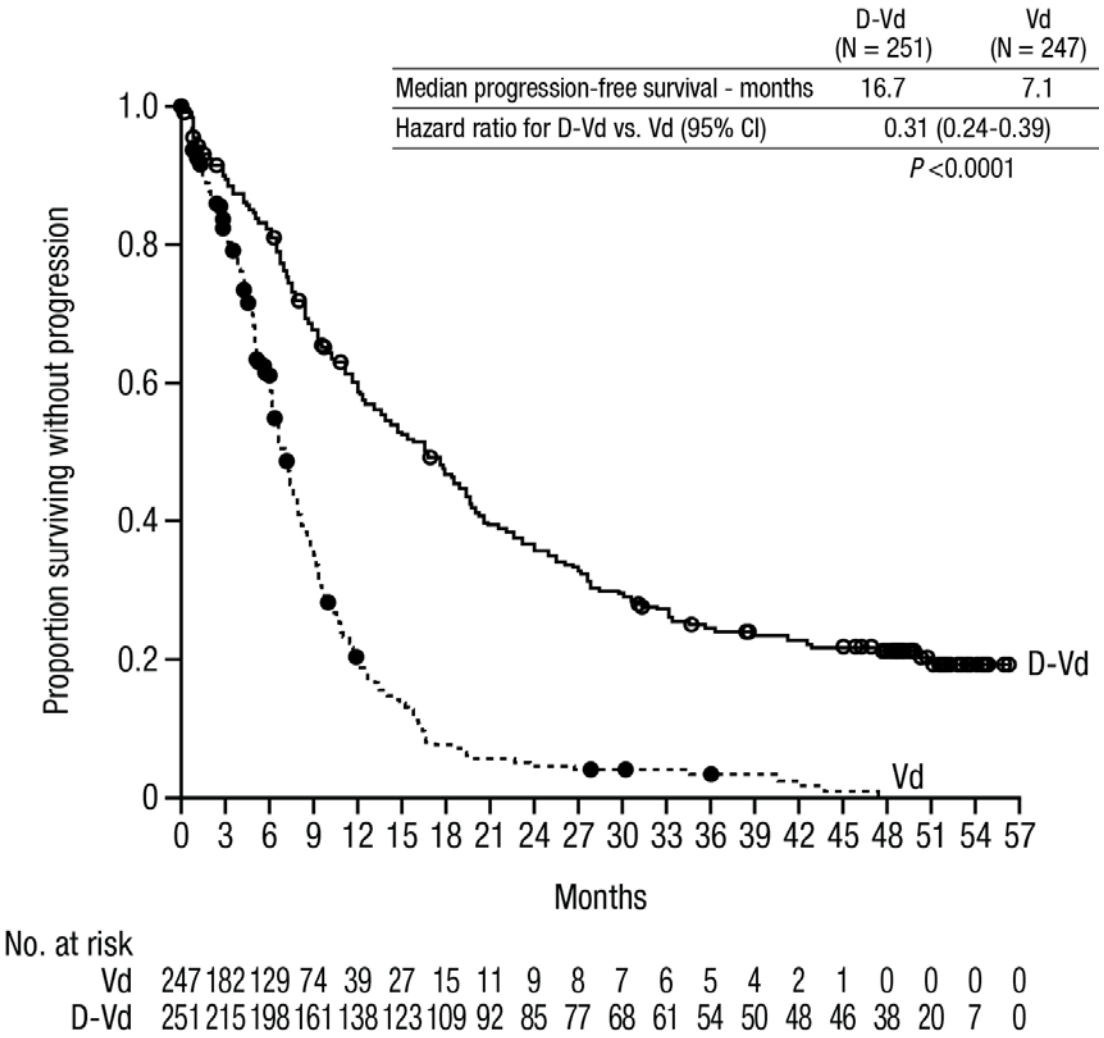
Median OS was not reached for either treatment group. With an overall median follow-up of 13.5 months, the hazard ratio for OS was 0.64 (95% CI: 0.40, 1.01; p=0.0534).

Combination treatment with bortezomib:
Study MMY3004, an open-label, randomised, active-controlled Phase III trial, compared treatment with intravenous daratumumab 16 mg/kg in combination with bortezomib and dexamethasone (DVd), to treatment with bortezomib and dexamethasone (Vd) in patients with relapsed or refractory multiple myeloma who had received at least one prior therapy. Bortezomib was administered by subcutaneous injection or intravenous infusion 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 each of the 8 bortezomib cycles (80 mg/week for two out of three weeks 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 intravenous daratumumab infusion, 20 mg of the dexamethasone dose was administered as a pre-infusion medication. intravenous daratumumab treatment was continued until disease progression or unacceptable toxicity.

A total of 498 patients were randomised; 251 to the DVd arm and 247 to the Vd arm. The baseline demographic and disease characteristics were similar between the intravenous daratumumab and the control arm. The median patient age was 64 years (range 30 to 88 years) and 12% were ≥75 years. 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. Thirty-three percent (33%) of patients were refractory to an IMiD only, and 28% were refractory to lenalidomide. Patients refractory to bortezomib were excluded from the study.

With a median follow-up of 7.4 months, the primary analysis of PFS in study MMY3004 demonstrated an improvement in the DVd arm as compared to the Vd arm; the median PFS had not been reached in the DVd arm and was 7.2 months in the Vd arm (HR [95% CI]: 0.39 [0.28, 0.53]; p-value<0.0001). 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 DVd arm compared with the Vd arm. Median PFS was 16.7 months in the DVd 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 DVd versus Vd (see Figure 5).

Figure 5: Kaplan-Meier Curve of PFS in Study MMY3004



Additional efficacy results from Study MMY3004 are presented in Table 13 below.

Table 13: Additional efficacy results from Study MMY3004

Response evaluable patient number	DVd (n=240)	Vd (n=234)
Overall response (sCR+CR+VGPR+PR) n(%)	199 (82.9)	148 (63.2)
P-value[a]	<0.0001	
Stringent complete response (sCR)	11 (4.6)	5 (2.1)
Complete response (CR)	35 (14.6)	16 (6.8)
Very good partial response (VGPR)	96 (40.0)	47 (20.1)
Partial response (PR)	57 (23.8)	80 (34.2)
Median Time to Response [months (range)]	0.9 (0.8, 1.4)	1.6 (1.5, 2.1)
Median Duration of Response [months (95% CI)]	NE (11.5, NE)	7.9 (6.7, 11.3)
MRD negative rate (95% CI)[b]	8.8% (5.6%, 13.0%)	1.2% (0.3%, 3.5%)
Odds ratio with 95% CI[c]	9.04 (2.53, 32.21)	
P-value[d]	0.0001	

DVd=daratumumab- bortezomib-dexamethasone; Vd=bortezomib-dexamethasone; MRD=minimal residual disease; CI=confidence interval; NE=not estimable.

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

[b] Based on Intent-to-treat population and threshold of 10^{-5}

[c] Mantel-Haenszel estimate of the common odds ratio is used. An odds ratio >1 indicates an advantage for DVd.

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

Median OS was not reached for either treatment group.With an overall median follow-up of 7.4 months (95% CI: 0.0, 14.9), the hazard ratio for OS was 0.77 (95% CI: 0.47, 1.26; p=0.2975).

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

Paediatric population
The European Medicines Agency has waived the obligation to submit the results of studies with DARZALEX in all subsets of the paediatric population in multiple myeloma (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Daratumumab exposure in a monotherapy study following the recommended 1,800 mg administration of DARZALEX subcutaneous formulation (weekly for 8 weeks, biweekly for 16 weeks, monthly thereafter) as compared to 16 mg/kg intravenous daratumumab for the same dosing schedule, showed non-inferiority for the co-primary endpoint of maximum C_{trough} (Cycle 3 Day 1 pre-dose), with mean ± SD of 593 ± 306 µg/mL compared to 522 ± 226 µg/mL for intravenous daratumumab, with a geometric mean ratio of 107.93% (90% CI: 95.74-121.67).

Following the recommended dose of 1,800 mg DARZALEX solution for subcutaneous injection, peak concentrations (C_{max}) increased 4.8-fold and total exposure ($AUC_{0\text{-}7\ days}$) increased 5.4-fold from first dose to last weekly dose (8^{th} dose). Highest trough concentrations for DARZALEX solution for subcutaneous injection are typically observed at the end of the weekly dosing regimens for both monotherapy and combination therapy.

The simulated trough concentrations following 6 weekly doses of 1,800 mg DARZALEX solution for subcutaneous injection for combination therapy were similar to 1,800 mg DARZALEX solution for subcutaneous injection monotherapy.

Absorption and distribution
At the recommended dose of 1,800 mg, the absolute bioavailability of DARZALEX solution for subcutaneous injection is 69%, with an absorption rate of 0.012 $hour^{-1}$, with peak concentrations occurring at 70 to 72 h (T_{max}).

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

Metabolism and elimination
Daratumumab exhibits both concentration and time-dependent pharmacokinetics with parallel linear and nonlinear (saturable) elimination that is characteristic of target-mediated clearance. The population PK model estimated mean clearance value of daratumumab is 4.96 mL/h (58.7% CV). The model-based geometric mean for half-life associated with linear elimination is 20.4 days (22.4% CV). For the monotherapy regimen, the steady state is achieved at approximately 5 months into every 4 weeks dosage at the recommended dose and schedule (1,800 mg; once weekly for 8 weeks, every 2 weeks for 16 weeks, and then every 4 weeks thereafter).

A population PK analysis was conducted using data from DARZALEX solution for subcutaneous injection monotherapy and combination therapy, and the predicted PK exposures are summarised in Table 14.

Table 14: Daratumumab exposure following administration of DARZALEX subcutaneous formulation (1,800 mg) or intravenous daratumumab (16 mg/kg) monotherapy

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

Special populations

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

Gender had a statistically significant effect on PK, with slightly higher exposure in females than males, but the difference in exposure is not considered clinically meaningful. No individualisation is necessary for patients on the basis of gender.

Renal impairment
No formal studies of DARZALEX subcutaneous formulation in patients with renal impairment have been conducted. Population PK analyses were performed based on pre-existing renal function data in patients receiving DARZALEX subcutaneous formulation monotherapy or various combination therapies, including 220 patients with normal renal function (creatinine clearance [CRCL] ≥90 mL/min), 273 with mild renal impairment (CRCL <90 and ≥60 mL/min), 215 with moderate renal impairment (CRCL <60 and ≥30 mL/min), and 33 with severe renal impairment or end stage renal disease (CRCL<30 mL/min). No clinically important differences in exposure to daratumumab were observed between patients with renal impairment and those with normal renal function.

Hepatic impairment
No formal studies of DARZALEX subcutaneous formulation in patients with hepatic impairment have been conducted.
Population PK analyses were performed in patients receiving DARZALEX subcutaneous formulation monotherapy or various combination therapies, including 655 patients with normal hepatic function (total bilirubin [TB] and aspartate aminotransferase [AST] ≤ upper limit of normal [ULN]), 82 with mild hepatic impairment [(total bilirubin ≤ ULN and AST > ULN) or (ULN < total bilirubin ≤1.5×ULN)] and 5 patients with moderate (1.5×ULN < total bilirubin ≤3×ULN) hepatic impairment. No clinically important differences in the exposure to daratumumab were observed between patients with normal hepatic function and mild hepatic impairment. There were very few patients with moderate hepatic impairment and no patients with severe hepatic impairment to make meaningful conclusions for these populations.

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

Body weight
The flat-dose administration of DARZALEX subcutaneous formulation 1,800 mg as monotherapy achieved adequate exposure for all body-weight subgroups. The mean Cycle 3 Day 1 C_{trough} in the lower body-weight subgroup (≤65 kg) was 60% higher and in the higher body weight (>85 kg)

subgroup, 12% lower than the intravenous daratumumab subgroup. In some patients with body weight >120 kg, lower exposure was observed which may result in reduced efficacy. However, this observation is based on limited number of patients.

5.3 Preclinical safety data

Toxicology data have been derived from studies with daratumumab in chimpanzees and with a surrogate anti-CD38 antibody in cynomolgus monkeys. No chronic toxicity testing has been conducted.

No animal studies have been performed to establish the carcinogenic potential of daratumumab.

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

No carcinogenicity, genotoxicity, or fertility studies were conducted for recombinant human hyaluronidase. There were no effects on reproductive tissues and function and no systemic exposure of hyaluronidase in monkeys given 22,000 U/kg/week subcutaneously (12 times higher than the human dose) for 39 weeks. As hyaluronidase is a recombinant form of the endogenous human hyaluronidase, no carcinogenity, mutagenesis, or effects on fertility are expected.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Recombinant human hyaluronidase (rHuPH20)
L-histidine
L-histidine hydrochloride monohydrate
L-methionine
Polysorbate 20
Sorbitol (E420)
Water for injections

6.2 Incompatibilities

This medicinal product must not be used with other materials except those mentioned in section 6.6.

6.3 Shelf life

Unopened vial
1 year

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).

Prepared syringe
Chemical and physical in-use stability in syringe has been demonstrated for 4 hours at ambient temperature up to 30°C (86°F) and ambient light. From a microbiological point of view, unless the method of opening precludes the risk of microbial contamination, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user.

6.4 Special precautions for storage

Store in a refrigerator (2°C-8°C).

Do not freeze.
Store in the original package in order to protect from light.

For storage conditions of the opened medicinal product (see section 6.3).

6.5 Nature and contents of container

15 mL solution in a Type 1 glass vial with an elastomeric closure and an aluminium seal with a flip-off button containing 1,800 mg of daratumumab. Pack size of 1 vial.

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, discoloration 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. MARKETING AUTHORISATION HOLDER

Janssen-Cilag International NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/16/1101/004

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 20 May 2016
Date of latest renewal: 24 April 2017

10. DATE OF REVISION OF THE TEXT

4th June 2020

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu